

Systematic Review

Effectiveness of Medilac-S as an Adjuvant to Conventional Irritable Bowel Syndrome Treatments: A Systematic Review with Meta-Analysis

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Abstract: Numerous clinical studies published in the Chinese language support the use of Medilac-S (*Bacillus subtilis* R0179 and *Enterococcus faecium* R0026; non-commercial name IBacilluS+) as an adjuvant in various indications, including ulcerative colitis, irritable bowel syndrome, acute gastritis, and *Helicobacter pylori* therapy. This systematic review with a meta-analysis was conducted to summarize clinical studies evaluating the efficacy of this probiotic formulation as an adjuvant to conventional IBS medications. The systematic literature searches in six international and Chinese databases identified 37 eligible studies, of which 33 reported the efficacy of Medilac-S adjunctive therapy using a standardized categorical scale. These 33 studies were included in the meta-analysis using a random-effect model with a stratification by IBS subtype. Overall, Medilac-S significantly improved the efficacy of conventional IBS treatment (RR = 1.21; 95% CI: 1.17–1.25; and $p < 0.0001$) with an average probability of treatment effectiveness being 21% higher with the probiotic adjuvant, regardless of the subtype. Adverse events, reported in 78% of the trials, were described as mild-to-moderate and self-resolving, with a similar incidence in the probiotic adjuvant (6.2%; $n = 1347$) and control (5.9%; $n = 1331$) groups. The results of this meta-analysis strengthen the conclusions that Medilac-S is a safe and effective adjuvant to a variety of conventional treatments in IBS patients.

Keywords: probiotics; irritable bowel syndrome; Medilac-S; meta-analysis; systematic review



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1. Introduction

Irritable bowel syndrome (IBS) is a common and difficult-to-treat chronic intestinal disorder classified by the Rome Foundation under the umbrella of the Disorders of Gut-Brain Interaction (DGBIs; formerly Functional Gastrointestinal Disorders, FGIDs) [1]. Typically, IBS is characterized by a chronic alteration in bowel habits (frequency or form), accompanied by abdominal pain related to bowel movements [2]. Depending on the frequency of specific stool forms, IBS can be subtyped into four categories: diarrhea-predominant (IBS-D), constipation-predominant (IBS-C), mixed occurrence of both diarrhea and constipation (IBS-M), or unspecified (IBS-U) when not corresponding to the criteria for the three other subtypes. The incidence of IBS varies largely by country and depends on the iteration of the Rome diagnostic criteria used. Estimates based on the Rome III criteria have shown that IBS affects approximately 10% of the global population. However, based on the Rome IV criteria released in 2016 [3], the incidence was reduced to 3.5% in most countries [4,5]. The Rome IV criteria no longer recognize abdominal “discomfort” or bloating in the definition of IBS, and the abdominal pain threshold has been

raised compared to Rome III [1]. Accordingly, nearly half of Rome III-diagnosed IBS patients no longer fulfill the IBS criteria based on Rome IV, which is considered to represent a more severe subgroup of the Rome III-diagnosed IBS population [6,7]. However, Rome IV-diagnosed populations were reported as less stable than the Rome III-diagnosed population, with more patients fluctuating to another functional bowel disorder or IBS subtype on the FGID spectrum within 12 months of diagnosis [8]. In the United States, Canada, and the United Kingdom, the reduction in IBS incidence using Rome IV was accompanied by a corollary increase in functional constipation or functional diarrhea diagnoses [9]. Expert opinions have raised the question of diagnostic thresholds being largely based on Western populations, which may reduce the sensitivity or accuracy for the clinical IBS population in Asian countries [5,10]. In China, the Rome III criteria remain in use because it is considered by Chinese experts as more appropriate for the Chinese IBS population, of whom a large proportion reports symptoms of bloating or abdominal discomfort but often without abdominal pain [5,11].

After a usually long delay to obtain an IBS diagnosis, treatment relies primarily on diet or lifestyle modifications to reduce or alleviate symptoms, with the need to also use symptom-targeted pharmacological interventions in certain cases [12–14]. Standard IBS treatments vary according to countries because of regulatory but also cultural reasons. For instance, Western medicine recommends the adoption of low-FODMAP or gluten-free diets as the first line of treatment for IBS, while, in China, food intolerance, food allergies, or intake of specific “offending” foods are viewed as more important for the onset of IBS than FODMAPs [5,15,16]. As the second line, however, similar classes of pharmacological treatments are used in both Western and Asian countries, including laxatives, antidiarrheals, antispasmodics, antidepressants, or intestinal adsorbents [17,18]. Despite the variety of treatment options available to control symptoms, their efficacy remains variable and is often temporary, and adverse events can occur in some patients [19]. Therefore, alternative therapeutic modalities for IBS are needed and often sought by patients. Probiotics, as a group, are generally considered as potentially effective and are recommended in a number of clinical guidelines for symptom alleviation in IBS, although mostly without specific recommendations on the strain(s) or regimen to use [19,20].

A large body of evidence from IBS research conducted in China is published in Chinese language journals, making these studies less accessible to international research and medical communities [5]. Since the previous systematic review in 2012 [21], several studies have assessed the efficacy of a probiotic formulation containing *Bacillus subtilis* R0179 and *Enterococcus faecium* R0026 (Medilac-S; non-commercial name IBacilluS+) in IBS patients, either alone or as an adjuvant to standard oral medications. This formulation, which is registered as a pharmaceutical and has been marketed by Hanmi Pharmaceuticals Co. Ltd. (Seoul, Republic of Korea) in Asia since the mid-1980s mainly in South Korea and China and more recently in Vietnam since 2010, was also shown to significantly improve the efficacy of standard treatments in Chinese patients with ulcerative colitis [22]. Medilac-S and the “double-strength” formulation (Medilac-DS) are approved for use in the treatment of gastrointestinal symptoms (i.e., diarrhea, constipation, dyspepsia, and bloating) that are caused by microbiota dysbiosis following the use of antibiotics or other microbiota-disruptive medications. In Canada, this probiotic formulation is approved for the reduction in diarrhea duration in adolescents ≥ 12 years old and adults with IBS. The main objective of this systematic review and meta-analysis was to summarize the current literature and assess the efficacy of Medilac-S when used as an adjuvant to conventional oral medications in IBS, with a stratification by subtype.

2. Materials and Methods

2.1. Systematic Search and Screening of Studies

The protocol of this systematic review was prospectively registered on OSF (<http://doi.org/10.17605/OSF.IO/XRTWZ>; accessed on 31 August 2021), and the results are presented according to the PRISMA guidelines. A systematic literature search was conducted

up to September 2021 in 6 databases (Pubmed, Google Scholar, China National Knowledge Infrastructure (CNKI), VIP Search, Wanfang Data, and Chinese Biomedical Database) using various combinations of the following search terms: *Bacillus subtilis* (枯草杆菌), *Enterococcus faecium* (屎肠球菌), Medilac-S or Medilac-DS known as MeiChangAn (美常安), and probiotic (益生菌), microecological preparations (微生态制剂), Irritable Bowel Syndrome (肠易激综合征), random (随机), or control (对照). A total of 5213 articles were screened by the title and abstract (Figure 1) and 129 unique articles were kept for assessment by full text. A full-text assessment was performed using a pre-defined extraction form. The articles were translated using Google Translate, and the translations were validated by a native Chinese speaker. The data were extracted independently by 2 authors (X.X. and T.T.) and then revised independently by a third author (A.T.) and validated by a native Chinese speaker. The included studies were those evaluating the efficacy of Medilac-S as an adjuvant to a standard oral medication in IBS patients and using a parallel comparator arm with the same standard treatment without Medilac-S. The presence of additional arms with either Medilac-S[®]-only or another treatment was disregarded during the eligibility screening; however, the eligible studies comprising a Medilac-S-only arm were included in a subgroup analysis. After the exclusion of 92 studies based on full-text screening, with reasons (full text unavailable (n = 5), ineligible comparator arms (n = 44), ineligible interventions (n = 38), and ineligible indication (n = 5)), 37 studies were included in the qualitative analysis (Figure 1). The study authors were not contacted to provide additional data. The comparator arms were deemed ineligible when they did not allow for assessing the effect of the probiotic specifically, either by including the probiotic in all arms or by providing different standard oral medications in the groups with and without Medilac-S. Interventions were deemed ineligible when they were not from a standard IBS medication class provided orally, such as Chinese herbal medicines, acupuncture, or if the medications were administered by enema. Studies on functional diarrhea, functional constipation, or small intestine bacterial overgrowth (SIBO) were excluded.

