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Viviana Fara Brindicci
University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII"
Vanessa Nadia Dargenio
University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII"
Giovanni La Grasta
University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII"
Stefania Paola Castellaneta
University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII"
Federico Schettini
Santissima Annunziata Hospital
Ruggiero Francavilla
ruggiero.francavilla@uniba.it

University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII"
Fernanda Cristofori
University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII"

Research Article

Keywords: Lactiplantibacillus plantarum 299v, Irritable Bowel Syndrome, Systematic Review, Meta-analysis, Probiotics, Abdominal Pain.

Posted Date: August 4th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10425498/v1

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Additional Declarations: No competing interests reported.

The Effects of Lactiplantibacillus plantarum 299v on Irritable Bowel Syndrome: A Systematic Review with Meta-analysis

Viviana Fara Brindicci[1,2,*], Vanessa Nadia Dargenio[1,*], Giovanni La Grasta[1], Stefania Paola Castellaneta[1], Federico Schettini[3], Ruggiero Francavilla[1] and Fernanda Cristofori[1]

1. Interdisciplinary Department of Medicine, Pediatric Section, University of Bari "Aldo Moro", Children's Hospital "Giovanni XXIII", 70126 Bari, Italy.
2. U.O.C. Pediatrics and Neonatology, San Paolo Hospital, ASL BARI, 70100 Bari, Italy.
3. Neonatology And Neonatal Intensive Care, Santissima Annunziata Hospital, 74121 Taranto, Italy.

* Both authors have equally contributed to the work and listed in alphabetic order, they should be considered joint first author.

Corresponding Author: Ruggiero Francavilla MD, PhD, Children's Hospital 'Giovanni XXIII', University of Bari "Aldo Moro", Via Giovanni Amendola, 207, 70126 Bari, Italy. E-mail: ruggiero.francavilla@uniba.it; ORCID number: 0000-0002-4603-974X

Author Contribution Information: V.F.B. and V.N.D. contributed equally to this work and share first authorship. Conceptualization, methodology and formal analysis: V.F.B., V.N.D., S.P.C., R.F.; investigation: V.F.B., V.N.D., G.L.G., F.S.; data curation, V.F.B., V.N.D., F.C.; original draft preparation, V.F.B., V.N.D.; writing-review and editing, R.F., V.N.D, F.C., V.F.B., G.L.G., S.P.C., F.S.; supervision, R.F. and F.C.. All authors have read and agreed to the published version of the manuscript.

Funding: None to declare.

Competing Interests: The authors have no competing interests to declare that are relevant to the content of this article. The funders had no role in the study's design, in the collection, analyses, or interpretation of data, in the writing of the manuscript, or in the decision to publish the results.

Data availability statement: The data presented in this study are available at the request of the corresponding author.

ABSTRACT

Background: *Lactiplantibacillus (L.) plantarum* 299v DSM 9843 is a probiotic strain that showed safety and properties potentially beneficial in managing irritable bowel syndrome (IBS).

Objective: To systematically review and meta-analyze the effects of *L. plantarum* 299v in participants of randomized controlled trials (RCTs) with IBS.

Materials and Methods: We searched PubMed/MEDLINE, Embase, Scopus, and the Cochrane Central Register of Controlled Trials. A meta-analysis was performed using a random-effects model, pooling the outcomes of abdominal pain, bloating/flatulence, constipation, global symptoms. The trial was registered in PROSPERO (registration number CRD420261322875).

Results: Six RCTs enrolling 527 adult patients with IBS were included. *L. plantarum* 299v significantly reduced abdominal pain scores (SMD = −2.16; 95% CI: −3.59 to −0.72; $p = 0.003$), abdominal pain severity (SMD = −0.39; 95% CI: −0.67 to −0.12; $p = 0.005$), daily abdominal pain frequency (SMD = −0.66; 95% CI: −1.02 to −0.30; $p = 0.0004$) compared with placebo. The improvement rates of abdominal pain (RR = 4.83; 95% CI: 1.94–11.99; $p = 0.0007$), bloating/flatulence (RR = 1.96; 95% CI: 1.06–3.61; $p = 0.03$) and global symptoms (RR = 4.69; 95% CI, 1.46–15.14; $p = 0.010$) were significantly higher in the probiotic group. No significant effect was observed for constipation (RR= 1.39; 95% CI, 0.32–6.11; $p = 0.66$).

Conclusion: Meta-analytic evidence supports the capacity of *L. plantarum* 299v to relieve abdominal pain, bloating, flatulence, and general symptoms. The observed diet-dependent response underscores the need for future research to investigate combined probiotic dietary interventions.

Keywords: *Lactiplantibacillus plantarum* 299v; Irritable Bowel Syndrome; Systematic Review; Meta-analysis; Probiotics; Abdominal Pain.

INTRODUCTION

Irritable bowel syndrome (IBS) is a multifactorial functional disorder of the gastrointestinal tract, whose pathogenesis involves a complex interplay between gut-brain axis dysregulation, visceral hypersensitivity, intestinal dysmotility, and alterations in gut microbiota composition [1,2].

Given the recognized role of microbial dysbiosis in disease onset and symptom perpetuation, probiotics have increasingly been considered a therapeutic strategy for restoring intestinal homeostasis [3].

