# A Systematic Review and Meta-Analysis of Kiwifruit's Impact on Functional Constipation

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Kiwifruit is rich in nutrients and fibers that benefit the digestive system. Despite various clinical investigations on the efficacy of kiwifruit for constipation, conflicting results are present. Therefore, the purpose of this meta-analysis was to evaluate the effectiveness of kiwifruit in treating functional constipation. The study's main goal is to quantify the frequency of defecation. Randomized-controlled trials (RCTs) were explored from four databases, including Cochrane Library, ProQuest, Science Direct, and MEDLINE, with Google Scholar as an additional database for hand-searching purposes. The Risk of Bias 2 (RoB2) and Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) tools were employed to evaluate the certainty of evidence. The meta-analysis was carried out using RevMan. After critically appraising the individual articles, the study includes five randomized controlled trials (RCTs). The results indicated that defecation frequency improved considerably, with a p-value of 0.0008 and a weighted mean difference (WMD) of 0.07. However, the GRADE analysis showed low-quality evidence. Kiwifruit may be a secure and efficient treatment for people with functional constipation. However, further high-quality clinical investigations are needed to confirm these results.

Keywords: Constipation; Defecation Frequency; Kiwifruit; Meta-Analysis; Systematic Review.

Functional constipation occurs when the waste disposal system does not function correctly without comorbidities and medication side effects. This type of constipation can be caused by slow food transit and obstruction in the gastrointestinal tract <sup>1</sup>. According to a systematic review of patients with constipation from 1990 to 2020, the prevalence of functional constipation was 15.3% <sup>2</sup>. Meanwhile, a study conducted in Japan with 5,155 participants reported that the incidence of functional constipation was 52.2% compared to other types of chronic constipation <sup>3</sup>. Dietary adjustment and lifestyle modification can serve as effective preventive measures and alternatives to pharmacological medications, which may entail potential side effects like magnesium toxicity, cramping, and nutrient malabsorption<sup>4,5</sup>. By implementing these changes, individuals can help prevent the onset of this disorder and alleviate constipation without relying solely on

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medication<sup>5,6</sup>. Dietary fiber, categorized as a type of bulk laxative medication, is widely regarded as the safest treatment option when compared to other classes of laxatives<sup>4</sup>. As a result, it is highly recommended for effectively managing functional constipation. Fiber can enhance stool water retention, create gel-like substances to lubricate the stool, increase stool volume, and stimulate peristalsis, aiding in regular bowel movements <sup>2</sup>. In addition to fiber, certain functional foods like psyllium and wheat bran can contribute to maintaining a healthy gut. It is noteworthy that multiple studies have consistently recommended whole green kiwifruit as an effective remedy for relieving constipation over an extended period of time7-10.

Kiwifruit belongs to the genus Actinidia and contains about 1.4 - 3 g of fiber per 100 g, with one-third soluble fiber and two-thirds insoluble fiber <sup>7</sup>. The most common kiwifruit species are Actinidia deliciosa and Actinidia chinensis, known as green and gold kiwifruit, respectively. In addition to fiber, kiwifruit also contains vitamins, minerals, phytonutrients, and proteins, including actinidin, a natural proteolytic enzyme that helps in protein breakdown and digestion 7,11. Numerous randomized controlled trials (RCTs) showed that kiwifruit can enhance bowel movement frequency, with conflicting results <sup>12–14</sup>. Therefore, this systematic review and meta-analysis was undertaken to provide an up-to-date study on the effectiveness of kiwifruit in treating functional constipation symptoms. The scope of this research included kiwifruit species, namely Actinidia chinensis var. deliciosa, which consists of both green and gold kiwifruit.

## **METHODS**

#### **Research Design**

We prepared this meta-analysis using the Cochrane Handbook for Systematic Reviews of Interventions as a guideline.<sup>15</sup>. The results were reported according to the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement.