2.2. Data Synthesis and Statistical Analyses

The data extraction master file was used to summarize the study characteristics of the included studies, including the study date, population, arms, probiotic regimen, efficacy outcome measures, and adverse events. In addition, the summary tables provide an overview of the 37 studies in terms of the IBS diagnostic guideline used and subtypes, primary standard treatment class, probiotic regimen (dose and duration), and subgroup analysis of the studies that also included a Medilac-S-only arm. A random-effect model was used for the meta-analysis of the primary outcome, which included a stratification by IBS subtypes as prospectively defined in the protocol. The primary outcome of the review was the clinical efficacy rate, which was evaluated in 33 of the 37 studies using the responder rate on a categorical scale typically used in Chinese studies (i.e., the proportion of patients in each treatment arm who satisfy the treatment responder definition, which uses a 3- or 4-point categorical scale based on the symptoms severity, namely, cured and/or markedly effective, effective, and ineffective). The raw data were converted into relative risk (RR) with 95% confidence intervals (CI) for the meta-analysis. The meta-analysis was conducted in R version 4.2.1, using the meta package [23,24]. Weighing was calculated using the inverse variance method, the restricted maximum-likelihood estimator was used for τ^2 , and the Q-profile method was used for the confidence interval of τ^2 and τ . Heterogeneity among the studies was assessed using I² and τ^2 . The efficacy results of the 4 studies that did not use the categorical scale method and did not allow for calculating an RR were not included in the meta-analysis but were summarized qualitatively. The a priori subgroup analyses included the IBS subtype (IBS-C, IBS-D, IBS-M, or no subtype).

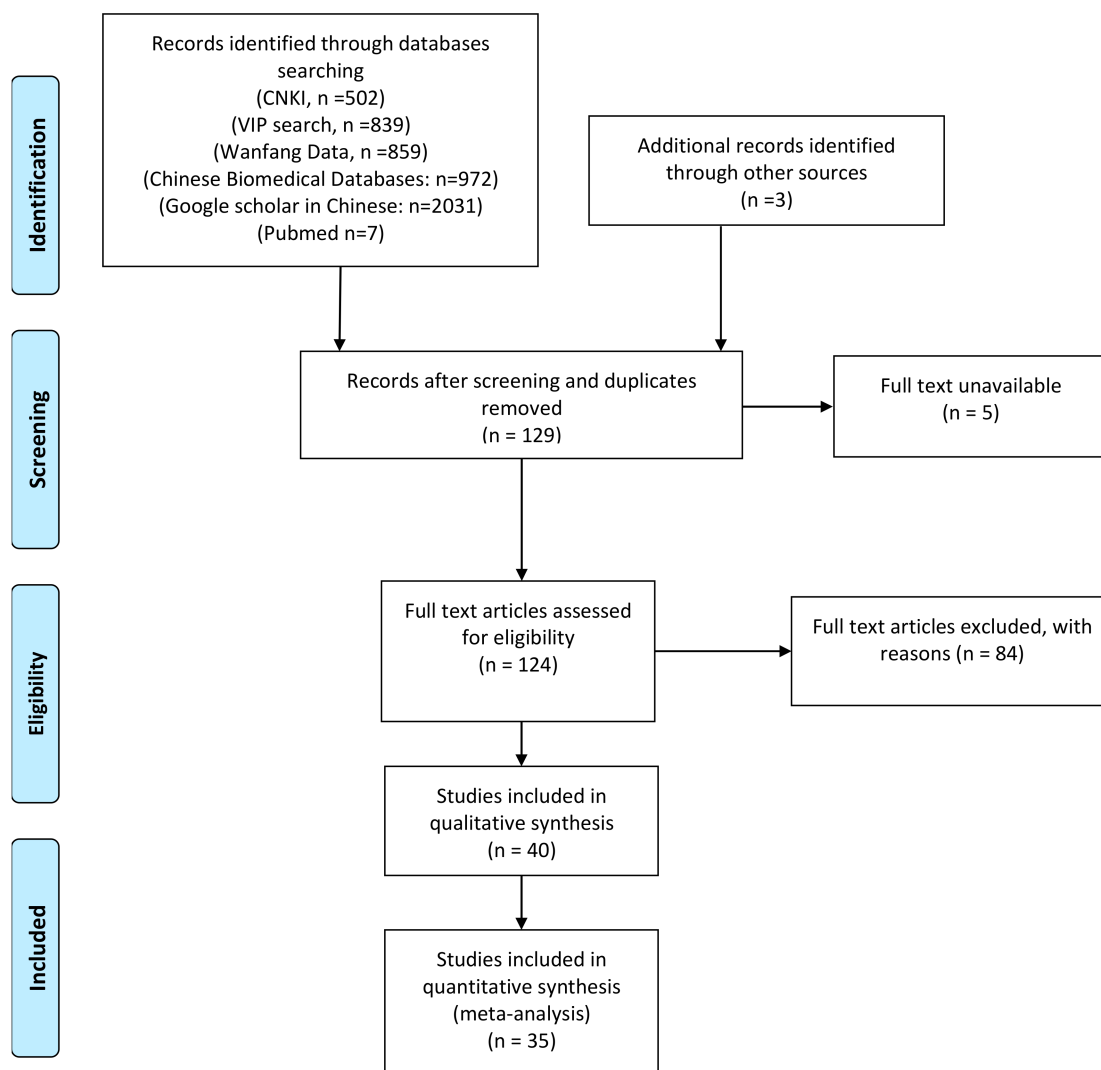


Figure 1. Flowchart of the literature search and study selection.

2.3. Quality Assessment of Studies

The risk of bias of the 33 studies included in the meta-analysis was assessed by 2 authors independently (X.X., A.T.) by using the Cochrane Collaboration's tool (2011) [25]. Disagreements were resolved by a third assessor (T.A.T.). Publication bias was assessed using funnel plots and the Egger test, and the trim-and-fill method by Tweedy was used as a sensitivity analysis to assess the potential impact of publication reporting bias on the meta-analysis results.

3. Results

3.1. Study Design and Population Characteristics

Out of 124 studies assessed for eligibility by full text (Figure 1), 37 studies met the inclusion criteria and were included in the qualitative review. As per the eligibility criteria, all the included studies used Medilac-S as an adjuvant to a standard IBS treatment and comprised a suitable comparator arm (same standard treatment without Medilac-S). The 37 included studies enrolled a total of 3516 adults in eligible groups (1750 in the comparator standard treatment arms and 1766 in the standard treatment + Medilac-S adjuvant arms). The participants were aged between 16 and 87 years old, with most studies (27/37) reporting an average age between 35 and 45 years old and 3 studies reporting an average age > 60 years old (Table 1). While not all studies described the course of disease in their

population, 57% of the studies (21/37) reported a diagnosis of at least 3 months or more, with 10 studies including participants living with the disease for up to 10–15 years.

