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Systematic Review

Effect of Prebiotics and Synbiotics Carried by Food over Irritable Bowel Syndrome Symptoms: A Systematic Review

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Abstract: Irritable bowel syndrome (IBS) is a chronic condition that affects 11.2% of the world's population. The management of gut microbiota using probiotic and synbiotic agents might be a valid alternative to assist in the treatment of IBS. The focus of this study was to evaluate the effects of prebiotic and synbiotic compounds carried by different foods on major symptoms of IBS through a systematic literature review. MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and LILACS were accessed during July 2021. The studies included in this review were the ones that tested volunteers older than 16 years of age and were conducted using a randomized, controlled clinical trial. The risk of bias was assessed by using the Cochrane risk-of-bias tool for randomized trials (RoB2). Furthermore, the data found were qualitatively evaluated due to the studies' differences. Two papers were able to fit the criteria, with a total sample size of 280 participants. No datum was found regarding the use of prebiotics in the treatment of IBS. Synbiotic agents, however, had a positive effect on gastrointestinal symptoms and the participants' overall bowel satisfaction; however, it was not possible to reach a consensus on which effects. Further studies regarding the use of synbiotics and prebiotics must be carried out to determine which effects are the most significant in the treatment of IBS.

Keywords: irritable bowel syndrome; mucous colitis; *Lactobacillus*; *Bifidobacterium*; dairy products; yogurt

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1. Introduction

Irritable bowel syndrome (IBS) is a chronic condition that affects 11.2% of the world's population [1]. It is characterized, according to The Rome Foundation, by recurrent abdominal pain for the past three months, associated with at least one of the following symptoms: changes in defecation, changes in stool frequency, or changes in stool's form/appearance [2]. IBS may also be classified into four subtypes, according to the major symptoms linked to the condition. IBS-C (IBS with predominant constipation) occurs when more than 25% of bowel movements are classified as type 1 or 2 and less than 25% with type 6 or 7, according to the Bristol Stool Scale. IBS-D (IBS with predominant diarrhea) occurs when more than 25% of bowel movements are classified either as type 6 or 7 and less than 25% with type 1 or 2, according to the Bristol Stool Scale. Cases in which patients have more than 25% of bowel movements as either type 1 or 2 and more than 25% as type 6, or 7, according to the Bristol Stool Scale, are classified as IBS-M (IBS with mixed bowel habits). Lastly, IBS-U, or

unsubtyped, is used to describe cases in which the patients' symptoms do not fit in any of the other three categories [2]. IBS's pathogenicity has not been completely uncovered yet; however, in recent years, many etiological hypotheses have been formulated, such as changes related to the gut-brain axis increasing intestinal hypersensitivity, low-grade intestinal inflammation, modification of the intestinal microflora, diet, and disturbances in serotonin metabolism [3–5]. With this in mind, many pharmacological therapies have been developed over the years, including the modulation of the intestinal microbiome using antibiotics, probiotics, prebiotics, and synbiotics, which has shown the potential to reduce some of IBS's symptoms [6].

Probiotics can be described as live microorganisms that, when administered in adequate amounts, offer health benefits to their host [7], with *Lactobacillus* and *Bifidobacterium* currently being the most well-studied genera. Prebiotics, meanwhile, are defined as a substrate to be selectively used by microorganisms already present in the host's gut, which will then provide certain health benefits. Among prebiotic compounds, fructans (fructoligosaccharides and inulin) and galactans (galactoligosaccharides) are the most studied types [8]. When both probiotic agents and prebiotic compounds are used in tandem, the resulting product is classified as a synbiotic [9].

Despite evidence supporting the idea that the microbiome found in the gut plays an important role in the physiology of IBS and clinical trials have successfully demonstrated the efficacy of prebiotics and synbiotics as therapeutic agents in the treatment of some IBS symptoms, however, it remains a challenge to know for certain how effective these products when it comes to the treatment of IBS [10]. This is mostly due to the use of different methodologies in each study, not to mention factors such as sex, ethnicity, age, the participants' regular diet, and even the environment in which they are inserted [11]. The challenge is even greater when using food as carriers, for each agent must be tested for each matrix since it is not possible to assume that they will behave equally in all foods [12]. However, despite the challenges, the use of food as carriers has several advantages, since their chemical composition, water activity, oxygen concentration, pH, and the synergic potential between food and added probiotics can be manipulated in order to improve their performance as carriers of probiotic or prebiotic agents [13]. The use of food as a matrix also allows for the development of products that are already accepted by a given population, facilitating its daily administration and the maintenance of the minimum daily intake of the target probiotic [14]. In 2016, FAO published a guideline for probiotics in food, in which experts agreed that while there is adequate scientific evidence to the claim that the consumption of probiotics can offer health benefits to the one who consumes these products, there is still a need for systematic research in this field [15]. Considering this, even though there are already some systematic reviews focusing on the effectiveness of prebiotics and synbiotics in the treatment of IBS [10,16,17], no reviews studying the effect of food products as carriers were found. Therefore, the objective of the present study is to contribute to the scientific advance in this field of research by answering if the use of prebiotic and synbiotic foods is able to assist in reducing the major symptoms of IBS in adult patients. As such, contributing to the advancement of this field of research.

2. Materials and Methods

This systematic review was performed according to Cochrane Handbook for Systematic Reviews of Interventions (v. 6.2) and followed the writing guidelines of Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) (v. 2020). To avoid selection bias, inclusion and exclusion criteria were defined before the literature search. To be eligible, studies had to fit the inclusion criterion, that were: (a) randomized and controlled clinical trials using food carried prebiotics or synbiotics in the treatment of major symptoms of IBS; (b) patients were diagnosed with IBS via Rome Criteria (I, II, III, or IV); (c) all participants must be over 16 years of age. Studies were also considered eligible if they stated the blinding method used for the tests, with a double-blind approach being preferred.

Studies that: (a) included patients below 16 years of age; (b) had other interventions associated with the treatment of IBS symptoms; (c) used prebiotics or synbiotics carried in non-food-based matrixes (such as powders, pills, gels, or tablets); (d) were not randomized or did not possess a control group; (e) did not present data on gastrointestinal symptoms after the intervention; were not considered eligible.

Studies that were partially eligible or that presented incomplete or unclear data had their authors contacted via e-mail for further inquiry. Duplicate studies were excluded from the review.

The literature search was initially performed on 27 July 2021, and updated on 7 January 2022, using four different databases [18]: PubMed/MEDLINE (via NCBI), EMBASE (via Elsevier), The Cochrane Central Register of Controlled Trials (CENTRAL) (via Cochrane Library) e LILACS (via Bireme).