#### **Eligibility Criteria**

Using the population, intervention, comparator, and outcome (PICO) approach, participants were chosen based on inclusion criteria. The inclusion criteria were healthy patients with functional constipation aged e" 18 years and no history of comorbidities. Meanwhile, the intervention criteria were kiwifruit in whole fruit or supplement form, non-combination, with the placebo or without therapy as the comparator. The primary outcome was bowel movement, with defecation frequency as the measured parameter. The secondary outcome included straining events, stool texture, and side effects of kiwifruit. This analysis focused on studies with both parallel and crossover RCT designs. Meanwhile, studies that did not comply with predetermined PICO criteria, including those involving patients taking laxatives or dietary fiber supplements, were excluded.

#### Literature Search

A research librarian guided the search protocol for this review. Literature searches were conducted until May 2023 on several databases, including Cochrane Central Register of Controlled Trials (CENTRAL), Medline, Science Direct, and ProQuest.For the Medline, CENTRAL, and Proquest databases, the exact MeSH terms used included: (((((actinidia[MeSH Terms]) OR (Actinidia\*[Title/Abstract])) OR (kiwifruit[Title/ Abstract])) OR (kiwi[Title/Abstract])) OR ("Actinidia chinensis" [Title/Abstract])) OR ("Actinidia deliciosa"[Title/Abstract]) AND (randomizedcontrolledtrial[Filter])) AND ((constipation[MeSH Terms]) OR (constipation[Title/Abstract])). RCT was used as a filter for Medline, whereas books, book chapters, conference papers and proceedings, dissertations and theses, articles, evidence-based healthcare, and other sources were used as filters for Proquest. Meanwhile, for the Science Direct database, we used exact keywords as follows: (Actinidia OR kiwifruit OR kiwi OR "Actinidia chinensis" OR "Actinidia deliciosa") AND (constipation). For an additional search, we conducted a hand search via the Google Scholar database to find related articles. Selection of Studies and Data Extraction

To assess the feasibility of research that satisfied the inclusion criteria, two researchers independently reviewed the title, abstract, and contents of full-text papers. The selected studies were tabulated based on PICO analysis. Related interventions were mentioned in detail regarding species and varieties of kiwi fruit, dosage form, dosage, and frequency of interventions. The flow from the literature searches to the study selection was carried out following the guidelines from the PRISMA, and any discrepancies were explored until an agreement was reached.

### **Qualitative Analysis**

Two researchers independently analyzed the quality of each RCT study by conducting critical appraisals based on Cochrane Review guidelines. The qualitative analysis was carried out using the Risk of Bias 2 (RoB2) instrument, and the risk of bias was evaluated across six major domains. For parallel RCT studies, the five domains included were the randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Furthermore, period and carryover effects, or Domain S, were assessed as additional domains for cross-over RCT studies. Questions from each domain can be answered with multiple choices, such as "Yes," "Probably Yes," "No," "Probably No," or "No Information." The overall risk of bias criteria was expressed as "Low" for