Most of the studies reported using a recognized IBS diagnosis guideline, with ~65% of the studies (24/37) using Rome III, 3 studies using Rome II, and none using Rome IV. The Chinese IBS guidelines were used in two studies, while six studies reported using a standard diagnostic guideline without providing the source and two studies did not specify using a diagnostic guideline. Most of the studies were focused on IBS-D (17/37; 16 in the meta-analysis) and IBS-C (11/37; 8 in the meta-analysis); 1 study specifically enrolled participants with IBS-M and 8 studies did not specify any subtype.

Table 1. Details of included studies (n = 37), classified by IBS subtype.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
IBS-C						
Luo, ZQ et al. (2016) [26]	February 2014–February 2015	100 participants, 20–77 years old (average ~40 y) Rome III	Trimebutine maleate, n = 50 Trimebutine maleate + Medilac-S, n = 50	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale; see Figure 2). Symptoms severity scores (abdominal pain, bloating, constipation, BM number) were significantly lower compared to the control group ($p < 0.05$). ‡ GI hormones levels significantly improved over the control group (all, $p < 0.05$). Motilin ↑, vasoactive intestinal peptide ↓, Somatostatin ↓.	Mild, self-resolving diarrhea in 3 participants of the combination group.
Wang, XF (2018) [27]	March 2015–February 2016	86 participants, 21–57 years old (average ~37 y) Diagnostic guideline used (no source)	Lactulose, n = 42 Lactulose + Medilac-S, n = 44	1 cap. TID (1.5×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale). BSS and number of BM improved significantly and similarly in both groups.	None observed.
Zhao, LL (2016) [28]	February 2014–February 2016	150 participants, 27–63 years old (average ~39 y) Diagnostic guideline used (no source)	Lactulose, n = 50 Medilac-S, n = 50 Lactulose + Medilac-S, n = 50	2 caps. TID (3.0×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale). The improvement in individual symptom scores (abdominal pain, decreased appetite) was significantly superior in the combination group (all, $p < 0.05$). ‡	Similar AE incidence in all groups (mild, self-resolving diarrhea: 1 case in lactulose and combination groups; abdominal distension: 1 case in the lactulose group; no adverse event in the Medilac-S group).
Du, J (2015) [29]	2010–2012	90 participants, 26–65 years old Rome III	Lactulose, n = 30 Medilac-S, n = 30 Lactulose + Medilac-S, n = 30	2 caps. TID (3.0×10^9 cfu/d) For 5 weeks	Clinical efficacy rate (categorical scale).	Similar AE incidence in all groups (mild, self-resolving diarrhea: 2 cases in lactulose and combination group; abdominal distension: 4 cases in the lactulose group; no adverse event in the Medilac-S group).