The search strategy was constructed alongside the librarian at the Federal University of Santa Catarina (Florianopolis—SC, Brazil), considering the main question of this review: "Is there an effect in the use of food carried prebiotics and synbiotics on the improvement of gastrointestinal symptoms in adult patients with irritable bowel syndrome?" as well as the PICOT criteria, as shown in Table 1. The chosen search strategy was: ("Prebiotics" OR "Prebiotic" OR "Synbiotics" OR "Synbiotic" OR "Synbiotics" OR "Synbiotic") AND ("Irritable Bowel Syndrome" OR "Irritable Bowel Syndromes" OR "IBS" OR "Irritable Colon" OR "Mucous Colitides" OR "Mucous Colitis"). Title, abstract, and keyword filters were set in place, and the studies' language was set to English, Portuguese, and Spanish, for each database. No restrictions for publishing date were made, and all studies that matched the search strategy, independent of the year of publication were considered. The complete search strategy used in each of the databases is described in Appendix A.

Table 1. PICOT* criteria used to determine the search's question and strategy.

PICOT	Inclusion and Exclusion Criteria
Patient	Patients suffering from any type of irritable bowel syndrome, diagnosed by a physician according to Rome Criteria I, II, III, or IV. No restrictions for age, sex, ethnic group, or geographic location.
Intervention	Prebiotic or synbiotic foods for patients suffering from irritable bowel syndrome.
Control	Non-intervention or placebo.
Outcome	Evaluation of the intervention's effects over the patient's irritable bowel syndrome symptoms.
Type of study	Controlled randomized clinical trial.

* PICOT: Acronym where each letter feres to: "P"—population/patients; "I"—intervention; "C"—comparison/control; "O"—outcome; "T"—type of study or design.

All studies found through the search strategy were exported into Mendeley (Mendeley Desktop® v. 1.19.8), with any doubles being automatically removed. The studies' selection occurred in two independent phases: Phase (1) Two reviewers read the studies' titles and abstracts independently, selecting those that fit the previously described PICOT criteria; Phase (2) The studies selected in Phase 1 were read in full and independently by each reviewer and then judged considering the previously inclusion and exclusion criteria. In case of disagreement between the reviewers, the topic was discussed until a consensus was reached, and, when necessary, a third reviewer with experience in the field of probiotic, prebiotic, and symbiotic foods had the final decision. The reference lists for the studies that were included in Phase 2 were manually analyzed, and studies that fit the established criteria were included after being reviewed twice, according to the guidelines established by the Practical Guide of Systematic Review and Metanalysis [19].

In order to extract data from the selected studies, the first reviewer exported the major data points into a spreadsheet, while the second reviewer oversaw the process, checked the exported data, and ensured they were correctly distributed. In case of diverging opinions between the reviewers, the studies were checked once more until a consensus was reached; when necessary, a third reviewer was introduced and had the final decision. The primary outcome of interest was the assessment of gastrointestinal symptoms after the intervention

(abdominal symptoms and bowel habits), while the secondary outcome of interest focused on whether there were any adverse effects after the intervention.

The following clinical data were extracted from each study: authors, year and place where the study was conducted, patient's age and sex, IBS subtype (when applicable), prebiotics or synbiotics used (including dose and species when applicable), food matrix used as a carrier, intervention duration, number of patients in the control group and in the intervention group, diagnostic criteria used (Rome I, II, III or IV), and the tool used to define improvement or cure of gastrointestinal symptoms. During the extraction stage, studies containing incomplete data had their authors contacted, and in case no response was obtained, the articles were excluded.

Risk-of-bias assessment was performed by using the Cochrane risk-of-bias tool for randomized trials (RoB2). This tool allows one to check the risk of bias in five levels: bias arising from the randomization process; bias due to deviations from intended interventions; bias due to missing outcome data; bias in the measurement of the outcome; and bias in the selection of the reported result. The first reviewer was responsible for completing the table provided by RoB2 in which each question must be answered with yes (Y), possibly yes (PY), possibly no (PN), no (N), or no information (NI), meanwhile the second reviewer checked if the table was correctly filled out. In case of disagreement, it was discussed until consensus was reached. The answers were then evaluated according to the algorithm provided by the tool to classify the result as: low risk of bias; some concerns; or high risk of bias.

For qualitative analysis, the studies had their data grouped according to the analyzed IBS subtype (IBS-C, IBS-D, IBS-M, and IBS-U) and according to the type of evaluated gastrointestinal symptoms (abdominal symptoms or bowel habits). To evaluate the measured effects, the *p*-value was used, with a value < 0.05 being statistically significant. Variations in the intervention and control groups before and after the intervention were also collected. The overall quality of evidence was evaluated using the Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach based on methodological limitations, data adequacy, coherence, and relevance [20], and is presented in Appendix B.

3. Results

3.1. Study Selection

The study selection process is shown in Figure 1. Based on the search strategy, 660 articles were found, out of which 279 were duplicates and excluded, leaving a total of 390 studies to be evaluated according to the eligibility criteria. After a preliminary evaluation of titles and abstracts, 53 articles remained to be read in full. Out of these 53 articles, 9 did not analyze the outcome or intervention of interest, 23 used supplements as carriers, 10 were not available in full, 2 were in languages other than English, Portuguese, or Spanish, 3 were review articles, 3 were duplicates, 2 had incomplete data, and 1 was an uncontrolled clinical trial. The authors of the studies containing incomplete data were contacted via e-mail, and those that did not reply were excluded. Only one study met all eligibility criteria. After reading the reference list of articles included, one more study that met the eligibility criteria and was relevant to the scope of the review was included. Thus, in the end, two studies, dated 2012 and 2019, were selected for data extraction.