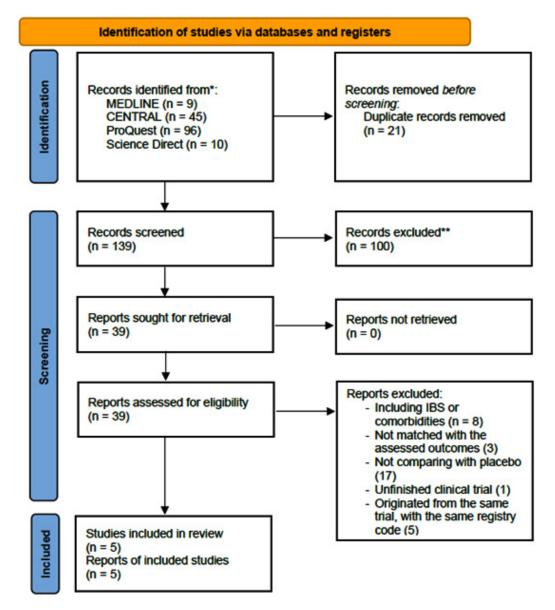


Fig. 1. PRISMA Flowchart

Treatment	Duration	4weeks	21days for each treatment period, with washout period
Design of	Study	Randomized, double-blind, placebin- controlled, parallel-group	Randomized, double-blind, placebo- cross-over cross-over
Outcomes	Secondary	<ul> <li>Straining: not measured</li> <li>Stool texture:</li> <li>*Preduction of stool types 1</li> <li>and 2; increase in stool types 3, 4, and 5 in both groups.</li> <li>Adverse effects:</li> <li>intervention subjects (flatulence ploating on 2</li> <li>subjects; no 2</li> <li>subjects; no 2</li> <li>subjects; no 2</li> </ul>	<ul> <li>Straining: no significant difference between the between the kiwifruit and placebo</li> <li>Placebo</li> <li>Placebo</li> <li>Placebo</li> <li>Stool texture: no significant difference between the kiwifruit group and placebo;</li> <li>Adverse effects: mild bloating; nausea, vomiting; signiform and theretion and theretion and the kiwifruit group after the kiwifruit intervention and treatment treatment</li> </ul>
Oute	Primary	Defecation frequency (daily average per week): increased frequency of frequency of frequency of means ± SE) (means ± SE) (	Defecation frequency: no singularant difference between the kinkifuit group (mkifuit group placebo placebo placebo placebo placebo
ator	Dosage Form	1 sachet dissolved in cold water at breakfast	2 capsules per day; 1 norming and 1 evening
Comparator	Type of Kiwifruit	Placebo powder, sprunder, citric acid, fructose, sucralose, and tropical flavors)	Placebo (magnesium stearate)
Intervention	Dosage Form	1 sachet colisoived in colisoived in breakfast (5.5 g of kiwi per sachet)	2 capsules per monving and 1 in the evening (1 capsule contained 500 mained 500 min of kiwi fruit)
Inter	Type of Kiwifruit Dosage Form	Kivia powder (gren kiwfruit extract)	Green kwifruit extract
Participants	Enrolled	82 (43) in the interventio n group, 44 placebo group, and 5 drop- outs)	32, with 8 drop- outs due to missig Contact (1); family crisis (1); drug consumption (3); not disciplined following the intervention (2)
Number of Pa	Eligible	8	99 97
2	Screened	138	110
Participants	Characteristics	Healthy adults with occasional constipation (19 - 64 years), following the ROME III criteria <sup>a</sup>	Healthy adults with occasional constipation (23 - 59 years)
Cturds	Annie	Udani et.al(2013) <sup>12</sup>	Kindley-sides et al.(2015) 17

Table 1. Characteristic of Studies

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3 days for each treatment treatment with 14 days washout period	28days for treatment period, with 14 days washout period	3 weeks for each cycle, without a wash-out period	ard stools
Randomized, 3 c cross-over tre pe da da	Randomized, 28 double-blind, ea placebe- tre placebe- tross-over da wi da ea ea ea ea ea ea ea ea ea ea ea ea ea	Randomized, 3 v eaa wif	is, lumpy or h
Straining: not Straining: not measured Stool texture: stools kwifruit group than in the placebo; p=0.011 Adverse effects: no significant nause, bloating and abdominal gas		e joint,	a ROME III definition of functional constipation: at least two of the following symptoms exist: Straining during more than 1/4 (25%) of defecations, lumpy or hard stools
Defecation frequency: significant increase in the kiwifruit group (man±5D: 1.46±0.66) compared to placeb (1.14 ± 0.46) p=0.034	Defecation frequency: no significant increase in the kiwifruit group	Significant A improvement in fit defecation at frequency, stool consistency, stool volume, and ease volume, and ease of defecation (p-0.05 for all measurements)	ng more than $1/4$ (2
2 times a day for 3 days	2,400 mg(capsule/da y)	,	raining duri
Placebo(mal todextrin)	Placebo(Iso malt)	Without treatment	ms exist: St
2 kiwifruit without skin 2 times a day for 3 days (1 kiwi fruit: ±150g)	Actazine-L 600 mg capsule/day' mg capsules/day mg capsules/day capsules/day capsules/day	100 g kiwifruit per 30 kg of body weight	llowing sympto:
Green kiwifruit	Actazine (green kuwiruit) and Gold (gold old form form	Green kiwifruit	vo of the fo
14 (2 drop-outs)	9 (2) subjects for different groups – healthy subjects without symptoms of constipation)	38 elderly (4 subjects did not return data sets), 48 adults	ion: at least ty
16	29	42 elderly, 48 adults	constipat
	5	42 elderly, 48 adults	unctional e
Healthy adults with constipation (21 - 33 years), coring <2 based on the Gastrointestinal System Rating Scale <sup>31</sup>	Healthy adults with occasional constipation (38 – 54 years), following the ROME III definition <sup>a</sup>	Healthy elderly (>60 years), with preliminary data including healthy adults (18-50 years)	I definition of f
Wilkin-Smith et al.(2015) <sup>13</sup>	Ansell et al.(2015) <sup>14</sup>	Rush et al. (2002) <sup>18</sup>	<b>a ROME III</b>