Evidence from two Cochrane systematic reviews suggests a potential, albeit uncertain, benefit of probiotics in pediatric IBS and functional abdominal pain. An earlier review demonstrated that children with IBS treated with probiotics were significantly more likely to experience pain improvement at zero to three months post-intervention compared to placebo (OR 3.01, 95% CI 1.77–5.13) [4]. A more recent update concluded that probiotics and synbiotics may be more efficacious than placebo in achieving treatment success, although the overall certainty of the evidence remains low, and insufficient data preclude definitive conclusions regarding pain resolution, quality of life, and functional outcomes[3].

The role of probiotics in pediatric functional gastrointestinal disorders has been acknowledged in the international guidelines. In 2023, a position paper from the European Society for Paediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) issued weak recommendations, supported by moderate certainty of evidence, for *Lactobacillus reuteri* DSM 17938 and *Lactobacillus rhamnosus* GG in children with functional abdominal pain disorders and IBS, respectively [5]. The latest joint guidelines of ESPGHAN and North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) further supported this approach, conditionally recommending multistrain probiotics and synbiotics for functional abdominal pain disorders, and specifically endorsing *Lactobacillus rhamnosus* GG as a treatment option for pediatric IBS, based on moderate certainty evidence and a small but consistent effect size [6].

However, current guidelines still rate the overall quality of evidence as low to moderate, with strain-specific guidance available only for a small number of thoroughly investigated microorganisms. This highlights the need to explore additional probiotic candidates with well-characterized biological profiles and plausible mechanistic rationales for their efficacy in IBS. Among the strains investigated to date, *Lactiplantibacillus (L.) plantarum* 299v (DSM 9843) is a promising candidate, given its documented properties, including enhanced intestinal adhesion, modulation of gut microbiota composition, reduction of intestinal permeability, and anti-inflammatory activity [7]. However, despite its widespread commercial availability and increasing clinical use, a comprehensive and systematic appraisal of its efficacy in IBS is lacking. Therefore, this study aimed to address this gap using a two-step approach: first, a narrative review of the biological characteristics of *L. plantarum* 299v potentially relevant to IBS pathophysiology; and second, a systematic review and meta-analysis of randomized controlled trials (RCTs) evaluating its efficacy in patients with a confirmed diagnosis of IBS to provide a rigorous and updated synthesis of the available evidence. For consistency, the probiotic strain *Lactiplantibacillus plantarum* 299v (DSM 9843) is hereafter referred to as *L. plantarum 299v*.

1.1 Resistance And Adhesion Capacity

L. plantarum strains are frequently found in traditional plant-based fermented foods, such as olives, capers, sauerkraut, sourdough, and wine [8]. Various strains, including *L. plantarum 299v*, are common members of the normal intestinal microbiota in healthy adults [9].

L. plantarum 299v has been proven safe for human use, is free of side effects, and does not contribute to antibiotic resistance [7, 10]. In particular, *L. plantarum* 299v presents several biological properties that support its potential therapeutic use, especially in IBS [7, 11].

This strain survives passage through the gastrointestinal tract: indeed, it is able to resist both low pH in the stomach and high pH in the duodenum [12,13]. After gastrointestinal passage, this specific strain can adhere to and reside in the human colonic mucosa via a specific mechanism of mannose adhesion [7]. This interaction is mediated by an adhesin located on the bacterial cell wall, mannose-specific adhesin (MSA), which recognizes and binds to mannose residues expressed on the surface of intestinal epithelial cells, higher than other *Lactobacillus* spp. strains [14]. Such mannose-dependent adhesion facilitates close contact between the bacterium and host epithelium, promoting temporary colonization, persistence in the gut, and potential modulation of local physiological processes, while also contributing to the competitive exclusion of intestinal pathogens that bind to the same mannose receptor sites [7, 14, 15]. Notably, *L. plantarum* 299v has been re-isolated from fecal samples even more than ten days after the first day of administration and has exhibited antibacterial properties against multiple pathogenic agents [11, 13].

1.2 Immunomodulatory Features

L. plantarum 299v also fortifies the innate immune defenses of the gut-associated lymphoid tissue (GALT) by enhancing the production of the protective mucin barrier [16]. Recent experimental investigations have revealed that *L. plantarum* 299v stimulates both transcription and excretion of the mucin glycoproteins MUC2 and MUC3 in intestinal goblet cells[17]. In particular, *L. plantarum* 299v upregulates MUC2 and MUC3 mucin gene expression through an adherence-dependent mechanism mediated by its mannose-specific adhesin. This enhanced transcription correlates with extracellular mucin secretion, which subsequently inhibits adherence of enteropathogenic *E. coli* to intestinal epithelial cells [16, 17]. The rapid response (within one hour) suggests that mucin upregulation represents an inducible innate immune defense mechanism of intestinal epithelial cells against beneficial microbes [17].

Of particular significance are the immunomodulatory properties of *L. plantarum* 299v. Research indicates that this strain can beneficially regulate the immune response, primarily through the upregulation of the anti-inflammatory cytokine interleukin-10 (IL-10) [11]. Studies conducted on mononuclear cells isolated from the inflamed colonic mucosa of ulcerative colitis patients have shown that *L. plantarum* 299v stimulates IL-10 secretion by both macrophages and T-cells without triggering a parallel increase in pro-inflammatory mediators such as IL-1β, TNF-α, or IFN-γ [18]. This selective cytokine profile suggests that this strain may promote immune tolerance and help contain dysregulated inflammatory responses in the gut [18].