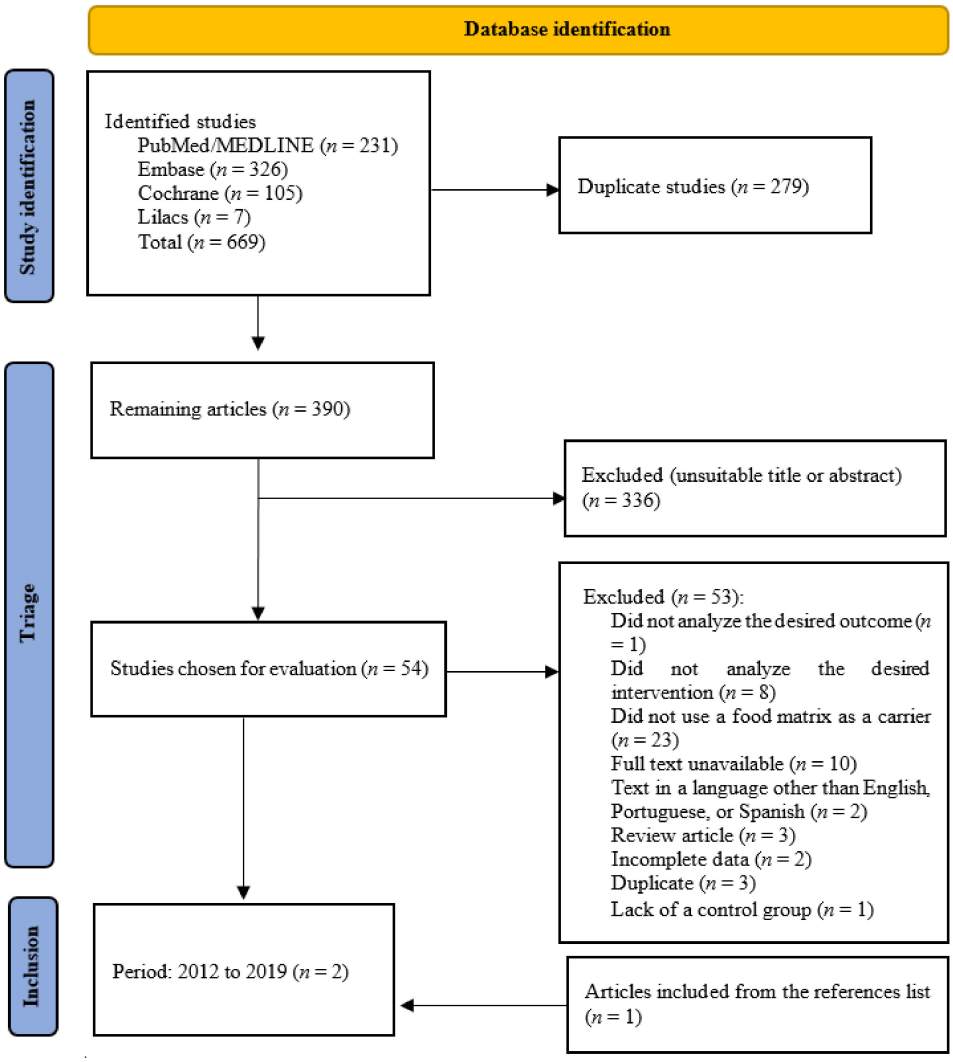

Figure 1. Flowchart of studies' selection.

3.2. Characteristics of the Studies

The details of the eligible studies are shown in Table 2. Both studies diagnosed their volunteers according to Rome Criteria III. In the first study, by Min et al. [21], all IBS subtypes were included, with 35.0% of the patients being diagnosed with IBS-C; 29.9% diagnosed with IBS-D; 8.5% with IBS-M; and 26.5% with IBS-U. Meanwhile, in the second study, by Bahrudin et al. [22], only patients diagnosed with IBS-C were included.

The study by Min et al. [21] was conducted in South Korea, while Bahrudin et al. [22] conducted theirs in Malaysia. Both studies were also classified as double-blind, randomized clinical trials (RCT). The assays used male and female patients older than 18 years of age.

Both studies also evaluated the use of synbiotic food products to treat major IBS symptoms, and in total, 280 volunteers among both eligible studies were included in this systematic review. In the study by Bahrudin et al. [19], the intervention period lasted 1 week, while Min et al. [21] established an intervention period of 8 weeks. The administration vehicles were yogurt [21] and a milk-based drink (ingredients: water, sugar, skimmed bovine powdered milk, stabilizers (polydextrose), fermented milk (water, acidity regulator, skimmed bovine powdered milk, and *Lactobacillus*), acidity regulator, soybean fiber, and flavoring) [22], in daily doses of 300 and 350 mL, for Min et al. [21] and Bahrudin et al. [22], respectively. Furthermore, Min et al. [21] administered synbiotics consisting of the combination of *Bifidobacterium animalis* subsp. *lactis* ($\geq 10^{11}$ CFU/serving) with acacia fiber, *Bifidobacterium* enhancer solution, and yogurt starter cultures: *Streptococcus thermophilus*

($\geq 3 \times 10^9$ CFU/serving) and *Lactobacillus acidophilus* ($\geq 10^9$ CFU/serving). On the other hand, Bahrudin et al. [22] opted to use a combination of *Lactobacillus helveticus* and polydextrose (1.5 g/100 mL). In both studies, the control group received the same product but without the prebiotic component (acacia or polydextrose) added to the formulation.

Table 2. Characteristics of the studies included in this review.

Study (Year)	Country	Methodology	Diagnosis Criteria	Age Range/Sex	IBS Subtype	Intervention—Daily Dose	Control Group—Daily Dose	Intervention Period (Weeks)	Symptom Evaluation Criteria	Outcomes
Min et al. [21]	South Korea	RCT	Rome III	18–70, males and females	35% IBS-C; 29.9% IBS-D; 8.5% IBS-M; 26.5% IBS-U	300 mL of yogurt. *Bifidobacterium animalis* (≥ufc/serving) + *Bifidobacterium* booster + acacia fiber + starter culture (n = 58)	300 mL of yogurt. *Bifidobacterium animalis* (≥ufc/serving) starter culture (n = 59)	8	VAS; Frequency measurement, and BSS	Abdominal symptoms and bowel habits.
Bahrudin et al. [22]	Malaysia	RCT	Rome III	>18, males and females	IBS -C	350 mL of milk-based drink. *Lactobacillus helveticus* + Polydextrose (1.5 g/100 mL) (n = 79)	350 mL of milk-based drink. *Lactobacillus helveticus* (n = 84)	1	Garrigues Constipation Questionaries	Stool hardness; Strain; Incomplete evacuation; Bowel blockage; Need to press onto perineum; Defecation time > 10 min; Improvement on constipation.

Notes: RCT: randomized clinical trial; IBS-C: irritable bowel syndrome with constipation; IBS-D: irritable bowel syndrome with diarrhea; IBS-M: irritable bowel syndrome with mixed symptoms; IBS-U: irritable bowel syndrome with unclassified symptoms; VAS: visual analog scale; BSS: Bristol Stool Scale.

3.3. Risk of Bias

Focusing on the outcomes of interest, Bahrudin et al. [22] evaluated constipation-related symptoms (improvement in constipation, strain during evacuation, incomplete evacuation, stool hardness, sensation of bowel blockage, need to press onto the perineum during defecation and defecation taking up more than 10 min). Min et al. [21] evaluated abdominal symptoms (abdominal pain, frequency of abdominal pain, bloating and flatulence), bowel habits (frequency of defecation, defecation duration, sense of urgency, strain, feeling of incomplete evacuation, stool consistency, satisfaction with bowel habits), and improvement in overall gastrointestinal symptoms.