obstruction/blockage more than 1/4 (25%) of defecations, manual maneuvers to facilitate more than 1/4 (25%) of defecations (e.g., digital evacuation, support of the pelvic (Bristol Stool Form Scale 1-2) more than <sup>1/4</sup> (25%) of defecations, the sensation of incomplete evacuation more than <sup>1/4</sup> (25%) of defecations, the sense of anorectal b Based on the Bristol Stool Scale. Type 1: a separate hard lump (like a nut); type 2: sausage-shaped and lumpy; type 3: sausage-shaped with cracks on the surface; type 4: shaped like a sausage or snake (smooth and soft); type 5: loose lumps of soft lumps (easily oozes); type 6: fine cut with rough edges; type 7: watery (entirely liquid) 34 floor), fewer than three SBM per week, loose stools are rarely present without the use of laxatives, insufficient criteria for irritable bowel syndrome 32,33.

d High-dose Actazin c Low-dose Actazin

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the low RoB, "Some Concerns" for some domains that need attention but are not in the form of a high RoB, and "High" for the high RoB. GRADE tool was used in systematic reviews to assess the quality of an evidence body. This tool graded the RoB, indirectness, inconsistency, the risk of publication bias, and imprecision. The conclusion of the GRADE was reflected in the certainty level, which started from very low to high certainty <sup>16</sup>. **Quantitative Analysis** 

The meta-analysis was conducted using the fixed-effect model generated from the Cochrane Collaboration's Review Manager software version 5.4.1, and the included studies were displayed through a forest plot. The results were presented as a weighted mean difference (WMD) or standardized mean difference (SMD) for continuous outcomes. For continuous data on the same scale, weighted mean difference (WMD) was used to present the overall meta-analysis result, and 95% confidence intervals (CI95%) were applied. Heterogeneity was also evaluated and presented as  $I^2 > 50\%$ .

# **RESULTS AND DISCUSSION**

## **Selection of Studies**

The literature search was conducted until May 2023 using the 2020 PRISMA flowchart guide, which was divided into three flow sections: identification, screening, and inclusion, as presented in Figure 1. Numerous studies were excluded for several reasons, including irrelevant reporting outcomes, participants who also had comorbid irritable bowel syndrome, used non-

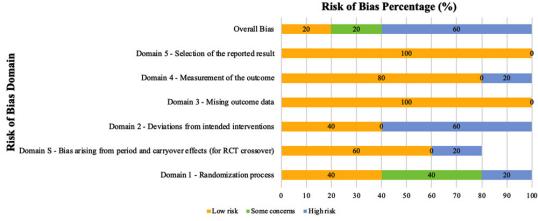


Fig. 2. Overall Results of Risk of Bias (RoB2)

Study	D1	DS	D2	D3	D4	D5	Overall Bias
Study AUdani et al. (2013)	+	N/A	+	+	+	+	+
Study BKindleysides et al. (2015)	1	+	+	+	+	+	1
Study CWilkin-Smith et al. (2019)	_	+	-	+	-	+	-
Study DAnsell et al. (2015)	+	+	-	+	+	+	-
Study ERush et al. (2002)	1	-	-	+	-	+	-