The immunomodulatory properties of *L. plantarum* 299v extend to the adaptive immune compartment [19]. In particular, this strain has been found to upregulate CD25 and HLA-DR [20] on both CD4+ and CD8+ T lymphocytes, with CD8+ cells showing the most marked response. The fact that activation and memory markers were broadly upregulated across the entire CD8+ population, rather than within a defined antigen-specific subset, points to a non-clonal mechanism of immune activation [19]. These observations suggest that *L. plantarum* 299v enhances T-cell responsiveness, at least in part, by activating antigen-presenting cells [19].

1.3 Gut Permeability

L. plantarum 299v contributes to maintaining gut barrier integrity by reducing paracellular permeability [21]. This capability was initially demonstrated in a 1996 study, where the strain effectively counteracted increased permeability in a rat model of methotrexate-induced colitis [22]. Subsequent research has broadly supported the role of *Lactobacilli* in mitigating such permeability, which can be triggered by diverse insults, including cytokines, chemicals, and pathogens [21]. Specifically, *L. plantarum* 299v enhances the structural integrity of the intestinal epithelium by directly upregulating key tight junction proteins, namely zonula occludens-1 (ZO-1) and occludin, thereby fortifying the paracellular seal [23]. This capacity has been demonstrated by Mangell et al. through experiments in the rat intestine, which conclusively demonstrated that sustained pretreatment with *L. plantarum* 299v prevents *E. coli*-induced intestinal permeability in rats, while short-term or intermittent administration shows no protective effect [24].

1.4 Gut Microbiota And Metabolites

L. plantarum 299v significantly influenced the gut microbiota composition and metabolic output. Johansson et al. provided direct evidence that sustained consumption of *L. plantarum* 299v significantly modulates the colonic environment in healthy humans [25]. Their randomized, double-blind, controlled trial demonstrated that ingestion of a rose-hip drink containing *L. plantarum* 299v for 3 weeks led to a statistically significant increase in fecal concentrations of total carboxylic acids, acetic acid, and propionic acid compared to the control group. This shift may indicate enhanced fermentation in the colon. The researchers also documented a significant reduction in the number of sulphite-reducing clostridia and a notable improvement in bowel function, characterized by increased stool volume and decreased flatulence in the probiotic group. Crucially, Johansson et al. confirmed the strain's ability to survive gastrointestinal transit and recovered high levels of *L. plantarum* 299v in the feces of all subjects in the treatment group. Collectively, the findings of this study underscore that *L. plantarum* 299v intake directly enhances short-chain fatty acid (SCFAs) production, beneficially modulates the gut microbiota, and improves gastrointestinal comfort [25]. In another RCT, Wullt et al. investigated the impact of *L. plantarum* 299v on fecal SCFAs levels during metronidazole therapy in 19 patients with *Clostridium difficile*–associated diarrhea. Following antibiotic treatment, total SCFAs significantly decreased only in the placebo group; therefore, supplementation with this probiotic may mitigate the side effects of antibiotics on gut microbiota and metabolic profiles [26].

MATERIALS AND METHODS

2.1 Protocol and Reporting

This systematic review and meta-analysis was conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [27] and adhered to the standards outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines [28]. The protocol was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD420261322875).

2.2 Search Strategy

PubMed/MEDLINE, Embase, Scopus, and CENTRAL were the databases utilized for our literature research, up to January 2026, without any restrictions.

The search strategy combined Medical Subject Headings (MeSH) terms with free-text keywords. The search terms applied were ("*Lactiplantibacillus plantarum* 299v" OR "*Lactobacillus plantarum* 299v" OR "LP299v" OR "DSM 9843") AND ("irritable bowel syndrome" OR "IBS" OR "functional bowel disorder") AND ("randomized controlled trial" OR "RCT" OR "clinical trial"). In addition, the reference lists of all retrieved full-text articles and relevant review articles were screened to identify any additional eligible citations. The full search strategy for each database is provided in Supplementary Material 1.

2.3 Eligibility Criteria

We considered only randomized, double-blind, placebo-controlled trials involving patients with a confirmed diagnosis of IBS. No restrictions were applied with respect to participant age, article language, or date of publication. The intervention of interest was *L. plantarum* 299v (DSM 9843) administered as a single-strain preparation, compared with placebo. Studies were required to report at least one clinical outcome of IBS. Trials were excluded if they were non-randomized or non-placebo-controlled, without reported clinical outcomes, or if they used multi-strain probiotic formulations in which the contribution of *L. plantarum* 299v could not be separately assessed.

2.4 Outcomes

The primary outcomes were as follows: (i) change in abdominal pain scores from baseline to the end of the intervention period; (ii) improvement in abdominal pain severity scores; (iii) daily frequency of abdominal pain relief, defined as the proportion of patients reporting adequate relief of abdominal pain over the treatment period; (iv) abdominal pain improvement rate; and (v) overall improvement in global symptoms, assessed by patient global assessment or equivalent composite measure. Secondary outcomes included changes in individual symptoms (bloating, flatulence, stool frequency, and stool consistency), quality of life, and incidence of treatment-related side effects.