In the clinical trial performed by Bahrudin et al. [22], the answers given by the participants were evaluated using Garrigues' Constipation Questionnaire [23]. Min et al. [21] opted to use the Visual Analogic Scale (VAS) to evaluate abdominal pain/discomfort, bloating, and satisfaction with bowel habits; a frequency measurement to evaluate abdominal pain/discomfort, flatulence, and defecation; and Bristol Stool Scale to evaluate stool consistency.

Risk-of-bias analysis was carried out using the tool provided by Cochrane (RoB2), with the results shown in Table 3. Both studies were classified as having "some concerns". The study by Min et al. [21] was characterized as containing some bias concerns in the randomization process due to the author's failure to report the method used to allocate each treatment. The study by Bahrudin et al. [22] was classified as having "some concerns" in two categories: bias arising from the randomization process, also for not reporting the methodology used to allocate each treatment, and bias in the selection of the reported result, as the authors did not specify the intention of analysis for their symptoms of interest, and due to the possibility that the final numerical result was selected due to multiple eligible data analyses.

Table 3. Risk-of-bias assessment.

Study (Year)	Bias Arising from the Randomization Process	Bias Due to Deviations from Intended Intervention	Bias Due to Missing Outcome Data	Bias in Measurement of the Outcome	Bias in Selection of the Reported Result	Global Risk
Bahrudin et al. [22]	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns
Min et al. [21]	Some concerns	Low risk	Low risk	Low risk	Low risk	Some concerns

3.4. Individual Analysis of the Studies

3.4.1. Gastrointestinal Symptoms in IBS-C Patients

For *p*-value analysis, Bahrudin et al. [22] were contacted via e-mail due to the lack of information in the published study itself. BothBahrudin et al. [22] and Min et al. [21] reported the outcomes for strain during evacuation and incomplete evacuation in patients with IBS-C. There was a significant improvement between the test and control groups for both outcomes in the study by Bahrudin et al. [22], while in the study by Min et al. [21], no significant improvement was observed for these outcomes after the intervention period.

Min et al. [21] also evaluated the outcomes of satisfaction with bowel habits, defecation frequency (times per week), stool consistency, urgency, and defecation duration (min) in patients with IBS-C. There was no significant improvement for any of these outcomes between the test and control groups. Similarly, Bahrudin et al. [22] evaluated the stool hardness, sensation of bowel blockage, need to press onto the perineum, spending more than 10 min for complete evacuation, and improvements to constipation. They reported significant improvements between the test and control groups for the latter two outcomes. However, no significant improvements were observed between the test and control groups for the other evaluated symptoms. Data regarding bowel habits in patients with IBS-C can be seen in Table 4.

Table 4. Comparison of intestinal habits among patients suffering from IBS-C.

Study (Year)	Evluated Symptom	Test Group [c]—Start	Test Group [c]—End	Control Group [b]—Start	Control Group [b]—End	*p*-Value between Groups
Min et al. [21]	Strain	94.70%	57.9% ($p = 0.016$)	81.8%	54.5% ($p = 0.146$)	0.321
	Incomplete evacuation	78.90%	36.80% ($p = 0.021$)	72.70%	40.90% ($p = 0.016$)	0.776
	Satisfaction with bowel habits	-	26.32 ($p = 0$)	-	17.05 ($p = 0.004$)	0.21
	Defecation frequency (times per week)	-	1.79 ($p = 0.002$)	-	1.96 ($p = 0.032$)	0.872
	Stool consistency	-	0.789 ($p = 0.789$)	-	1.09 ($p = 0.001$)	0.386
	Urgency	21.1%	21.1% ($p = 1$)	13.6%	27.3% ($p = 0.375$)	0.336
	Defecation duration	-	−2.61 ($p = 0.106$)	-	−4.25 ($p < 0.001$)	0.358

Table 4. *Cont.*

Study (Year)	Evluated Symptom	Test Group [c]—Start	Test Group [c]—End	Control Group [b]—Start	Control Group [b]—End	*p*-Value between Groups
Bahrudin et al. [22]	Strain	91%	56%	77%	48%	0.04
	Incomplete evacuation	84%	56%	93%	47%	0.04
	Stool hardness	97%	66%	90%	64%	0.05
	Sensation of blockage	74%	47%	83%	39%	0.67
	Need to press onto the perineum	57%	37%	75%	23%	0.67
	Defecation lasting more than 10 min	85%	69%	52%	43%	0.04
	Constipation relief	100%	81%	100%	84%	0.03

c. Bahrudin et al. [22] number of patients = 79; Min et al. [21] number of patients = 19.; b. Bahrudin et al. [22] number of patients in the control group = 84; Min et al. [21] number of patients in the control group = 22.

Only Min et al. [21] evaluated abdominal symptoms in patients with IBS-C. With significant improvement in overall IBS symptoms being reported for patients belonging to the test group. However, there was no statistically significant improvement between groups for abdominal pain/discomfort, frequency of abdominal pain/discomfort, bloating, and flatulence. The complete data can be seen in Table 5.

Table 5. Abdominal symptoms outcomes for patients suffering from IBS-C.

Study (Year)	Evaluated Symptom	Variance (1) Test Group	Variance (1) Control Group	*p*-Value
Min et al. [21]	Abdominal pain/discomfort	−19.74 ($p = 0.001$)	−21.59 ($p = 0.001$)	0.8
	Frequency of abdominal pain/discomfort	−0.61 ($p = 0.032$)	−0.6 ($p = 0.029$)	0.979
	Bloating	−19.74 ($p = 0.007$)	−12.5 ($p = 0.031$)	0.393
	Flatulence (per week)	0.08 ($p = 0.952$)	0.5 ($p = 0.577$)	0.785
	Overall reduction in IBS-C symptoms	72 ± 18.4	50.0 ± 21.8	<0.001

(1) Variance between the intervention's start and end.

3.4.2. Gastrointestinal Symptoms in Patients Suffering from IBS-D

The bowel habits of patients with IBS-D were only reported in the study by Min et al. [21]. A significant improvement in satisfaction with intestinal habits was observed in the test group after the intervention period. However, no significant improvements were reported for sensation of incomplete evacuation, stool consistency, defecation frequency, duration of defecation, urgency, and strain. The complete data can be seen in Table 6.

Table 6. Bowel habits outcomes for patients suffering from IBS-D.