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
Wang, L (2015) [30]	September 2012–September 2014	79 participants, 61–87 years old (average ~71 y) Rome III	Lactulose, n = 26 Medilac-S, n = 26 Lactulose + Medilac-S, n = 27	2 caps. TID (3.0×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale). Faster treatment onset in the combination group ($p < 0.05$). Superior relief of abdominal pain and distension in the combination group ($p < 0.05$). ‡	Similar AE incidence in all groups. All cases resolved without medication. (Combination group: 3 cases of diarrhea (11.1%), lactulose group: 3 cases of bloating/abdominal distension (11.5%), Medilac-S group: 2 cases of bloating (7.6%).)
Bai, L (2012) [31]	March 2010–April 2012	204 participants, 22–85 years old (average ~39 y) Rome III	Lactulose, n = 51 Medilac-S, n = 51 Lactulose + Medilac-S, n = 52 (Phenolphthalein, n = 50)	2 caps. TID (3.0×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale). Except Phenolphthalein, post-treatment symptom scores improved significantly in all groups ($p < 0.05$). The improvement was significantly better in the combination group vs. the three other groups ($p < 0.05$). ‡	None observed.
Xiao, Y et al. (2014) [32]	April 2013–February 2014	94 participants, 52–84 years old (average ~69 y) Diagnostic criteria used (no source)	Mosapride, n = 47 Mosapride + Medilac-S, n = 47	4 caps. TID (6.0×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale). The abdominal pain (stomachache) and discomfort score was significantly lower in the combination group after treatment ($p < 0.05$). ‡	None observed.
Shang, QL (2021) [33]	March 2018–October 2019	74 participants, 24–73 years old (average ~44 y) No guideline specified for the diagnosis	Mosapride + Lactulose, n = 37 Mosapride + Lactulose + Medilac-S, n = 37	2 caps. TID (3.0×10^9 cfu/d) For 4 weeks	Clinical efficacy rate (categorical scale). Individual symptom scores (bloating, abdominal pain, constipation) significantly improved in both groups ($p < 0.05$). ‡ GI hormones (vasoactive intestinal peptide (VIP) and somatostatin (SS)) decreased after treatment and were lower in the combination group.	n.r.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
Yang et al., 2016 [34]	October 2008–December 2011	231 participants, 16–63 years old (median age ~37 y) Rome III	Lactulose, n = 84 Lactulose + Medilac-S, n = 71 (Mosapride Citrate, n = 76)	2 caps. TID (3.0×10^9 cfu/d) 8 weeks	Superior improvement in constipation score ^S in the combination group ($p < 0.05$). ‡ BSS and number of BM improved significantly in all groups.	Similar AE incidence in all groups, all self-resolving. (Mild diarrhea: 14 in lactulose group, 10 cases in combination group; mild abdominal distension: 20 cases in the lactulose group, 23 cases in the combination group).
Sun et al., 2013 [35]	February 2010–August 2011	120 participants (average ~52 y *) Rome II	Lactulose, n = 40 Lactulose + Medilac-S, n = 40 (Mosapride, n = 40)	2 caps. TID (3.0×10^9 cfu/d) 2 weeks	Bristol Stool Scale score: significant improvement (before–after) in all groups ($p < 0.05$); no significant difference in the number of participants with stool scores IV–VI in Lactulose + Medilac-S vs. Lactulose at the end of intake.	Similar AE incidence in both groups; all symptoms resolved after reducing lactulose intake. (Mild diarrhea: 3 in lactulose group, 1 case in combination group; bloating: 4 cases in the lactulose group, 1 case in the combination group). No abnormalities on the routine blood, urine, and hepatic and kidney function parameters.
Xu et al., 2014 [36]	January 2011–September 2013	98 participants, 23–60 y old Rome III	Mosapride + Lactulose, n = 33 Mosapride + Medilac-S, n = 30 Mosapride + Lactulose + Medilac-S, n = 35	2 caps. TID (3×10^9 cfu/d) 2 weeks	Except for the Bristol Stool Scale score and bloating that improved similarly in all groups, the improvement in abdominal pain ‡ and quality of life (Chinese SF-36) were significantly superior in the combination group ($p < 0.05$).	n.r.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
IBS-D						
Wang, JP (2019) [37]	September 2016–September 2017	64 participants, 20–68 years old (average ~41 y) Diagnostic guideline used (no source)	Trimebutine maleate, n = 32 Trimebutine maleate + Medilac-S, n = 32	2 caps. TID (3×10^9 cfu/d) For 12 weeks	Clinical efficacy (categorical scale). Significantly superior reduction in abdominal pain ‡ and diarrhea symptoms in the combination group ($p < 0.05$). Significant improvement in Bristol score (↑ types III and IV, ↓ types V–VII) in the combination group ($p < 0.05$).	AEs were similar in both groups: 2 cases in the control group (loss of appetite, nausea) and 3 cases in the combination group (loss of appetite, nausea, constipation).
Wang, TQ et al. (2014) [38]	n.r.	76 participants, average 37 years old * Rome III	Trimebutine maleate, n = 35 Trimebutine maleate + Medilac-S, n = 41	2 caps. TID (3×10^9 cfu/d) For 2–4 weeks	Clinical efficacy (categorical scale).	There were 4 cases and 3 cases of dizziness, abdominal pain, and other adverse reactions in combination and control groups, respectively. Only 1 case in the combination group discontinued treatment.
Wang, TH (2013) [39]	September 2008–February 2012	117 participants, 18–65 years old (average 36.5 y) Rome III	Trimebutine maleate, n = 65 Medilac-S, n = 22 Trimebutine maleate + Medilac-S, n = 30	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	n.r.
Li, J (2012) [40]	September 2010–April 2011	150 participants, 23–59 years old, (average ~38 y) Rome II	Pinaverium bromide, n = 50 Medilac-S, n = 50 Pinaverium bromide + Medilac-S, n = 50	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale)	No abnormality in blood, urine, stool routine, liver and kidney function tests, and electrocardiogram. One case of mild, self-resolving constipation in the combination group.
Xu, BF et al. (2012) [41]	2010–2011	85 participants, 19–76 years old (average 45.2 y) Rome III	Pinaverium bromide, n = 40 Pinaverium bromide + Medilac-S, n = 45	1 cap TID (1.5×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale). IL-1B decreased and IL-10 increased in the combination group ($p < 0.05$). No change in the control group.	Symptoms of drowsiness and dizziness in 9 patients in the combination group. All liver and kidney function parameters in normal range.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
Yuan, SF et al. (2011) [42]	2005–2010	60 participants, average 43 years old * Chinese guideline (2003)	Trimebutine maleate, n = 30 Trimebutine maleate + Medilac-S, n = 30	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	None observed.
Qin and Bai (2009) [43]	August 2007–February 2008	86 participants, 19–66 years old (average 41 y) Rome III	Trimebutine maleate, n = 28 Medilac-S, n = 30 Trimebutine maleate + Medilac-S, n = 28	2 caps. TID (3×10^9 cfu/d) For 2 weeks + 4-week follow-up	Clinical efficacy (categorical scale). Recurrence rate after 4-week follow-up, lower in combination (4/28; 14.3%) and Medilac-S (5/30; 16.7%) groups compared to trimebutine maleate (9/28; 32.1%) ($p < 0.01$).	There were no obvious adverse drug reactions deemed associated with Medilac-S. No abnormal laboratory test results in the three groups. In the trimebutine maleate and combination groups: 3 and 5 cases, respectively, displayed symptoms such as numbness in the limbs, dizziness, and thirst, which all disappeared after reducing the dose of trimebutine maleate.
Zhang, XF et al. (2009) [44]	September 2007–April 2008	60 participants, 20–66 years old (average 35.5 y) Rome III	Pinaverium bromide, n = 30 Pinaverium bromide + Medilac-S, n = 30	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale). Superior Bristol score improvement in the combination group ($p = 0.016$). Superior reduction in abdominal symptom scores in the combination group ($p = 0.004$). ‡	A few participants reported common side effects of pinaverium bromide (mild gastrointestinal discomfort, and rash-like allergic reactions). No abnormal results in routine blood tests and biochemical tests.
You, T (2016) [45]	March 2015–March 2016	186 participants, 21–65 years old (average ~31 y) No guideline specified for the diagnosis	Smecta, n = 62 Medilac-S, n = 62 Smecta + Medilac-S, n = 62	2 caps. TID (3×10^9 cfu/d) For 2 weeks + 2 weeks follow-up	Clinical efficacy (categorical scale). Superior improvements in abdominal pain and diarrhea frequency, ‡ and shorter hospital stay in the combination group ($p < 0.05$). Note: absence of recurrence during follow-up included in the markedly effective definition.	n.r.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
Yang, GC (2013) [46]	April 2011–April 2012	120 participants, 19–75 years old (average 43.5 y) Rome III	Montmorillonite, n = 40 Medilac-S, n = 40 Montmorillonite + Medilac-S, n = 40	2 caps. TID (3×10^9 cfu/d) For 2 weeks	Clinical efficacy (categorical scale). Superior improvements in individual symptoms (abdominal pain or discomfort, bloating, defecation pattern, defecation process ‡; all, $p < 0.05$) in the combination group.	All AEs reported were mild. In the Medilac-S group: 2 cases of nausea and 1 case of dizziness; in the combination group: 1 case of nausea.
Liu, GH (2012) [47]	2010–2011	90 participants, 19–65 years old (average 38 y) Rome III	Smecta, n = 30 Medilac-S, n = 30 Smecta + Medilac-S, n = 30	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	None observed.
You, B et al. (2011) [48]	January 2008–April 2010	176 participants, 18–63 years old (average 41 y) Rome III	Montmorillonite, n = 58 Medilac-S, n = 60 Montmorillonite + Medilac-S, n = 58	2 caps. TID (3×10^9 cfu/d) For 2 weeks + 4-week follow-up	Clinical efficacy (categorical scale). More participants in the combination group reported improvements in abdominal pain and diarrhea scores at 3 days and 14 days of treatment ($p < 0.05$). ‡ Recurrence rate 4 weeks after treatment was significantly lower in the combination (10.3%) and Medilac-S (11.6%) groups compared to standard treatment (32.7%); $p < 0.01$.	AEs were similar between groups (drowsiness, dizziness, and sleepiness) in 5 (combination), 4 (Medilac-S), and 3 (Montmorillonite) participants. All values for blood, urine, stool panel, and liver and kidney functions were within normal range.
Ding, GW (2012) [49]	January 2009–August 2011	134 participants, 18–60 years old (average 39.5 y) Rome III	Flupentixol + Melitracen + Montmorillonite, n = 44 Flupentixol + Melitracen + Medilac-S, n = 44 Flupentixol + Melitracen + Montmorillonite + Medilac-S, n = 46	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	n.r.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
Li and Shi (2010) [50]	April 2009–April 2010	156 participants, 18–67 y old (average 35 y) Rome III	Doxepin, n = 52 Medilac-S, n = 52 Doxepin + Medilac, n = 52	2 caps. TID (3×10^9 cfu/d) For 4 weeks + 12 weeks follow-up	Clinical efficacy (categorical scale). Note: absence of recurrence included in the markedly effective definition.	All AEs were mild and disappeared with a reduction in dosage. Three cases in the doxepin group (dry mouth, dizziness, lethargy), one case of headache in the Medilac-S group.
Li, JG (2010) [51]		140 participants, 16–60 y old Rome III	Loperamide, n = 68 Loperamide + Medilac-S, n = 72	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	None observed.
Su and Wu (2021) [52]	February 2019–February 2020	92 participants, 23–69 y old (average ~41.5 y) (Note: IBS-D with abdominal distension) Rome III-like diagnostic criteria described (no source)	Itopride, n = 46 Itopride + Medilac-S, n = 46	1 cap. TID (1.5×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale). Significantly superior improvement in IBS-SSS score and bloating score in the combination group ($p < 0.001$). ‡ Significantly higher <i>Lactobacilli</i> and <i>Enterococci</i> and lower yeast-like fungi counts in the combination group.	AEs were similar between groups: 3 cases (loss of appetite, nausea/vomiting, constipation) in the combination group; 5 cases in the Itopride group (2 loss of appetite, 3 nausea/vomiting).
Lu and Dong, 2007 [53]	January 2005–October 2006	60 participants, 18–63 years (average 27 y) Chinese guideline (2003)	Smecta, n = 18 Medilac-S, n = 21 Smecta + Medilac-S, n = 21	2 caps. TID (3×10^9 cfu/d) 1 week	Faster resolution (starting on day 3) and significantly lower scores after 7 days in the combination group (abdominal symptom scores, ‡ daily average bowel movements, and Bristol stool traits; all $p < 0.05$).	None observed.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
IBS-M						
Chen, H et al. (2011) [54]	April 2006–August 2008	151 participants, 19–65 years old (average ~42 y) Rome III	Trimebutine maleate, n = 50 Medilac-S, n = 50 Trimebutine maleate + Medilac-S, n = 51	2 caps. TID (3×10^9 cfu/d) For 8 weeks	Clinical efficacy (categorical scale).	AEs were mild and self-resolving. Two cases (dizziness, headache) in the combination group; two cases in the trimebutine maleate group (dizziness, headache); and one case of nausea in the Medilac-S group.
IBS (not subtyped)						
Li, CL (2020) [55]	April 2016–April 2018	135 participants, 18–54 years old (average 36.5 y) Diagnostic guideline used (no source)	Trimebutine maleate, n = 67 Trimebutine maleate + Medilac-S, n = 68	1 cap. TID (1.5×10^9 cfu/d) For 12 weeks	Clinical efficacy (categorical scale). After 12 weeks, significant \uparrow in Bristol stool types ϕ -IV and \downarrow types V-VII in the combination group vs. trimebutine maleate ($p < 0.05$).	AE incidence rate was 4.41% (3/68; headache, nausea, thirst) in the combination group, compared with 2.99% (2/67; thirst, dizziness) in the control group (n.s.).
Wang, JR (2013) [56]	January 2009–December 2011	102 participants, 21–71 years old (average 42.5 y) Rome III	Trimebutine maleate, n = 25 Medilac-S, n = 26 Trimebutine maleate + Medilac-S, n = 25 (Trimebutine maleate + fluoxetine hydrochloride + Medilac-S, n = 26)	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	None observed. No abnormalities in liver and kidney function tests.
Li, FQ (2012) [57]	March 2010–March 2012	113 participants, average 40 years old * Rome III	Pinaverium bromide, n = 38 Medilac-S, n = 31 Pinaverium bromide + Medilac-S, n = 44	2 caps. TID (3×10^9 cfu/d) For 2 weeks	Clinical efficacy (categorical scale).	All AEs were mild and self-resolving. Pinaverium bromide group (2 cases; nausea and loss of appetite), Medilac-S (1 case; nausea), combination group (1 case; dizziness).
Tao, YS et al. (2012) [58]	August 2008–August 2011	152 participants, 18–62 years old (average 40 y) Rome III	Trimebutine maleate, n = 66 Trimebutine maleate + Medilac-S, n = 86	2 caps TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	n.r.