2.5 Study Selection

The study selection was conducted independently by two authors (V.F.B. and V.N.D.), screening all retrieved records sequentially by titles, abstracts, and full-text articles against the eligibility criteria. Any discrepancies were initially addressed through discussions between the two reviewers. A third senior investigator (R.F.) was consulted to provide a final determination in cases where consensus between the two investigators could not be reached.

2.6 Data Extraction

The extracted data were collected using a Microsoft Excel spreadsheet. For each included study, the following variables were systematically collected: study design, country, sample size, patient characteristics, diagnostic criteria used, intervention dose and formulation, treatment duration, comparator, primary and secondary efficacy outcomes and their measurement instruments, and adverse events (AEs). Data extraction was conducted independently by two investigators (V.F.B. and V.N.D.) to minimize any bias. Any discrepancies were resolved through discussion and, when necessary, by consulting a third senior investigator (R.F.). Missing or incomplete data were recorded as "not available" (N/A).

2.7 Risk of Bias Assessment and Quality of Evidence

The risk of bias was assessed using the Cochrane Risk of Bias tool (RoB 2.0). The following domains were evaluated for each study: randomization process, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, missing outcome data, and selection of reported results. Each domain was rated as having a low, unclear, or high risk. An overall risk of bias judgment was assigned to each study based on domain-level ratings. Discrepancies between the reviewers (V.F.B. and V.N.D.) were resolved through discussion and, when necessary, consultation with a third reviewer (R.F.). The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) framework was employed to assess the certainty of the evidence for both primary and secondary outcomes [29]. Evidence was evaluated across five domains: risk of bias, inconsistency, indirectness, imprecision, and publication bias, and classified as high, moderate, low, or very low certainty.

2.8 Statistical Analysis

The systematic review has been conducted with a qualitative analysis of the eligible RCTs. The Review Manager (RevMan, version 7.2.0) was used for statistical analysis of the meta-analysis. Dichotomous outcomes (relief of abdominal pain over the treatment period) were assessed on a per-protocol basis and expressed as relative risk (RR) with 95% confidence intervals (CIs). Continuous outcomes were pooled using standardized mean differences (SMDs) with 95% CIs. A DerSimonian and Laird random-effects model was used for the meta-analysis to account for the expected clinical and methodological heterogeneity. Between-study heterogeneity was evaluated using Cochran's Q test and quantified with I^2; $I^2 > 50\%$ or a Q-test p-value < 0.05 was considered indicative of substantial heterogeneity [30]. To enhance precision with a limited number of studies, the Hartung-Knack-Sidik-Jonkman (HKSJ) adjustment was applied to 95% CIs. Sensitivity analyses were performed to evaluate the robustness of the pooled estimates by iteratively excluding each study. Publication bias was assessed using funnel plot inspection and Egger's regression test. Statistical significance was set at $p < 0.05$ for all tests.

RESULTS

3.1 Study Selection and Risk of Bias Assessment

After removing duplicates and non-eligible studies, six RCTs [10,11,31–34] were included in this review (Figure 1). A further publication by Stevenson et al. (focusing on fecal microbiota and dietary correlates) was excluded because it was conducted on a subset of participants from the previous RCT[10,35]. The risk of bias assessment revealed an overall acceptable methodological quality profile across the included studies (Figure 2). Using the GRADE framework, the overall certainty of evidence was rated from moderate to high for both the primary and secondary outcomes mainly due to heterogeneity (full details in Supplementary Table 1).

3.2 Study Characteristics

The six included studies enrolled a total of 527 adult participants (intention-to-treat). No pediatric trials have been conducted. Treatment duration ranged from 4 (4 RCTs [11,31–34]) to 8 weeks (1 RCT [10]). All the studies were placebo-controlled. One study was a double-blind, placebo-controlled, crossover trial and was not considered since paired data, required for the meta-analysis, were not available [33] (Figure 1). Some included trials enrolled patients with heterogeneous IBS subtypes, including both constipation-predominant (C-IBS) and diarrhea-predominant (D-IBS) [10,31,34]. Ducrotté et al. reported only the percentage of patients with D-IBS without providing additional details regarding the proportions of C-IBS or mixed-type IBS participants [11]. In the remaining studies, no information regarding the IBS subtype of participants was reported [32,33]. The diagnosis of IBS was made using the Rome criteria I [32], II [10,33], and III [11,34], with the exception of Niedzielin et al., who used the Manning criteria [31]. One study administered a daily probiotic dose of 6×10^{9} CFU [33], two studies administered 1×10^{10} CFU [10,11], two studies administered 2×10^{10} CFU [31, 32], and one study used a higher dose of 5×10^{10} CFU per day [34]. The details of the qualitative analysis are presented in Table 1.

3.3 Meta-analysis of Efficacy for IBS

Change in abdominal pain score

The analysis to evaluate the effect of *L. plantarum* 299v on abdominal pain severity in patients with IBS included three studies [10,32,34], comprising 120 patients in the probiotic group and 105 patients in the placebo group (Figure 3). The pooled analysis demonstrated an SMD in abdominal pain scores of -2.16 (95% CI −3.59 to −0.72) in favor of the probiotic group, indicating a significant overall effect ($p = 0.003$). However, substantial statistical heterogeneity was observed across the included studies ($I^2 = 94\%$). Sensitivity analysis excluding the outlier study [32] yielded a pooled SMD of −1.16 (95% CI: −1.49 to −0.84; $p < 0.00001$) with no heterogeneity ($I^2 = 0\%$). This effect remained statistically significant and consistent across the remaining studies. The test for funnel plot asymmetry was not statistically significant (t = -4.533, df = 2, $p = 0.1382$), although the p-value approached the conventional threshold. The limit estimate as the standard error approached zero was b = 1.4003 (95% CI: -8.1525 to 10.9531).