Study (Year)	Evaluated Symptom	Variance (1) Test Group	Variance (1) Control Group	*p*-Value
Min et al. [21]	Defecation frequency	−1.76 ($p = 0.381$)	0 ($p = 1$)	0.451
	Defecation duration (min)	−0.08 ($p = 0.938$)	−0.97 ($p = 0.3$)	0.52
	Urgency	−2 ($p = 0.625$)	−1 ($p = 1$)	0.867
	Strain	−5 ($p = 0.063$)	−5 ($p = 0.063$)	0.707
	Feeling of incomplete evacuation	−7 ($p = 0.039$)	−7 ($p = 0.016$)	0.826
	Stool consistency	−1.26 ($p = 0.001$)	−0.63 ($p = 0.036$)	0.738
	Satisfaction with bowel habits	32.9 ($p = 0$)	7.81 ($p = 0.173$)	0.006

(1) Variance between the intervention's start and end.

The study by Min et al. [21] was also the only one to report outcomes for abdominal symptoms in patients with IBS-D. There was no improvement after the intervention for abdominal discomfort/pain, frequency of abdominal discomfort/pain, bloating, flatulence, and for the overall symptoms of IBS. The complete data can be seen in Table 7.

Table 7. Abdominal symptom outcomes for patients suffering from IBS-D.

Study (Year)	Evaluated Symptom	Variance (1) Test Group	Variance (1) Control Group	*p*-Value
Min et al. [21]	Abdominal pain/discomfort	−26.68 ($p = 0$)	−9.38 ($p = 0.083$)	0.05
	Frequency of abdominal pain/discomfort	−1.82 ($p = 0.036$)	−0.34 ($p = 0.245$)	0.117
	Bloating	−18.42 ($p = 0.012$)	−6.25 ($p = 0.164$)	0.146
	Flatulence (per week)	−0.55 ($p = 0.503$)	0.84 ($p = 0.255$)	0.212
	Overall reduction in IBS-C symptoms	61.8 ± 17.4	51.6 ± 14.3	0.07

(1) Variance between the intervention's start and end.

3.4.3. Gastrointestinal Symptoms for Patients Suffering from IBS-M

Data regarding patients suffering from IBS-M were, once more, reported only by Min et al. [21] and, according to the authors, there was no significant improvement for any of the outcomes related to abdominal symptoms, bowel habits, or global symptoms of IBS.

3.4.4. Gastrointestinal Symptoms in All Patients

According to Min et al. [21], the test group displayed a statistically significant improvement when compared to the control group when it comes to satisfaction with bowel habits. However, there were no significant improvements in frequency and duration of defecation, urgency, strain, feeling of incomplete evacuation, and stool consistency during or after the intervention period. Furthermore, while there was a statistically significant improvement in overall IBS symptoms, no statistically significant improvement between groups for abdominal pain/discomfort, frequency of abdominal pain/discomfort, bloating, and flatulence was found.

3.4.5. Adverse Effects

Bahrudin et al. [22] reported that 27.8% of patients in the test group and 21.4% of patients in the control group described a reduction in the consistency of their stools as an adverse effect. In the same study, one patient in the test group (1.3%) and two in the control group (2.8%) reported moderate abdominal discomfort. However, Min et al. [21] reported no adverse effects of the intervention.

4. Discussion

Although the use of prebiotics and synbiotics to treat irritable bowel syndrome has become the target for many different studies, the literature still has a small number of systematic reviews on the subject [10,16,17] and, so far, no study has been developed with the primary focus of evaluating the effect of prebiotic and synbiotic foods on IBS.

Through the adopted search strategy, there were no studies that used only food carried prebiotics; thus, it was not possible to assess the effect of these agents on the gastrointestinal symptoms of patients suffering from IBS. This result agrees with currently available systematic reviews that have found a small number of trials using prebiotics in the treatment of IBS, all of them carried by supplements [10,16,17]. The present review further highlights the need to develop well-conducted clinical trials using foods as carrier agents for prebiotics, as well as the need to evaluate their effects on IBS.

As for the effect of synbiotic foods, a significant improvement in overall IBS symptoms and satisfaction with bowel habits was observed in patients who received yogurt containing *Bifidobacterium animalis* associated with acacia fiber and starter cultures of *Streptococcus thermophilus* and *Lactobacillus acidophilus* [20]. A significant improvement in constipation, strain, feeling of incomplete evacuation, and evacuations lasting longer than 10 min was also observed in patients with IBS who consumed a drink containing *Lactobacillus helveticus* and polydextrose [21]. However, when the IBS subtypes were individually evaluated, individuals receiving the same intervention had different results regarding the analyzed symptoms.

In the study by Min et al. [21], individuals with IBS-C displayed a significant improvement for overall IBS symptoms, while patients with IBS-D had significant improvement only for satisfaction with bowel habits. Furthermore, patients with IBS-M had no significant improvements for any of the evaluated outcomes. These results agree with metagenomic studies that demonstrate that there are differences in the composition of gut microbiota between different IBS subtypes [24]. These differences suggest the necessity to develop specific gut modulation strategies for each of the IBS subtypes.

The *Bifidobacterium* genus has been the target of studies in patients suffering from IBS, and the systematic reviews developed so far have found out that patients who received interventions with this particular genus had significant improvements in the overall symptoms of the syndrome [10,16], similarly to what has been found during the present review. Acacia fiber is a soluble fiber derived from acacia gum, with only one study showing it to have a bifidogenic effect, that is, assisting in the growth of bacteria of the *Bifidobacterium* genus [25]. However, so far, there is not enough evidence on the effects of acacia fiber as a prebiotic substance.

A study by Asha and Khalil [16] also found that products containing *Lactobacillus* helped in the reduction in symptoms such as abdominal pain and flatulence. These claims, however, could not be verified in this review since the study containing a synbiotic agent with *L. helveticus* did not analyze these outcomes. Unlike acacia fiber, polydextrose has more robust evidence of its prebiotic effects, and systematic reviews on the subject have already been published [26].

However, according to the International Scientific Association of Probiotics and Prebiotics (ISAPP) [9], in order for a product to be considered synbiotic, it needs to have sufficient evidence of its selective use by gut microbiota (for complementary synbiotics) or its selective use by the co-administered microorganism (synergist synbiotics). Furthermore, according to ISAPP, at least one study with an adequate methodology that proves its evi-

dence regarding health benefits and selectivity is necessary. Therefore, further studies with these synbiotics are required to verify their selectivity.

This systematic review pointed out that the use of synbiotic products appears to have specific beneficial effects on each IBS subtype, and improvements in global IBS symptoms, such as constipation, and bowel habits were observed across both studies. However, it is not possible to draw conclusions about its effects or optimal composition.