Description: + Low risk ! Some concerns - High risk

DS: Period and carry-over effects

D1: Randomization process

D2: Deviations from intended intervention

D3: Missing outcome ßdata

D4: Measurement of the outcome

D5: Selection of the reported result

N/A: Parallel group

ts	ct bsolute Certainty 5% CI)	MD 0.07 ⊕⊕OO Low higher (0.03 higher to 0.11 higher)	<ul> <li>Explanations:</li> <li>Explanations:</li> <li>a) Two studies were not blinded (Wilkinson-Smith et al., 2019; Rush et al., 2002); hence, concealment of the allocation sequence was not optimal, and the outcome was assessed without blinding; Kindleysides et al. And Rush et al. (2019) and Ansell et al., (2015) failed to implement the optimal sample size power.</li> <li>(2019) and Ansell et al., (2015) failed to implement the optimal sample size power.</li> <li>b) Inconsistency reflects the heterogeneity of results, with I<sup>2</sup> = 46%, meaning insignificant heterogeneity.</li> <li>d) When the study included few participants and had wide confidence intervals, it could lower the rating of the certainty of the evidence (WMD 0,07 (95% CI: 0,03 - 0,11).</li> <li>e) Regarding publication bias, specifically for the continuous outcome, the testing for funnel plot asymmetry is Egger's test (a linear regression of the intervention of the rivention effect estimates on their standard errors weighted by their inverse variance). Still, it cannot be applied for the continuous outcome.</li> <li>f) Plausible residual confounding that did not implement diet control (Wilkinson-Smith et al., 2019; Rush et al., 2002).</li> </ul>
Analysis Resul	Effect Relative Absolute (95% CI) (95% CI)	- Z 5-7	on-Smith et al., 2019; Rush et al., 2002); hence, concealment of the allocation sequence was not c Kindleysides et al. And Rush et al., 2002); hence, concealment of the randomization process; Wilkins mplement the optimal sample size power. • of results, with $I^2 = 46\%$ , meaning insignificant heterogeneity. that assessed five domains (population, intervention, comparator, direct comparison, and outcome) ints and had wide confidence intervals, it could lower the rating of the certainty of the evidence (W for the continuous outcome, the testing for funnel plot asymmetry is Egger's test (a linear regression of eighted by their inverse variance). Still, it cannot be applied for the continuous outcome. not implement diet control (Wilkinson-Smith et al., 2019; Rush et al., 2002).
(GRADE)	tients Placebo	377	the alloca he random direct con f the certa Egger's te t al., 2002
Evaluations (	No. of Patients Kiwifruit Placebo	385	cealment of details of th rogeneity. comparator, r the rating o r the rating o asymmetry is applied for th 2019; Rush e
elopment, and	L Other Considerations	All plausible residual confounding would reduce the demonstrated effect <sup>e,f</sup>	02); hence, con not explain the ver. significant hete n, intervention, ζ, it could lower for funnel plot a ll, it cannot be a Smith et al., 2
sessment, Dev	nent Imprecision C	Serious <sup>d</sup>	tush et al., 20 kush et al. did mple size pov %, meaning in ins (populatio ence intervals ne, the testing variance). Sti rol (Wilkinsoi
endations, Ass	Certainty Assessment cy Indirectness Im	Not serious <sup>e</sup>	et al., 2019; R les et al. And F les et al. And F the optimal sa the optimal sa sed five doma ad wide confid ad wide confid their inverse ment diet cont
Table 3. Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) Analysis Results	Certainty Assessment Inconsistency Indirectness Imprecision 0	Not serious <sup>b</sup>	Wilkinson-Smith uding: Kindleysid led to implement geneity of results ectness that asses articipants and ha articipants and ha fically for the cor rrors weighted by hat did not imple
able 3. Gra	Risk of Bias	Very serious <sup>a</sup>	blinded ( rithout blir (2015) fai the hetero bout indir ded few p bias, speci standard e founding t
Ĥ	Study besign	Defecation Frequency 15 Randomised trials	Explanations: a) Two studies were not blinded (Wilkinson-Smith et al., 2019; Rush et al., 2002); hence, concealment of the allocation sequence outcome was assessed without blinding; Kindleysides et al. And Rush et al. did not explain the details of the randomization proce (2019) and Ansell et al., (2015) failed to implement the optimal sample size power. b) Inconsistency reflects the heterogeneity of results, with $I^2 = 46\%$ , meaning insignificant heterogeneity. c) Based on judgments about indirectness that assessed five domains (population, intervention, comparator, direct comparison, and d) When the study included few participants and had wide confidence intervals, it could lower the rating of the certainty of the er CI: 0,03 - 0,11). e) Regarding publication bias, specifically for the continuous outcome, the testing for funnel plot asymmetry is Egger's test (a linear re effect estimates on their standard errors weighted by their inverse variance). Still, it cannot be applied for the continuous outcome. f) Plausible residual confounding that did not implement diet control (Wilkinson-Smith et al., 2019; Rush et al., 2002).
	No. of Studies	Defeca 15	Explan a) Two outcorr (2019) b) Inco c) Base d) Whe CI: 0,0.0 c) Rega effect e e) Rega