Abdominal pain severity scores

In the pooled analysis, *L. plantarum* 299v significantly reduced abdominal pain severity scores compared with placebo (SMD = −0.39, 95% CI: −0.67 to −0.12, $p = 0.005$), with low heterogeneity across the three studies ($I^2 = 38\%$; Figure 4).

Daily frequency of abdominal pain

Compared with placebo, *L. plantarum* 299v was associated with a significant reduction in daily abdominal pain frequency (SMD −0.66, 95% CI −1.02 to −0.30; $p = 0.0004$). Heterogeneity was moderate ($I^2 = 57\%$; Figure 5).

Abdominal pain improvement rate

L. plantarum 299v was associated with a significantly higher rate of abdominal pain improvement than placebo (RR 4.83, 95% CI 1.94–11.99; $p = 0.0007$). However, significant heterogeneity was observed ($I^2 = 71\%$; Figure 6).

Bloating/Flatulence improvement rate

Two RCTs including a total of 85 participants with bloating/flatulence (43 in the *L. plantarum* 299v group and 42 in the placebo group), were analyzed to evaluate the effect of probiotic treatment on bloating/flatulence rate [31,32]. The pooled analysis showed a statistically significant reduction in bloating favoring *L. plantarum* 299v compared with placebo (RR = 1.96, 95% CI 1.06–3.61, $p = 0.03$). Heterogeneity was low ($I^2 = 0\%$), supporting the consistency of the treatment effect across studies (Figure 7). Overall, these findings suggest that *L. plantarum* 299v is associated with a significant improvement in bloating/flatulence symptoms compared with the placebo.

Constipation improvement rate

Two RCTs including 32 participants (15 in the *L. plantarum* 299v group and 17 in the placebo group), were analyzed to evaluate the effect of probiotic treatment on the constipation improvement rate [31,32]. The pooled analysis showed no statistically significant difference between the groups (RR = 1.39, 95% CI 0.32–6.11; $p = 0.66$). Individually, one study [31] suggested a trend toward benefit (RR = 3.30, 95% CI, 0.85–12.75), while the other [32] showed no effect (RR = 0.72, 95% CI, 0.32–1.60). There was substantial heterogeneity across the studies ($I^2 = 72\%$, $p = 0.06$; Figure 8), indicating variability in the study results. Overall, the current evidence does not support a significant improvement in constipation rates following treatment with *L. plantarum* 299v compared to placebo.

Global symptomatology improvement rate

Three RCTs were analyzed to evaluate the effect of *L. plantarum* 299v on the rate of improvement in general digestive symptoms in patients with IBS [11,31,32]. The pooled analysis showed a statistically significant benefit favoring *L. plantarum* 299v compared with placebo (RR = 4.69, 95% CI 1.46–15.14), with an overall effect significantly different between the groups ($p = 0.010$; Figure 9). However, there was substantial heterogeneity across studies ($I^2 = 84\%$), indicating considerable variability in the treatment effect magnitude. Given the high heterogeneity, a sensitivity analysis was performed excluding the study by Nobaek et al. [32], which showed a smaller and non-significant effect (RR 1.70 [95% CI 0.78–3.69]). After exclusion, the pooled analysis included two trials [11,31] with 244 participants (125 in the *L. plantarum* 299v group and 119 in the placebo group). The pooled RR was 8.54 (95% CI 4.85-15.04), with a significant test for the overall effect ($p < 0.00001$). Heterogeneity was negligible ($I^2 = 0\%$), supporting the consistency of the large treatment effect across these two studies.

Overall, while the inclusion of all three trials suggests a significant benefit with substantial heterogeneity, the sensitivity analysis indicates that *L. plantarum* 299v is associated with a robust and consistent improvement in general digestive symptoms in IBS when considering the two studies with a lower risk of variability [11,31].

3.4 Safety

Adverse events were rare and mild in all the included trials. The overall tolerability of *L. plantarum* 299v was good.

DISCUSSION

This meta-analysis and systematic review, which examined six RCTs [10,11,31-34], indicates that *L. plantarum* 299v, in adults suffering from IBS, alleviates abdominal pain in terms of severity, frequency, and improvement rate, as well as bloating, when compared to a placebo. It did not show any advantage for constipation, and there was notable variability in several outcomes.

In terms of the main outcomes, probiotics consistently showed greater effectiveness than placebo in alleviating abdominal pain [10,32,34]. This was evident across various measures: a change in pain score (SMD = −2.16), severity (SMD = −0.39), daily frequency (SMD = −0.66), and improvement rate (RR = 4.83). All these comparisons were statistically significant. There was a marked improvement in patients experiencing bloating and flatulence, with a RR of 1.96 [31,32]. The overall symptomatology indicated a significant treatment effect, especially evident following the sensitivity analysis [11,31,32]. By omitting the study by Nobaek et al.[32] from the sensitivity analyses, the heterogeneity was significantly reduced, leading to results that were more consistent and easier to interpret. In the case of constipation, *L. plantarum* 299v did not show any advantage over a placebo [31,32]. The interpretation of this result was hindered by significant variability and a small sample size. This inconsistency probably indicates genuine differences among studies concerning patient profiles, dosing schedules, and outcome assessments, rather than mere random statistical variations.