Both studies included in this review used similar products as placebos for the control group, a dairy-based food matrix without any probiotic or synbiotic components. According to the Handbook for Good Clinical Research Practice (GCP) made available by the WHO [27], a well-controlled clinical trial must follow a design that allows comparison between the test and control groups so that the effects of the intervention can be determined and differentiated from other possible influences. In addition, the Guidelines for the Evaluation of Probiotics in Food, a joint report of FAO/WHO [28], recommends that for tests on probiotic foods, the placebo should be composed of the carrier food devoid of the probiotic to be tested.

During the literature search stage, this systematic review found at least two other studies focusing on the proposed topic [29,30]. However, both had methodological flaws that prevented their inclusion in this review. A study by Nobaek et al. [29] presented its results in such a way that it was not possible to extract any data regarding the control group. In addition, a study by Noorbakhsh et al. [30] presented only the data related to the test group, without identifying the control group at all.

This review also highlights the need for full disclosure of all data related to control and test groups. According to a document developed by the FDA [31], Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Guidance for Industry, the full presentation of all data regarding the intervention subjects and control groups is essential to allow for meta-analysis and to generate evidence that ensures an intervention is both safe and effective.

The present review also recommends the use of standardized scales that allow for comparisons between different studies when analyzing gastrointestinal symptoms and bowel disorders. An example of the successful use of standardizing scales is the method adopted by Min et al. [21]. The authors used the VAS Scale (VAS, 0 = no symptoms, 25 = mild, 50 = moderate, 75 = severe, 100 = very severe) for symptoms of abdominal pain/discomfort, bloating, satisfaction with bowel habits, and day to day discomfort; associated with a frequency measurement for flatulence, and defecation. They have also employed the Bristol Stool Scale [32] to evaluate stool consistency. This method is even more complete than when using only the VAS-IBS Scale [33] and allows for a thorough assessment of recurring gastrointestinal symptoms for all IBS subtypes.

Regarding the type of matrix used to carry synbiotics or prebiotics, defining what would be the best way to carry these compounds is a matter that requires further investigation, and the development of comparative studies between different matrixes is necessary. In the studies included in this review, both used a dairy-based matrix as a carrier, which is one of the most common ways of carrying probiotics and synbiotics in food. These products tend to be selected due to their favorable characteristics regarding the survival of probiotic microorganisms during storage [34]. However, it should be highlighted that the use of non-dairy-based food matrixes is a promising topic for future clinical trials, as some patients with IBS reported discomfort associated with ingestion of this type of food [35].

This review, however, is not free of limitations though. It was not possible to assess the effect of the interventions of interest through a meta-analysis due to important differences between the included studies and the lack of data for comparison in patients with IBS-D. However, further studies on the topic may assist in closing the gaps found during this systematic review.

5. Conclusions

The findings of this systematic review indicate that the use of synbiotics has the potential to reduce overall IBS symptoms and improve the patients' satisfaction with their bowel habits. However, it is not possible to draw any conclusions yet, mostly due to the great heterogenicity between the studies. Future clinical trials on this topic should consider the use of a placebo free of prebiotic and synbiotic components, an intervention period that allows for long-term evaluation, the use of unified tools for measuring outcomes (e.g., VAS Scale and Bristol Scale), and the individual analysis of outcomes for different IBS subtypes.

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Appendix A

Search strategy for each database

PubMed/MEDLINE: ("Prebiotics"[Title/Abstract] OR "Prebiotic"[Title/Abstract] OR "Synbiotics"[Title/Abstract] OR "Synbiotic"[Title/Abstract] OR "Symbiotics"[Title/Abstract] OR "Symbiotic"[Title/Abstract]) AND ("Irritable Bowel Syndrome"[Title/Abstract] OR "Irritable Bowel Syndromes"[Title/Abstract] OR "IBS"[Title/Abstract] OR "Irritable Colon"[Title/Abstract] OR "Mucous Colitides"[Title/Abstract] OR "Mucous Colitis"[Title/Abstract]).

Embase: ("Prebiotics" OR "Prebiotic" OR "Synbiotics" OR "Synbiotic" OR "Symbiotics" OR "Symbiotic") AND ("Irritable Bowel Syndrome" OR "Irritable Bowel Syndromes" OR "IBS" OR "Irritable Colon" OR "Mucous Colitides" OR "Mucous Colitis"), selecting the filter for Title, Abstract, Author keywords.

Cochrane: ("Prebiotics" OR "Prebiotic" OR "Synbiotics" OR "Synbiotic" OR "Symbiotics" OR "Symbiotic") AND ("Irritable Bowel Syndrome" OR "Irritable Bowel Syndromes" OR "IBS" OR "Irritable Colon" OR "Mucous Colitides" OR "Mucous Colitis"), selecting the filter for Title, Abstract, Keyword.

Lilacs: ("Prebiotics" OR "Prebiotic" OR "Synbiotics" OR "Synbiotic" OR "Symbiotics" OR "Symbiotic" OR Prebiótico* OR Simbiótico*) AND ("Irritable Bowel Syndrome" OR "Irritable Bowel Syndromes" OR "IBS" OR "Irritable Colon" OR "Mucous Colitides" OR "Mucous Colitis" OR "Síndrome do Intestino Irritável" OR "Síndrome de Intestino Irritável" OR "SII" OR "Colite Mucosa" OR "Colo Irritável" OR "Cólon Irritável" OR "Síndrome de Colo Irritável" OR "Síndrome de Cólon Irritável" OR "Síndrome do Colo Irritável" OR "Síndrome do Cólon Irritável" OR "Síndrome del Colon Irritable" OR "Síndrome del Intestino Irritable" OR "Colitis Mucosa" OR "Colon Irritable.

Appendix B

Overall quality of evidence was assessed using the Confidence in the Evidence from Reviews of Qualitative research (GRADE-CERQual) approach, and the results are presented in Tables A1 and A2.

Table A1. Summary of qualitative findings (SoQF).

Summary of Review Findings	Studies That Contribute to the Review Finding	CERQual Assessment of Confidence in the Evidence	Explanation of the CERQual Assessment
When IBS subtypes were individually evaluated, individuals receiving the same intervention had different results regarding the analyzed outcomes. Because of that, specific intestinal modulation strategies should be developed for each subtype of IBS.	[21]	Moderate confidence	Moderate concerns about adequacy.
Patients who received interventions with the *bifidobacterium* genus had significant improvements in the overall symptoms of the syndrome.	[21]	Low confidence	Moderate concerns about consistency and serious concerns about adequacy because of the low amount of data contributing to the finding.
The use of synbiotics has the potential to reduce overall IBS symptoms and improve the patients' satisfaction with their bowel habits.	[21,22]	Low confidence	Moderate concerns about methodological limitations and serious concerns about adequacy because of the low amount of data contributing to the finding.