Table 1. Cont.

Reference	Study Dates	Population, Age Diagnostic Criteria	Arms, n	Probiotic Regimen	Outcome Measures	Adverse Events
Liao, RB et al. (2011) [59]	August 2009–November 2010	98 participants, average 37.5 years old Rome III	Pinaverium bromide, n = 49 Pinaverium bromide + Medilac-S, n = 49	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	n.r.
Xu and Qiu (2015) [60]	January 2012–December 2014	457 participants (average 61 years old *) Rome III	Flupentixol + Melitracen + Pinaverium bromide, n = 152 Flupentixol + Melitracen + Pinaverium bromide + Medilac-S, n = 154 (Pinaverium Bromide + Medilac-S, n = 151)	2 caps. TID (3×10^9 cfu/d) For 2 weeks	Clinical efficacy (categorical scale).	Three subjects reported nausea and loss of appetite in the combination group, and three subjects from control group reported (nausea and dizziness).
Zhang, LF et al. (2010) [61]	June 2008–June 2009	123 participants, adults * Rome III	Amitriptyline, n = 39 Medilac-S, n = 41 Amitriptyline + Medilac-S, n = 43	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	n.r.
Chen, X (2008) [62]	January 2006–January 2008	144 participants, 22–73 years old (average 41.3 y) Rome II	Flupentixol + Melitracen, n = 46 Medilac-S, n = 48 Flupentixol + Melitracen + Medilac-S, n = 50	2 caps. TID (3×10^9 cfu/d) For 4 weeks	Clinical efficacy (categorical scale).	None observed. No abnormalities on kidney and liver function.

BID, twice a day; n.r., not reported; TID, three times per day; §, scoring according to Agachan et al. 1996 [63]; *, age range not specified. IBS-SSS, IBS Severity Survey Form Score; ‡, detailed symptom scores for abdominal pain, bloating, constipation, or diarrhea are presented in Table S1.

3.2. Probiotic Regimen and Standard IBS Medications

Most of the studies provided two capsules of Medilac-S three times per day (TID) before meals, resulting in a daily dose of 3 billion CFU, as reported previously for Medilac-S in IBS and other indications [21,22,64]. Supplementation was most frequently administered for 4 weeks, although the treatment durations varied between 1 and 12 weeks (Table 1). Only four studies included a follow-up period after treatment cessation; of these, only two reported on the reduction in recurrence rate in the combination group while the other two mentioned including the absence of recurrence in the markedly effective category definition. Typically, Medilac-S was provided as an adjuvant to a standard oral medication for IBS (Table 2). While intestinal adsorbents (smectite and montmorillonite powder) were used exclusively in IBS-D studies (n = 5), the laxative lactulose was used exclusively in IBS-C studies (n = 7 + 2 in combination with the gastroprokinetic agent mosapride). Gastroprokinetics, alone or in combination with lactulose, were used mainly in the IBS-C population (n = 3) but also in one study enrolling IBS-D participants with abdominal distension symptoms. Tricyclic antidepressants or antispasmodics were mainly used in IBS-D or in studies enrolling all subtypes.

Table 2. Conventional therapies used in included studies, per IBS subtype (n = 37).