On the whole, *L. plantarum* 299v appears to offer clinically relevant benefits for abdominal pain and bloating in IBS. However, larger, methodologically homogeneous trials are needed before firm conclusions can be drawn. These results are consistent with previous meta-analytic evidence.

A recent systematic review and meta-analysis by McFarland et al. provided a strain-specific evaluation of probiotics for IBS, identifying *L. plantarum* 299v as an effective strain [36]. In this meta-analysis, *L. plantarum* 299v demonstrated significant efficacy specifically for the frequency of abdominal pain relief (RR=4.6, 95% CI 1.9–11.0, $p = 0.001$), an outcome that was not assessed in the two neutral trials [10,33,36]. The heterogeneity in outcome measures used across trials, with Stevenson et al. reporting only changes in pain scores rather than pain relief frequency [10], and Sen's study lacking this specific endpoint [33], limits direct comparison but does not exclude the strain's efficacy for IBS symptoms. The study concluded that *L. plantarum* 299v is one of six single-strain probiotics with robust evidence supporting its use for at least one specific IBS symptom [36].

A more recent strain-specific systematic review and meta-analysis by Maslennikov et al. further supported the efficacy of *L. plantarum* 299v (DSM 9843) in IBS [37]. Incorporating six RCTs, the meta-analysis demonstrated that this strain significantly reduced the severity of abdominal pain and feelings of incomplete evacuation/disordered defecation. Notably, while Maslennikov et al. did not find a significant effect on bloating, our pooled analysis showed a benefit (RR 1.96; 95% CI 1.06–3.61). This discrepancy may reflect differences in the included studies: indeed, our analysis specifically measured bloating improvement rate, whereas Maslennikov et al. used continuous severity scores from a different set of studies [37]. Analyses exhibited varying levels of heterogeneity, with I^2 values spanning from 0.0% to 92.1%. This variation is likely attributable to discrepancies in outcome definitions, the length of treatment, and characteristics of participants. The occurrence of adverse effects was similar in both the probiotic and placebo groups, indicating that the probiotic has a satisfactory safety profile. Among five probiotic strains (particularly along with *Bifidobacterium longum* 35624, *Lactobacillus rhamnosus* GG, *Saccharomyces cerevisiae* CNCM I-3856, and *Bacillus*

coagulans Unique IS2), *L. plantarum* 299v was recognized as having meta-analytic evidence supporting its effectiveness in alleviating IBS symptoms [37].

A critical factor that may explain the heterogeneity observed across trials is the patients' baseline diet. Supporting this hypothesis, Ducrotté et al. reported that vegetarian patients with IBS experienced greater abdominal pain relief with *L. plantarum* 299v than non-vegetarians, suggesting that habitual dietary patterns may modulate the clinical efficacy of the strain [11]. This observation is particularly relevant given that patients with IBS frequently adopt dietary modifications to manage their symptoms, most notably a diet low in fermentable oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs) [38].

Johansson et al. demonstrated that *L. plantarum* 299v enhances colonic fermentation, as reflected by increased fecal concentrations of SCFAs, including acetate and propionate [25]. However, because the availability of fermentable substrates - and consequently SCFA production - may be diminished under a low-FODMAPs regimen [39], it remains uncertain whether probiotics can sustain SCFA synthesis under such restrictive dietary conditions. Johansson et al.'s findings were obtained in the absence of dietary restrictions, leaving this potential compensatory effect speculative. Accordingly, future RCTs are warranted to directly investigate whether combining *L. plantarum* 299v supplementation with a low-FODMAPs diet yields synergistic or additive benefits for IBS management.

However, this hypothesis has not yet been tested in IBS patients and empirical research is needed [40]. Therefore, the interaction between diet and probiotics may offer a new perspective for understanding the variability and formulating long-term management plans for IBS. To date, no study has yet specifically assessed the effects of combining *L. plantarum* 299v with dietary protocols. Future studies should explore whether integrating these approaches results in better outcomes than using each one separately. Moreover, standardizing outcome measures across RCTs would facilitate more reliable comparisons.

The generalizability of our findings is constrained by substantial between-study heterogeneity (I^2 ranging from 57% to 94% for several outcomes), which likely reflects variability in probiotic dosage (6×10^9 to 5×10^{10} CFU daily), treatment duration (4 to 8 weeks), diagnostic criteria (Manning versus Rome I–III), and, most critically, differences in outcome definitions and dietary patterns across study populations, as suggested by the diet-dependent response observed by Ducrotté et al. [11]. To account for this heterogeneity, we examined the consistency of the pooled effect estimates. For instance, the very high heterogeneity observed for the change in abdominal pain score indicates that the true effect in a future study could vary from a substantial benefit to no effect, thereby precluding a definitive conclusion regarding the consistency of the treatment effect. Consequently, these results should be interpreted as hypothesis-generating rather than confirmatory results. Future trials should adopt standardized outcome measures, stratify patients by dietary habits and IBS subtypes, and explore dose-response relationships to reduce heterogeneity and identify optimal responder populations.