Table A2. CERQual evidence profile.

Summary of Review Findings	Studies That Contribute to the Review Finding	Methodological Limitations Component	Coherence Component	Adequacy Component	Relevance Component	CERQual Assessment of Confidence in the Evidence	Explanation of the CERQual Assessment
When IBS subtypes were individually evaluated, individuals receiving the same intervention had different results regarding the analyzed outcomes. Because of that, specific bowel modulation strategies should be developed for each subtype of IBS.	[21]	Minor concerns about methodological limitations, which are unlikely to reduce confidence in the review finding.	Minor concerns about methodological limitations, which are unlikely to reduce confidence in the review finding.	Moderate concerns about adequacy that will likely reduce confidence in the review finding (only one study contributed to this finding, but this is a topic that has already been discussed by other studies and is a suggestion for further studies).	No concern regarding the relevance of the finding, and that will hardly reduce confidence in the review finding.	Moderate confidence	Moderate concern about adequacy.
Patients who received interventions with the *bifidobacterium* genus had significant improvements in the overall symptoms of the syndrome.	[21]	Minor concerns about methodological limitations, which are unlikely to reduce confidence in the review finding (failure to report treatment allocation method).	Moderate concerns about coherence likely to reduce confidence in the review finding.	Serious concerns regarding the adequacy of the studies since only one study contributed to this finding, and more studies would need to be carried out to be sure of the claim).	No concern regarding the relevance of the finding, and that will hardly reduce confidence in the review finding.	Low confidence	Moderate concerns about consistency and serious concern about adequacy because of the low amount of data contributing to the finding.

Table A2. *Cont.*

Summary of Review Findings	Studies That Contribute to the Review Finding	Methodological Limitations Component	Coherence Component	Adequacy Component	Relevance Component	CERQual Assessment of Confidence in the Evidence	Explanation of the CERQual Assessment
The use of synbiotics has the potential to reduce overall IBS symptoms and improve the patients' satisfaction with their bowel habits.	[21,22]	Moderate concerns about methodological limitations, which are likely to reduce confidence in the review finding. One of the studies does not intend to analyze the numerical results (possibility of selection of results). The two studies did not report the treatment allocation method.	Minor concerns about consistency may reduce the confidence of the review finding (although these data are based on data found in the studies, there was variation between symptoms of different subtypes of IBS).	Serious concerns about the adequacy of studies that reduce confidence in the finding. Only one study contributes to the finding of improvement in global IBS symptoms and, in relation to improved satisfaction with bowel habits, one of the studies has moderate informational capacity.	No concern regarding the relevance of the finding, and that will hardly reduce confidence in the review finding.	Low confidence	Moderate concerns for methodological limitations and serious for adequacy because of the low amount of data contributing to the finding.

References

1. Lovel, R.M.; Ford, A.C. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A meta-analysis. *Clin. Gastroenterol. Hepatol.* **2012**, *10*, 712–721. [CrossRef]
2. Mearin, F.; Lacy, B.E.; Chang, L.; Chey, W.D.; Lembro, A.J.; Simren, M.; Spiller, R. Bowel Disorders. *Gastroenterology* **2016**, *150*, 1393–1407. [CrossRef]
3. Chang, F. Irritable bowel syndrome: The evolution of multi-dimensional looking and multidisciplinary treatments. *World J. Gastroenterol.* **2014**, *20*, 2499–2514. [CrossRef]
4. Enck, P.; Aziz, Q.; Barbara, G.; Farmer, A.D.; Fukudo, S.; Mayer, E.A.; Niesler, B.; Quigley, E.M.M.; Rajilić-Stojanović, M.; Schemann, M.; et al. Irritable bowel syndrome. *Nat. Rev. Dis. Primers* **2016**, *2*, 16014. [CrossRef]
5. Ford, A.C.; Sperber, A.D.; Corsetti, M.; Camilleri, M. Irritable bowel syndrome. *Lancet* **2020**, *396*, 1675–1688. [CrossRef]
6. Simrén, M.; Barbara, G.; Flint, H.J.; Spigel, B.M.R.; Spiller, R.C.; Vanner, S.; Verdu, E.F.; Whorwell, P.J.; Zoetendal, E.G. Intestinal microbiota in functional bowel disorders: A Rome foundation report. *Gut* **2013**, *62*, 159–176. [CrossRef] [PubMed]
7. Hill, C.; Guarner, F.; Reid, G.; Gibson, G.R.; Merenstein, D.J.; Pot, B.; Moreli, L.; Canani, R.B.; Flint, H.J.; Salminen, S.; et al. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Grastroenterol. Hepatol.* **2014**, *11*, 506–514. [CrossRef] [PubMed]
8. Gibson, G.R.; Hutkins, R.; Sanders, M.E.; Prescott, S.L.; Reimer, R.A.; Salminen, S.J.; Scott, K.; Stanton, C.; Swanson, K.S.; Cani, P.D.; et al. Expert consensus document: The international scientific association for probiotics and prebiotics (isapp) consensus statement on the definition and scope of prebiotics. *Nat. Rev. Grastroenterol. Hepatol.* **2017**, *14*, 491–502. [CrossRef] [PubMed]
9. Swanson, K.S.; Gibson, G.R.; Hutkins, R.; Reimer, R.A.; Reid, G.; Verbeke, K.; Scott, K.P.; Holscher, H.D.; Azad, M.B.; Delzenn, N.M.; et al. The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of synbiotics. *Nat. Rev. Grastroenterol. Hepatol.* **2020**, *17*, 687–701. [CrossRef]
10. Ford, A.C.; Harris, L.A.; Lacy, B.E.; Quigley, E.M.M.; Moayyedi, P. Systematic review with meta-analysis: The efficacy of prebiotics, probiotics, synbiotics and antibiotics in irritable bowel syndrome. *Aliment. Pharmacol. Ther.* **2018**, *48*, 1044–1066. [CrossRef] [PubMed]
11. Barbara, G.; Feinle-Bisset, C.; Ghoshal, U.C.; Quigley, E.M.; Santos, J.; Vanner, S.; Vergnolle, N.; Zoetendal, E.G. The Intestinal Microenvironment and Functional Gastrointestinal Disorders. *Gastroenterology* **2016**, *150*, 1305–1318. [CrossRef] [PubMed]
12. Ranadheera, R.D.C.S.; Evans, C.A.; Adams, M.C.; Baines, S.K. In vitro analysis of gastrointestinal tolerance and intestinal cell adhesion of probiotics in goat's milk ice cream and yogurt. *Food Res. Int.* **2012**, *49*, 619–625. [CrossRef]
13. Vrese, M.; Schrezenmeir, J. Probiotics, prebiotics and synbiotics. *Adv. Biochem. Eng. Biotechnol.* **2008**, *111*, 1–66 101007/10_2008_097. [PubMed]
14. Ranadheera, R.D.C.S.; Baines, S.K.; Adams, M.C. Importance of food in probiotic efficacy. *Food Res. Int.* **2010**, *43*, 1–7. [CrossRef]
15. FAO; WHO. *Probiotics in Food, Health and Nutritional Properties and Guidelines for Evaluation*; FAO: Rome, Italy, 2006. Available online: https://www.fao.org/3/a0512e/a0512e.pdf (accessed on 6 January 2022).
16. Asha, M.Z.; Khalil, S.F.H. Efficacy and Safety of Probiotics, Prebiotics and Synbiotics in the Treatment of Irritable Bowel Syn-drome: A systematic review and meta-analysis. *Sultan Qaboos Univ. Med. J.* **2020**, *20*, 13. [CrossRef] [PubMed]