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	Tabl	le 4. Forest	Plot of I	Defecation	Table 4. Forest Plot of Defecation Frequency Outcome	Outcome			
Study or Subgroup	Mean	Kiwifruit SD	Total	Mean	Placebo SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI
Ansell et al. 2015 (Gold 2400) Ansell et al. 2015 (Green 2400) Ansell et al. 2015 (Green 2400) Kindleysides et al. 2015 (Green 600) Kindleysides et al. 2015 (Green 600) Rush et al. 2002 (Period 1 $1^{a}$ 3 Weeks for Adult) Rush et al. 2002 (Period 1 $2^{nd}$ 3 Weeks for Adult) Rush et al. 2002 (Period 1 $2^{nd}$ 3 Weeks for Adult) Rush et al. 2002 (Period 2 $1^{a}$ 3 Weeks for Adult) Rush et al. 2002 (Period 2 $1^{a}$ 3 Weeks for Adult) Rush et al. 2013 (Week 1) Udani et al. 2013 (Week 2) Udani et al. 2013 (Week 4) Wilkinson-Smith et al. 2019	0.99 0.88 0.92 4.5 1.3 1.4 1.24 1.24 1.26 1.26 0.33 0.61 0.47 0.47 0.42	$\begin{array}{c} 1.431\\ 1.418\\ 1.418\\ 1.418\\ 1.6971\\ 0.153\\ 0.204\\ 0.204\\ 0.204\\ 0.2748\\ 0.204\\ 0.21685\\ 0.3185\\ 0.356\\ 0.356\\ 0.056\end{array}$	14 3 3 3 3 2 6 6 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7 7	$\begin{array}{c} 0.96\\ 0.96\\ 0.96\\ 4.1\\ 1.26\\ 1.18\\ 1.17\\ 1.29\\ 1.29\\ 1.29\\ 1.29\\ 0.37\\ 0.37\\ 0.37\\ 0.37\\ 0.37\end{array}$	1.431 1.431 1.431 1.6971 0.141 0.188 0.328 0.141 0.328 0.141 0.316 0.4131 0.3869 0.3111 0.3869 0.3111 0.346	o o o % % % % % % % % % % % % % % % % %	$\begin{array}{c} 0.1\%\\ 0.1\%\\ 0.1\%\\ 0.1\%\\ 0.2\%\\ 12.1\%\\ 15.5\%\\ 1.5\%\\ 1.5\%\\ 6.7\%\\ 6.7\%\\ 0.8\%\\ 0.8\%\end{array}$	0.03 [-1.29, 1.35] -0.08 [-1.40, 1.24] -0.04 [-1.36, 1.28] 0.40 [-0.43, 1.23] 0.07 [-0.01, 0.15] 0.22 [0.11, 0.33] 0.01 [-0.09, 0.11] -0.03 [-0.13, 0.07] -0.19 [-0.47, 0.09] -0.01 [-0.13, 0.07] 0.01 [-0.13, 0.11] 0.26 [0.11, 0.41] 0.26 [0.11, 0.26] 0.32 [-0.10, 0.24]	
Total (95% CI) Heterogeneity: Chi <sup>2</sup> = 25.80, df = 14 (P = 0.03); $I^2$ = 46% Test for overall effect: Z = 3.37 (P = 0.0008)	= 46%		385			377	100%	0.07 [0.03, 0.11]	

placebo comparators, had unfinished clinical trials, and originated in the same trial. Databases yielded information on 160 studies in total. After critically appraising the individual studies, five studies were selected for systematic review and meta-analyses by considering feasibility study, inclusion, and exclusion criteria.