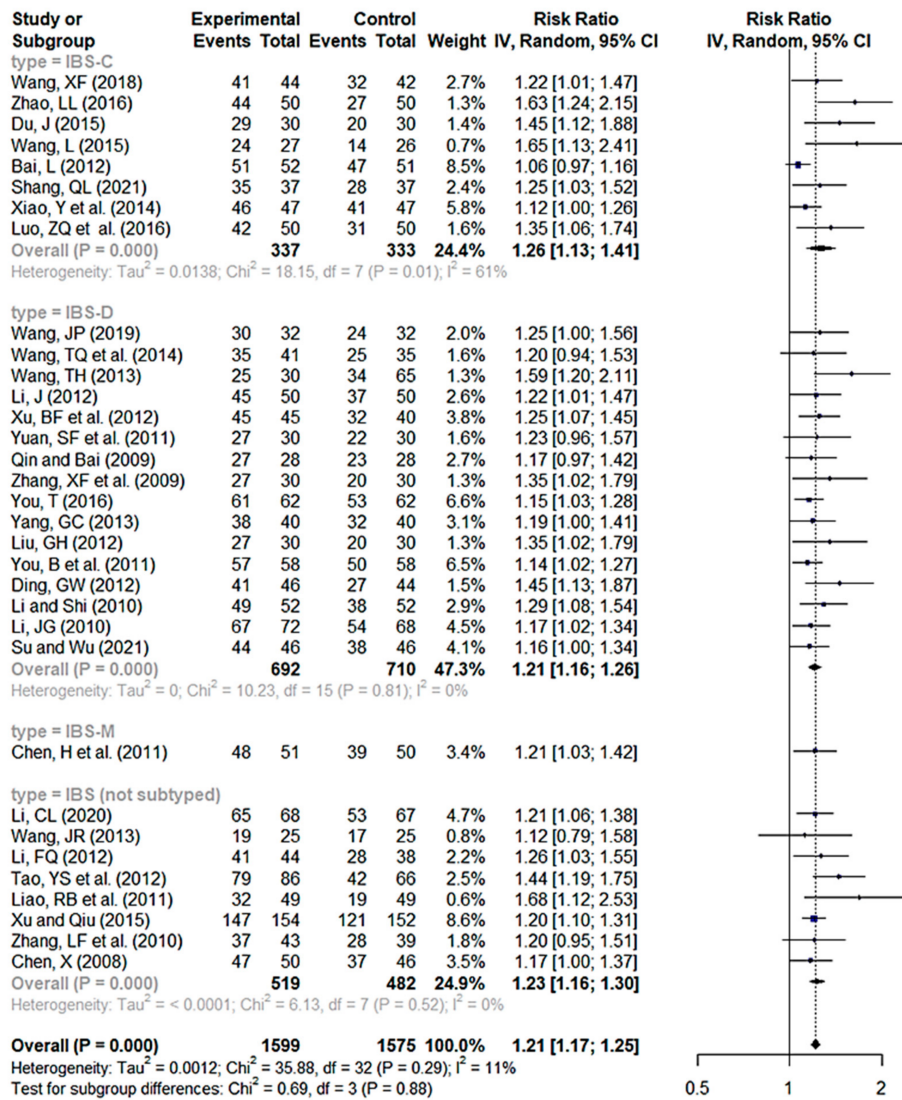
Concomitant Medication (Class; Main Mode of Action)	IBS-D	IBS-C	IBS-M	IBS (Not SubTyped)	Total
Smectite and Montmorillonite (Intestinal adsorbent; clays)	5				5
Trimebutine Maleate (Antispasmodic; antimuscarinic and weak μ -opioid receptor agonist)	5	1	1	3	10
Pinaverium Bromide (Antispasmodic; Ca^{2+} channel blocker)	3			2	5
Mosapride or Itopride (Gastroprokinetics; serotonin type-4 receptor agonist or antidopaminergic and anti-acetylcholinesterasic actions)	1 *	1			2
Lactulose (Laxative; osmotic)		7			7
Loperamide (Antidiarrheal; μ -opioid receptor agonist)	1				1
Doxepin or Amitriptyline (Tricyclic antidepressants (TCA))	1			1	2
Flupentixol + Melitracen (Antipsychotic + TCA)				1	1
Other combination of medications	1 ^a	2 ^b		1 ^c	4

*, IBS-D with abdominal distension; a, Flupentixol + Melitracen + Montmorillonite; b, Mosapride + Lactulose; c, Flupentixol + Melitracen + Pinaverium Bromide.

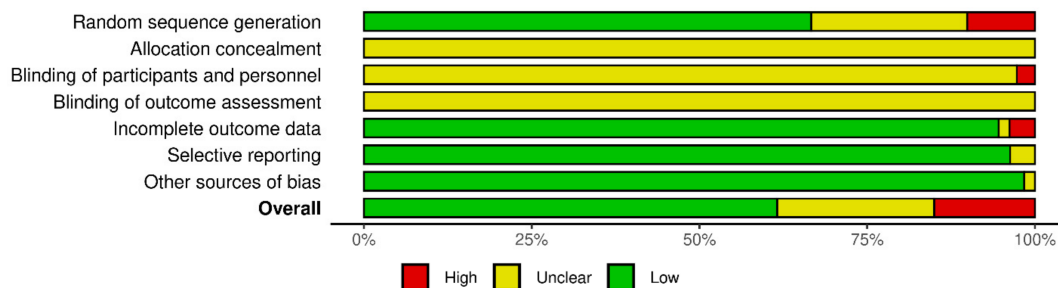
3.3. Meta-Analysis and Risk of Bias Analysis

Out of the 37 identified studies, 33 were included in the meta-analysis. These studies reported treatment efficacy rates using a categorical efficacy index (e.g., markedly effective, effective, or ineffective rates) based on the individual participants' scores attributed according to the clinical evaluation of symptoms. The number of participants in the markedly effective and effective categories (representing the total effective rate) versus ineffective were used to calculate relative risks (RR) with 95% confidence intervals (CI) for the meta-analysis (Figure 2A). The four studies that reported efficacy using individual symptom scores (continuous variable) were not included in the meta-analysis but are described below, in Section 3.4. Overall, the addition of Medilac-S to a standard IBS medication in-

creased the chance of treatment success, on average, by 21% (RR = 1.21; 95% CI: 1.17–1.25; $p < 0.0001$).



(a)



(b)

Figure 2. In all IBS subtypes, adjuvant Medilac-S administration improved the relative risk of standard treatment success in Chinese IBS patients. (a) Forest plot of the 33 studies, stratified by IBS subtype. Events refer to the number of participants included in the total effective rate (markedly effective + effective cases); total refers to the number of participants in the treatment (adjuvant Medilac-S) and control groups. (b) Weighted mosaic plot summarizing the risk of bias analysis of studies included in the meta-analysis. Generated using Robvis [65].

When considering all 33 studies, heterogeneity was present (11%) but not significantly ($p = 0.52$). Only the IBS-C subgroup displayed significant heterogeneity ($I^2 = 61\%$; $p = 0.01$), which appears to be driven by the variability amongst the five studies providing Medilac-S in combination with lactulose [28–31] (Figure 2). Both the IBS-D and IBS subgroups showed no heterogeneity ($I^2 = 0\%$).

Most studies were found to be at a low or unclear risk of bias, with four studies classified as a high risk of bias (Figure 2B) due to potential randomization [37,48], blinding (open RCT design) [43], or incomplete outcome data issues [41]. All but the open RCT study were classified as an unclear risk for allocation concealment and blinding because these steps were not described, as reported previously, which appears to be associated with regional reporting practices [22,66]. The funnel plot method was used to assess potential publication bias (Figure 3), and the asymmetry was significant (Egger's regression test; $t = 6.47$, $df = 31$, $p < 0.0001$) [67]. However, the trim-and-fill method by Duval and Tweedie [68] revealed that the addition of 13 studies to correct the asymmetry (Figure 3) did not affect the significance of the overall RR, which changed to 1.17 (95% CI: 1.13; 1.21; $p < 0.0001$).