17. Chlebicz-Wójcik, A.; Ślizewska, K. Probiotics, Prebiotics, and Synbiotics in the Irritable Bowel Syndrome Treatment: A review. *Biomolecules* **2021**, *11*, 1154. [CrossRef]
18. Ford, A.C.; Quigley, E.M.M.; Lacy, B.E.; Lembo, A.J.; Saito, Y.A.; Schiller, L.R.; Soffer, E.E.; Spiegel, B.M.R.; Moayyedi, P. Efficacy of Prebiotics, preobiotics, and synbiotics in irritable bowel syndrome and chronic idiopathic constipation: Systematic review aand meta-analysis. *Am. J. Gastroenterol.* **2014**, *109*, 1547–1561. [CrossRef] [PubMed]
19. Canto, G.L. *Revisões Sistemáticas da Literatura, Guia Prático*; Brazil Publishing: Curitiba, Brazil, 2020; p. 186.
20. CERQual—Confidence in the Evidence from Reviews of Qualitative Research. Available online: http://cerqual.org/whatisthecerqualapproach (accessed on 4 December 2021).
21. Min, Y.W.; Park, S.U.; Jang, Y.S.; Kim, Y.; Rhee, P.; Ko, S.H.; Joo, N.; Kim, S.I.; Kim, C.H.; Chang, D.K. Effect of composite yogurt enriched with acacia fiber and Bifidobacterium lactis. *World J. Gastroenterol.* **2012**, *18*, 4563. [CrossRef] [PubMed]
22. Bahrudin, M.F.; Rani, R.A.; Tamil, A.M.; Mokhtar, N.M.; Ali, R.A.R. Effectiveness of Sterilized Synbiotic Drink Containing Lactobacillus helveticus Comparable to Probiotic Alone in Patients with Constipation-Predominant Irritable Bowel Syndrome. *Dig. Dis. Sci.* **2019**, *65*, 541–549. [CrossRef]
23. Guarrigues, V.; Gálvez, C.; Ortiz, V.; Ponce, M.; Nos, P.; Ponce, J. Prevalence of constipation: Agreement among several criteria and evaluation of the diagnostic accuracy of qualifying symptoms and self-reported definition in a population-based survey in Spain. *Am. J. Epidemiol.* **2004**, *159*, 520–526. [CrossRef]
24. Meydan, C.; Afshinnekoo, E.; Rickard, N.; Daniels, G.; Kunces, L.; Hardy, T.; Lili, L.; Pesce, S.; Jacobson, P.; Mason, C.E.; et al. Improved gastrointestinal health for irritable bowel syndrome with metagenome-guided interventions. *Precis. Clin. Med.* **2020**, *3*, 136–146. [CrossRef]
25. Cherbut, C.; Michel, C.; Raison, V.; Kravtchenko, T.; Severine, M. Acacia Gum is a Bifidogenic Dietary Fibre with High Di-gestive Tolerance in Healthy Humans. *Microb. Ecol. Health Dis.* **2003**, *15*, 45–50. [CrossRef]
26. Carmo, M.M.R.; Walker, J.C.L.; Novello, D.; Caselato, V.M.; Sgarbieri, V.C.; Ouwehand, A.C.; Andreollo, N.A.; Hiane, P.A.; Santos, E.F. Polydextrose: Physiological function, and effects on health. *Nutrients* **2016**, *8*, 553. [CrossRef]
27. World Health Organization. *Handbook for Good Clinical Research Practice (GCP): Guidance for Implementation*; WHO: Geneva, Switzerland, 2002. Available online: https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf (accessed on 5 September 2021).
28. FAO; WHO. Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food. London, Ontario, Canada, 2002. Available online: https://www.who.int/foodsafety/fs_management/en/probiotic_guidelines.pdf (accessed on 5 September 2021).
29. Nobaek, S.; Johansson, M.L.; Molin, G.; Ahrné, S.; Jeppsson, B. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am. J. Gastroenterol.* **2000**, *95*, 1231–1238. [CrossRef]
30. Noorbakhsh, H.; Yavarmanesh, M.; Mortazavi, S.A.; Adibi, P.; Moazzami, A.A. Metabolomics analysis revealed metabolic changes in patients with diarrhea-predominant irritable bowel syndrome and metabolic responses to a synbiotic yogurt intervention. *Eur. J. Nutr.* **2019**, *58*, 3109–3119. [CrossRef]
31. FDA. *Guidance for Industry: Meta-Analyses of Randomized Controlled Clinical Trials to Evaluate the Safety of Human Drugs or Biological Products Fishers Lane*; U. S. Department of Health and Human Services Food and Drug Administration: Rockville, MD, USA, 2018. Available online: https://www.fda.gov/media/117976/download (accessed on 5 September 2021).
32. Lewis, S.J.; Heaton, K.W. Bristol Stool Form Scale as a Useful Guide to Intestinal Transit Time. *Scand. J. Gastroenterol.* **1997**, *32*, 920–924. [CrossRef]
33. Bengtsson, M.; Ohlsson, B.; Ulander, K. Development and psychometric testing of the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS). *BMC Gastroenterol.* **2007**, *7*, 16. [CrossRef]
34. Mani-López, E.; Palou, E.; López-Malo, A. Probiotic viability and storage stability of yogurts and fermented milks prepared with several mixtures of lactic acid bacteria. *J. Dairy Sci.* **2014**, *97*, 2578–2590. [CrossRef]
35. Cancaveric, I.; Rehman, M.; Iskander, B.; Lalani, S.; Malik, B.H. Is There a Correlation Between Irritable Bowel Syndrome and Lactose Intolerance? *Cureus* **2020**, *12*, 6–13. [CrossRef]