## **Characteristic of Studies**

The characteristics of each selected study are displayed in Table 1. From 2002 to 2018, the research included four cross-over RCT studies and one parallel RCT study. This study involved 175 subjects: 93 from a cross-over study and 82 from a parallel study design. There were more female subjects than males in the overall RCT studies. All participants in each study were healthy individuals with symptoms of constipation and aged between e"18 years old. Constipation was characterized as having less than three bowel movements each week, straining at least 25% of the defecation process, and experiencing a minimum of 25% of the bowel movement incompletely. Kiwifruit interventions varied in powder, extract, and whole fruit forms. The duration of the intervention ranged from three days to four weeks. Of the five studies, four utilized green kiwifruit, and one employed green and gold species 12-14,17.

# **Qualitative Analysis**

We used the RoB2 application to analyze the studies' quality. Our results indicate that lowrisk bias was present in one study, and high-risk bias was present in three studies, as in Table 2 and Figure 2. Among all studies, the highest RoB occurred in deviations from the intended intervention (D2). Finally, low certainty results were obtained after assessing the RoB by the GRADE system, as seen in Table 3.

## **Quantitative Analysis**

Five studies were analyzed quantitatively regarding defecation frequency as the primary outcome of this study. According to Ansell *et al.*, kiwifruit intervention consisted of low-dose green, high-dose green, and gold kiwifruit. Therefore, the outcome values were entered separately in the forest plot. Udani *et al.* displayed outcome scores separately for both the intervention and comparator groups from week 1 to week 4 in the forest plot following the original study <sup>12</sup>. Meanwhile, Rush *et al.* displayed two data sets: the preliminary data, including healthy adults, and the main data,

including healthy elderly <sup>18</sup>. According to the forest plots, the kiwifruit intervention significantly increased defecation frequency (p = 0.0008), with a WMD of 0.07 (95% CI 0.03–0.11), as seen in Table 4.

The inability to convert studies into forest plots is due to the small amount of research that expresses secondary outcomes by means, standard deviation (SD), or mean standard error (SE) and the fact that not all studies evaluate secondary outcomes. Although some minor side effects, such as flatulence, bloating, and nausea, were reported in several studies, no serious side effects were found after consuming kiwifruit. The two RCTs conducted by Wilkinson-Smith *et al.* and Ansell *et al.* demonstrated non-significant adverse effects between groups <sup>13,14</sup>.

The quantitative analysis of five studies showed that kiwifruit significantly increased the frequency of defecation. Our results are similar to the previous study, which included subjects with irritable bowel syndrome (IBS), where kiwifruit was effective in increasing defecation frequency. However, the prior meta-analysis's studies had a very high level of heterogeneity ( $I^{2}>50\%$ )<sup>19</sup>, while this analysis included more homogenous studies ( $I^{2}=46\%$ ). This indicated that kiwifruit could be recommended in constipation patients without comorbidities to support the role of fibers and actinidin in promoting defecation <sup>7,20</sup>. Heterogeneity is also an essential component of meta-analysis to draw overall conclusions <sup>21</sup>.

In this study, we also consider the term clinically significant, which can be used in which clinically relevant outcomes are used to assess the effectiveness of a treatment modality <sup>22</sup>. Despite statistically significant findings, the therapeutic advantages of kiwifruit are negligible. WMD was found to increase defecation frequency by 0.07, which is not considerably different from the placebo group. The clinical impact of kiwifruit on functional constipation has to be confirmed by more clinical studies.