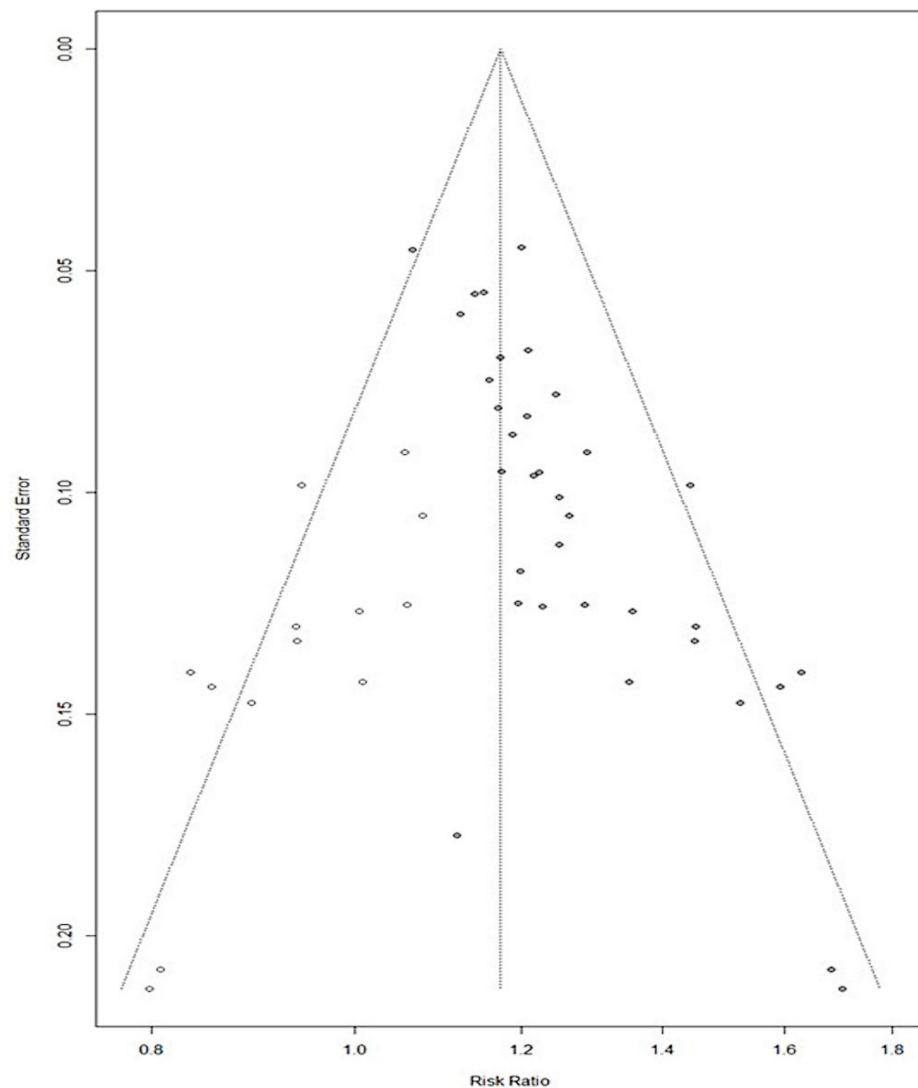


Figure 3. Funnel plot for publication bias, with trim-and-fill analysis. Black circles (on the right side) represent the actual studies and empty circles (on the left side) represent the studies that were added in the trim-and-fill analysis.

3.4. Other Outcome Measures of Efficacy

Among the 37 eligible studies, 4 studies (3 IBS-C and 1 IBS-D; included in Table 1) did not use the clinical efficacy scale (responder rate) to report outcomes and were therefore not included in the meta-analysis [34–36,53]. The three IBS-C studies compared the lactulose and lactulose + Medilac-S arms [34–36], but one of them also provided mosapride to all the participants [35]. Overall, the three studies reported a similar improvement in the Bristol Stool Scale scores between the groups [34–36], although two reported a superior improvement in the individual symptom scores in the Medilac-S adjuvant arms compared to standard treatment alone [34,36]. The IBS-D study provided Medilac-S in combination with Smecta and reported a superior improvement in symptoms in the Medilac-S adjuvant arm, as well as superior improvement in stool characteristics [53]. In addition, some studies used the categorical efficacy scale but also reported individual symptoms. These results are summarized in Table 1 and details on individual outcomes (when marked by a ‡) are provided in Table S1.

3.5. Subgroup Analysis of Studies with a Medilac-S-Only Arm

A subset of the studies in the meta-analysis also included a Medilac-S-only arm ($n = 17/33$) allowing an assessment of the effect of Medilac-S alone head-to-head with the standard therapy alone and the combination (Figure 4). This analysis, although not pre-planned, suggests that Medilac-S alone is not superior but also not significantly less effective than the standard treatments alone (active comparator). Except for pinaverium bromide, which did not reach significance in this subgroup analysis based on two studies ($p = 0.2506$), all the treatments were significantly more effective when provided in combination with Medilac-S (clays, $p = 0.0030$; lactulose, $p = 0.0004$; trimebutine maleate, $p = 0.0014$; and antidepressants/antipsychotics, $p = 0.0089$). This post-hoc subgroup analysis including a subset of eligible studies selected in an unbiased manner (based on the inclusion of a probiotic alone arm or not) supports the general conclusions that Medilac-S significantly enhances the efficacy of standard treatments when used as an adjuvant.

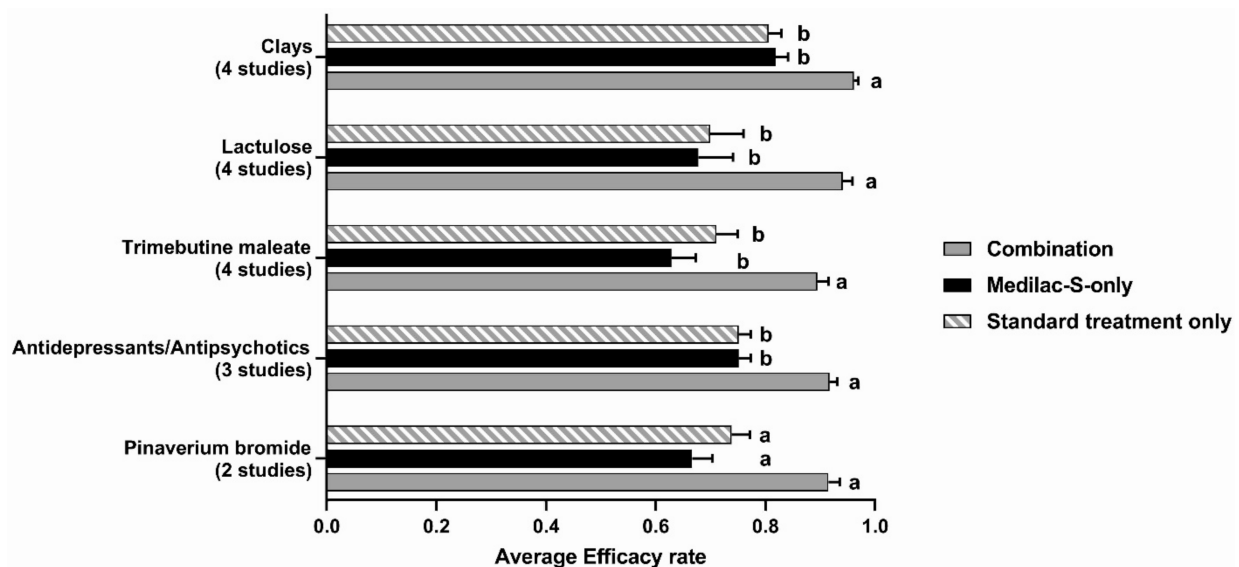


Figure 4. Comparison of effective rates by treatment in studies with a Medilac-S-only arm ($n = 17$). Statistically significant differences at $p < 0.05$ (within each standard treatment type) are represented by different letters.

3.6. Safety and Adverse Events

Out of the 37 included studies, 29 studies reported on adverse events (AEs). Among these, nine reported the absence of AEs in all groups [27,31,32,42,47,51,53,56,62] and one did not provide the exact number of AEs (“a few cases”) [44]. In 19 studies, AEs were de-

scribed as mild or self-resolving, or were resolved upon lowering the standard treatment dose [26,28–30,34,35,37,38,40,41,43,46,48,50,52,54,55,57,60]. The reported AEs included mild GI discomfort (diarrhea or constipation), nausea, dry mouth/thirst, vomiting, loss of appetite, dizziness, drowsiness, numbness of limbs, rash-like allergic reactions, or headache, many of which are known side effects of the various medication classes used (Table 2). The overall incidence of AEs was 5.9% (n = 1331) in the standard medication arms, 6.2% (n = 1347) in the combined Medilac-S and standard medication arms, and 1.8% (n = 595) in the Medilac-S-only arms, supporting the safety of Medilac-S in IBS populations treated with a variety of conventional therapies.