The primary strength of this meta-analytic review lies in its specific emphasis on the *L. plantarum* 299v strain. Moreover, the integration of a biological background provides a mechanistic context for clinical outcomes. However, this study has several limitations. In particular, the small number of eligible trials (n=6) restricts the statistical power of the pooled estimates. The considerable variation in results among studies suggests methodological, population, and outcome differences in RCTs. Moreover, all trials exclusively involved adult participants with IBS.

In conclusion, the analysis of combined data from six RCTs reveals that *L. plantarum* 299v outperforms a placebo in alleviating abdominal pain (in terms of severity, frequency, and response rate) and bloating in adults with IBS, while maintaining a positive safety profile. However, no impact on constipation was observed. Due to the notable

heterogeneity, the evidence suggests a conditional recommendation for using *L. plantarum* 299v as an additional treatment, especially for patients experiencing pain and bloating. Future studies should progress beyond confirmatory trials, aim to standardize outcomes across different studies, investigate also the pediatric population, and explore mechanistic questions, such as the interaction with diet.

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Table Legend

Table	Description
Table 1	Characteristics of the included randomized controlled trials about the effect of L. plantarum 299v in patients affected by irritable bowel syndrome

Figure Legend

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Figure 1	PRISMA 2020 flow diagram illustrating the study selection process
Figure 2	Risk of bias assessment for the randomized controlled trials included in the systematic review with meta-analysis. Figure 2(a): summary of review authors' judgments across seven domains of the Cochrane Risk of Bias tool for each included study. Green circles indicate low risk of bias, yellow circles indicate unclear risk, and red circles indicate high risk. Figure 2(b): proportion of studies rated as low, unclear, or high risk of bias for each domain
Figure 3	Forest plot of standardized mean differences (SMD) in abdominal pain scores between *Lactiplantibacillus plantarum 299v* and placebo groups. Individual study effects are shown as green squares with 95% confidence intervals (CIs). The pooled effect size is represented by the black diamond, indicating a significant reduction in pain scores favoring *L. plantarum 299v* (SMD = -2.16, 95% CI [-3.59, -0.72], P = 0.003). High heterogeneity was detected (I^2 = 94%)

Figure 4	Forest plot comparing the effect of *Lactiplantibacillus plantarum 299v* versus placebo on abdominal pain severity scores. The pooled estimate (black diamond) shows a significant reduction in abdominal pain severity scores favoring *L. plantarum 299v* (SMD = -0.39; 95% CI: [-0.67, -0.12]; P = 0.005). Moderate heterogeneity was observed (I2 = 38%)
Figure 5	Forest plot comparing the effect of *Lactiplantibacillus plantarum 299v* versus placebo on the daily frequency of abdominal pain. The pooled estimate (black diamond) shows a significant effect favoring *L. plantarum 299v* (SMD = -0.66; 95% CI: [-1.02, -0.30]; P = 0.0004). Moderate-to-high heterogeneity was observed (I2 = 57%)
Figure 6	Forest plot comparing the effect of *Lactiplantibacillus plantarum* 299v versus placebo groups on abdominal pain improvement rate. The pooled estimate (black diamond) shows a significant effect favoring *L. plantarum* 299v (RR = 4.83; 95% CI: [1.94, 11.99]; *P* = 0.0007). High heterogeneity was observed (I^2 = 71%)
Figure 7	Forest plot comparing the effect of *Lactiplantibacillus plantarum* 299v versus placebo groups on bloating/flatulence improvement rate. The pooled estimate (black diamond) shows a significant effect favoring *L. plantarum* 299v (RR = 1.96; 95% CI: [1.06, 3.61]; *P* = 0.03). No heterogeneity was observed (I^2 = 0%)
Figure 8	Forest plot comparing the effect of *Lactiplantibacillus plantarum* 299v versus placebo groups on constipation improvement rate. The pooled estimate (black diamond) shows no significant difference between the groups (RR

	= 1.39; 95% CI: [0.32, 6.11]; *P* = 0.66). High heterogeneity was observed (I^2 = 72%)
Figure 9	Forest plot comparing the rate of global improvement of digestive symptoms in irritable bowel syndrome between *Lactiplantibacillus plantarum* 299v and placebo groups. The pooled estimate (black diamond) shows a significant effect favoring *L. plantarum* 299v (RR = 4.69; 95% CI: [1.46, 15.14]; *P* = 0.010). High heterogeneity was observed (I^2 = 84%)

Supplementary Materials Legend

Supplementary Material	**Description**
Supplementary Material 1	Full search strings strategy utilized for each database for the selection of randomized controlled trials.
Supplementary Table 1	GRADE assessment of the certainty of evidence for each outcome.