Regarding quality, these results must be applied carefully; although promising heterogeneity levels exist, some studies had a high RoB. A study with the largest overall number of participants (n = 86) by Rush *et al.* had 68.9% of the overall weight of the defection frequency outcome, which significantly affected this meta-analysis since it

comprised more than half of the overall weighted effect, categorized as high RoB. Meanwhile, the second largest study, with 29.8% of the overall weighted effect, was ranked as low RoB, followed by high bias with 0.8% and 0.3% overall weighted effects from the third and fourth largest studies. Half of the studies had insufficient D2 components of RoB due to a failure in implementing the intervention on several participants to have sufficient power. Studies with D2 insufficiency had several participants drop out, lowering their power and influencing the study's validity <sup>23</sup>. Regarding the D1 component of RoB, the insufficiency was found in three studies, where no detailed explanation about the sequence allocation was shown, including the blinding process of allocation, specifically for the parallel RCT design study. The recipients of the intervention were known to both the participants and the researchers, which can interfere with the results. Two of the studies did not meet the criteria for the D4 component of RoB, and blinding of intervention was not performed. This study also used diary filling as a patientreported outcome. The absence of patients' blinding increased impact estimates by an average SD of 0.56 (0.71 to 0.41) when outcomes were patientreported, as indicated in the systematic review <sup>24</sup>, which can cause a potential bias. Regarding the DS component, one cross-over study did not implement a wash-out period that could lead to carry-over effects.

We carried out a GRADE analysis to evaluate the feasibility of this study <sup>25</sup>. Our result from the GRADE analysis emphasized the importance of further studies on kiwifruit's efficacy in overcoming constipation symptoms. Serious imprecision and the possibility of plausible residual confounding detected in two studies, where diet control still needs to be implemented, could be undiagnosed confounders, thus affecting the measured outcomes <sup>26</sup>.

The limitations of this meta-analysis included the variation between studies' dosages and formulations. Regarding the dosage, one study showed that consuming two kiwifruits every day can increase the laxative effect. It is also possible that the Wilkin-Smith et al. study showed significant results in increasing defecation after participants consumed two kiwifruits with an average weight of 150 g for one kiwi. Meanwhile, other studies used smaller doses of kiwifruit <sup>27</sup>. Although subgroup analysis was not performed due to the need for a larger number of studies and data, the meta-analysis of defecation frequency showed considerably low heterogeneity between studies. Secondly, the inability to perform sensitivity analysis is due to the limited number of studies included. To overcome the RoB, performing sensitivity analysis is highly recommended. The third weakness of this study is the varied definitions of constipation in the included studies that can cause differences among the subjects. ROME III was used in two studies, while the rest did not apply the standardized definition of functional constipation. Studies showed that varied definitions might lead to various prevalence 28, which could interfere with the study results. The fourth limitation is the limited access to EMBASE, which should have enhanced the comprehensiveness of the search. However, since we used the CENTRAL database, which supports EMBASE<sup>29</sup>, we anticipated that all articles would be noticed. Meanwhile, this limitation was compensated by using other databases <sup>30</sup>.

## CONCLUSION

Based on statistical research, daily ingestion of kiwifruit is regarded safe and may have a considerable impact on increasing the frequency of bowel movements. However, there is no clinical evidence to support this claim. Additional research is required to ascertain the clinical and statistical impact of kiwifruit on functional constipation.

## **Authors contribution**

Fonny Cokro: Conceptualization, Methodology, Formal Analysis, Investigation, Resources, Writing – Review and Editing; Ervina Vashti: Methodology, Investigation, Validation, Formal Analysis, Writing – Original Draft; Agustina Dwi Retno Nurcahyanti: Methodology, Formal Analysis, Investigation, Writing – Review, and Editing; Anton Sumarpo: Methodology, Formal Analysis, Investigation, Writing – Review, and Editing; Rungnapa Malasao: Methodology, Formal Analysis, Investigation, Writing – Review, and Editing; Rungnapa Malasao: Methodology, Formal Analysis, Investigation, Writing – Review, and Editing

#### **Conflict of Interest**

The authors declare there are no competing interests.

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