4. Discussion

Our meta-analysis of 33 studies resulted in a significant 21% increase in the likelihood of treatment effectiveness (RR = 1.21; 95% CI: 1.17–1.25; $p < 0.0001$) when Medilac-S is added as an adjuvant to conventional treatments, regardless of the subtype. Our results are in accordance with a previous systematic review from 2012, published in a Chinese journal [21], reporting a significant increase in IBS treatment efficacy with Medilac-S. However, Chen et al. (2012) included 15 studies assessing a variety of treatments (conventional, herbal medications, or Medilac-S alone), without a specific analysis of IBS subtypes [21]. These 15 studies were retrieved in our literature searches; however, only 8 of them were eligible according to our inclusion criteria [42–44,50,51,53,61,62]. Our meta-analysis includes 25 additional studies [26–33,37–41,45–49,52,54–60] strengthening the conclusion of the previous review by Chen et al. (2012) [21], and demonstrating that Medilac-S is safe and effective as an adjuvant to a variety of conventional, oral IBS treatments that are used in several countries.

Regarding the efficacy of Medilac-S in specific IBS subtypes, we found a significant level of heterogeneity among the IBS-C studies. This heterogeneity appears to be driven by the five studies providing Medilac-S in combination with lactulose. In Bai et al., 2012, the lactulose-only arm presented with a total effective rate of 92.2%, and the combination arm, 98.1%. The smaller difference in efficacy between the combination and control groups in that study results from the higher efficacy in the lactulose-alone arm compared to other studies using lactulose. Indeed, the average efficacy rate of lactulose-only arms in the other four studies is ~63% versus ~92% in the combination arms [27–30]. In addition, two IBS-C studies providing lactulose only were not included in the meta-analysis because they did not report outcomes using the same categorical efficacy rate scale as the other studies, which prevented the calculation of a comparable RR [34,35]. Both of these studies reported that the Bristol Stool Scale scores improved similarly between groups [34,35]. However, Yang et al., 2016, also reported a significantly superior improvement in constipation symptoms in the combination arm based on the Agachan et al., 1996, scoring method, which takes into account the frequency of bowel movements, painful evacuation, incomplete evacuation, abdominal pain, length of time per attempt, assistance for evacuation, unsuccessful attempts for evacuation per 24 h, and duration of constipation [34,63]. In addition, both IBS-C studies providing lactulose and mosapride in combination with Medilac-S also reported significantly superior improvements in symptom scores in the combination groups compared to the mosapride + lactulose arms [33,36]. Overall, we can conclude that the addition of Medilac-S to the laxative lactulose improves treatment efficacy in IBS-C, despite a significant heterogeneity brought by the Bai et al. 2012 study, in which the treatment efficacy was very high (>90%) in all groups [31]. Only one study enrolled participants with IBS-M. There was no heterogeneity amongst the IBS-D or IBS (not subtyped) studies despite the use of a variety of medications.

The different standard medication classes used in the studies included in the current review are generally also used to treat IBS symptoms in Western and European countries, including some laxatives, antidiarrheals, intestinal adsorbents, antispasmodics, and antidepressants [20,69,70]. Of course, the recommendations for specific molecules may differ according to the availability and approval of medications in each country. For example,

pinaverium bromide is not recommended by the AGA guidelines (not yet approved by the FDA), but this medication, which is currently approved in >60 countries including Canada, is recommended in the guidelines from several countries [20,69–71]. Similarly, trimebutine maleate is also recommended for IBS in some countries [71], but it is not FDA-approved. Osmotic laxatives, such as lactulose and polyethylene glycol, are also used as a first-line symptomatic treatment in IBS-C patients in several countries, although they are generally not recommended for chronic use in IBS as they do not help alleviate abdominal pain [72]. Moreover, with lactulose being a FODMAP that may cause bloating and gas in some patients, PEG is generally preferred to lactulose for compliance with a low-FODMAP diet [73]. The use of clay-type intestinal adsorbents against diarrhea is widespread, although not unanimous worldwide owing to the possible presence of elemental contaminants of toxic concerns naturally present in soils. The USA and Singapore have recommended not using certain bentonite clays, or restricted the indication of Smecta® to infants ≥ 2 years old and adults, while recommending against its use during pregnancy [74,75]. Smectite (also called dioctahedral smectite, diosmectite, bentonite, or montmorillonite) is an over-the-counter medication often recommended in Eastern Europe, France, and China for adults and children with acute diarrhea [76]. Assessing the efficacy of Medilac-S as an adjuvant to non-clay-type intestinal adsorbents could be of interest.

While the post hoc analysis of the efficacy of Medilac-S only (based on the 17 studies that included a Medilac-S-only arm) should be interpreted with caution, it shows that Medilac-S was not significantly less effective than the standard medications alone in this subset of studies (Figure 4). This analysis also confirms the general finding that the adjuvant effect of Medilac-S provides a significantly increased efficacy with most standard IBS medications. It is important to mention that the mechanisms behind the adjuvant effect of Medilac-S may differ depending on the standard medication administered. For example, the proposed mechanisms for the adjuvant effect with sulfasalazine in ulcerative colitis was that the probiotic strains expressing an azoreductase enzyme may help break down the pro-drug into its active moieties, thereby increasing treatment efficacy [22]. In IBS, the general mechanisms of action of the probiotic formulation may include its beneficial effects on the intestinal barrier integrity or inflammatory response as well as the synergistic activity with the conventional medications. For example, the strain *B. subtilis* R0179 was recently shown to exert prokinetic effects in a mouse model of constipation, which was associated with its ability to secrete the serotonin precursor tryptophan [77]. The probiotic formulation may also act by positively modulating the gut microbiota composition, as shown in mice and by in vitro fermentation with human fecal slurries [78–80].

A strength of this review is the high level of similarity in the design and dose between the included studies, which reduces heterogeneity. It is becoming recognized that, while informative in some contexts, the meta-analyses that include probiotics in general typically provide no specific guidance regarding which strains or doses are the most beneficial due to a high level of heterogeneity. More and more, recommendations indicate that probiotic strains should be assessed individually for their efficacy. Here, all the studies included an active comparator arm allowing to assess the adjuvant effect of a similar Medilac-S dose. Although the use of a placebo in controls could have been preferable, it is less likely to have influenced the results than in a study where probiotics are the only intervention. As typically observed in Chinese studies [22,64,66], the method used for allocation concealment and blinding are not described. However, most studies included herein reported using randomization methods, and the participants' flow and outcomes were well described. Overall, most of the included studies are generally shorter than the 8 weeks recommended by the FDA to assess the efficacy of IBS treatments; however, it is likely that a duration of 4 weeks or more (as seen in 29/37 studies; 78%) provides a sufficient amount of time to assess the effect of Medilac-S as an adjuvant to already validated conventional treatments. However, follow-up after treatment cessation was included in only four studies, with only two of them reporting on the recurrence rate. This point could be improved in future IBS studies with Medilac-S to obtain insights on its effect on symptom recurrence. Consider-

ing that the conventional medications in the included studies are not limited to Asia, it is likely that results could be extrapolated to Western and European populations. However, consideration should be given to the potential implication of genetic/ethnic background on drug metabolism, pharmacokinetics, or microbiota composition in the adjuvant effect of Medilac-S in IBS patients.

5. Conclusions

The results from this meta-analysis (RR = 1.21; 95% CI: 1.17–1.25; $p < 0.0001$) as well as the individual symptom scores support the conclusion that Medilac-S is a safe and effective adjuvant to IBS conventional medications. We also show that this formulation is as effective as an adjuvant with conventional medications in all subtypes.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/gastroent14040036/s1>, Table S1: Individual symptom scores.

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