Table 1. Characteristics of the included randomized controlled trials about the effect of L. plantarum 299v in patients affected by irritable bowel syndrome

Authors and year	Country	Age definition	Female (n, %)	Total patients (n, ITT/PP)	Control patients (n, ITT, PP)	Intervention patients (n, ITT, PP)	IBS type	Intervention	Total duration of intervention	Outcomes	Effect of interventions
Niedzielin et al. 2001	Poland	27 - 63 years	32, 80%	40, 40	20, 20	20, 20	Control group: - C-IBS: 11 patients (55%) - D-IBS: 0 patients - M-IBS: 9 patients (45%) Intervention group: - C-IBS: 10 patients (50%) - D-IBS: 1 patient (5%) - M-IBS: 9 patients (45%)	Test product: ProViva (Skanemejerier Sweden), a fruit drink containing 5% of an oatmeal soup fermented with *L. plantarum 299V* (DSM 9843) at a concentration of $5x10^7$ CFU/ml 200 ml twice a day: before breakfast and 2 h after the evening meal. $2×10^{10}$ CFU daily.	4 weeks	Assessment of IBS symptom: pain, constipation, diarrhea and flatulence	100% of intervention patients with abdominal pain resolution (p=0.0012). 95% of intervention patients with global symptom relief vs 15% in the control group (p<0.0001). C-IBS costipation improvement: 60% in intervention group vs 18% control group (p=0.048). 84% of control patients still suffered a pain at the end of the study.
Ducrotté et al. 2012	India	18-70 years	63, 29%	214, 204	106, 99	108, 105	Control group: - C-IBS: n/a - D-IBS: 63 patients, (60.3%) - M-IBS: n/a Intervention group: - C-IBS: n/a - D-IBS: 69 patients (63.89%) - M-IBS: n/a	Test product: 10 billion CFU of *L. plantarum 299V* (DSM 9843) per capsule in a potato starch and magnesium stearate base. One capsule daily. $1×10^{10}$ CFU daily.	4 weeks	Primary endpoint: the improvement of the frequency of abdominal pain episodes. Secondary endpoints: changes in severity of abdominal pain, changes in frequency and severity of abdominal bloating and in feeling of incomplete rectal emptying.	A significant decrease in the intervention group of abdominal pain frequency, stool frequency, bloating and feeling of incomplete emptying (p<0.05). The severity of the abdominal pain in the intervention group was lower in the vegetarians than in the non-vegetarians at weeks 2, 3 and 4 (p<0.05)

Nobaek et al. 2000	Sweden	>18 years	36, 60%	60, 52	30, 27	30, 25	n/a	Test product: 400 ml per day of a rose-hip drink containing $5x10^7$ CFU/ml of *L. plantarum 299V* (DSM 9843) and 0.009 g/ml oat flour. 400 ml once a day. $2×10^{10}$ CFU daily.	4 weeks	Parameters studied each day: number of defecations, fecal consistency, presence or absence of abundant gas. Record once a week of overall GI function (perfect–worst), defecation function (perfect–worst), pain (no pain–worst), and flatulence (no flatulence–worst) on VAS. Evaluation of clinical symptom at 12 months.	In the intervention group a significant decrease of flatulence (p<0.05). In the intervention group a significant improvement of overall GI and defecation function on the VAS (p< 0.01). Long-term effect of the improvement (at 12 months) in the intervention group.
Stevenson et al.	South Africa	>18 years	79, 98%	81, 65	27, 25	54, 40	Control group: - C-IBS: n/a - D-IBS: n/a - M-IBS: n/a Intervention group: - C-IBS: 17 patients (31.5%) - D-IBS: 23 patients (42.6%) - M-IBS: n/a	Test product: capsule containing $5x10^9$ CFU of *L. plantarum 299V* (DSM 9843). Two capsules daily. $1×10^{10}$ CFU daily.	8 weeks	Severity score of IBS. Quality of life score.	The entire study population (n=81) improved significantly over time in all study parameters (P < 0.0001) with no significant differences between control and intervention group. No significant differences between the C-IBS versus placebo and D-IBS versus placebo groups were found
Sen et al.	UK	18-65 years	11, 92%	12, 12	cross-over 12, 12	cross-over 12, 12	n/a	Test product: a rose-hip drink containing ProViva (Lund, Sweden) with $5x10^7$ CFU/ml of *L.plantarum 299V* (DSM 9843). 125 ml once a day. $6×10^9$ CFU daily.	4 weeks	Symptoms score of IBS. Evaluation of colonic fermentation through lactulose hydrogen brath test.	No symptomatic relief. No alteration in colonic fermentation.
Moeen-Ul-Haq et al.	Pakistan	>18 years	45, 41.7%	120, 108	60, 53	60, 55	Control group: - C-IBS: 12 patients (22.6%) - D-IBS: 15 patients (28.3%) - M-IBS: 26 patients (49.1%) Intervention group: - C-IBS: 16 patients (29.1%)	Test product containing $5x10^{10}$ CFU of *L. Plantarum 299V* (DSM9843).	4 weeks	Primary endopoint: frequency of abdominal pain (VAS) Secondary endopoints: severity of abdominal pain, of bloating and feeling of partial rectal emptying (VAS)	No difference between the two groups in the frequency of abdominal pain (p=0.15), the severity of bloating (p=0.34) and the feeling of partial rectal emotying (p=0.19).

							- D-IBS: 18 patients (32.7%) - M-IBS: 21 patients (38.2%)	$5x10^{10}$ CFU daily.			

CFU, Colony Forming Units; VAS, Visual Analogue Scale; GI, gastrointestinal; n/a, not available; C-IBS, constipation-predominant irritable bowel syndrome; D-IBS, diarrhea-predominant irritable bowel syndrome; M-IBS, mixed-type irritable bowel syndrome.

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process

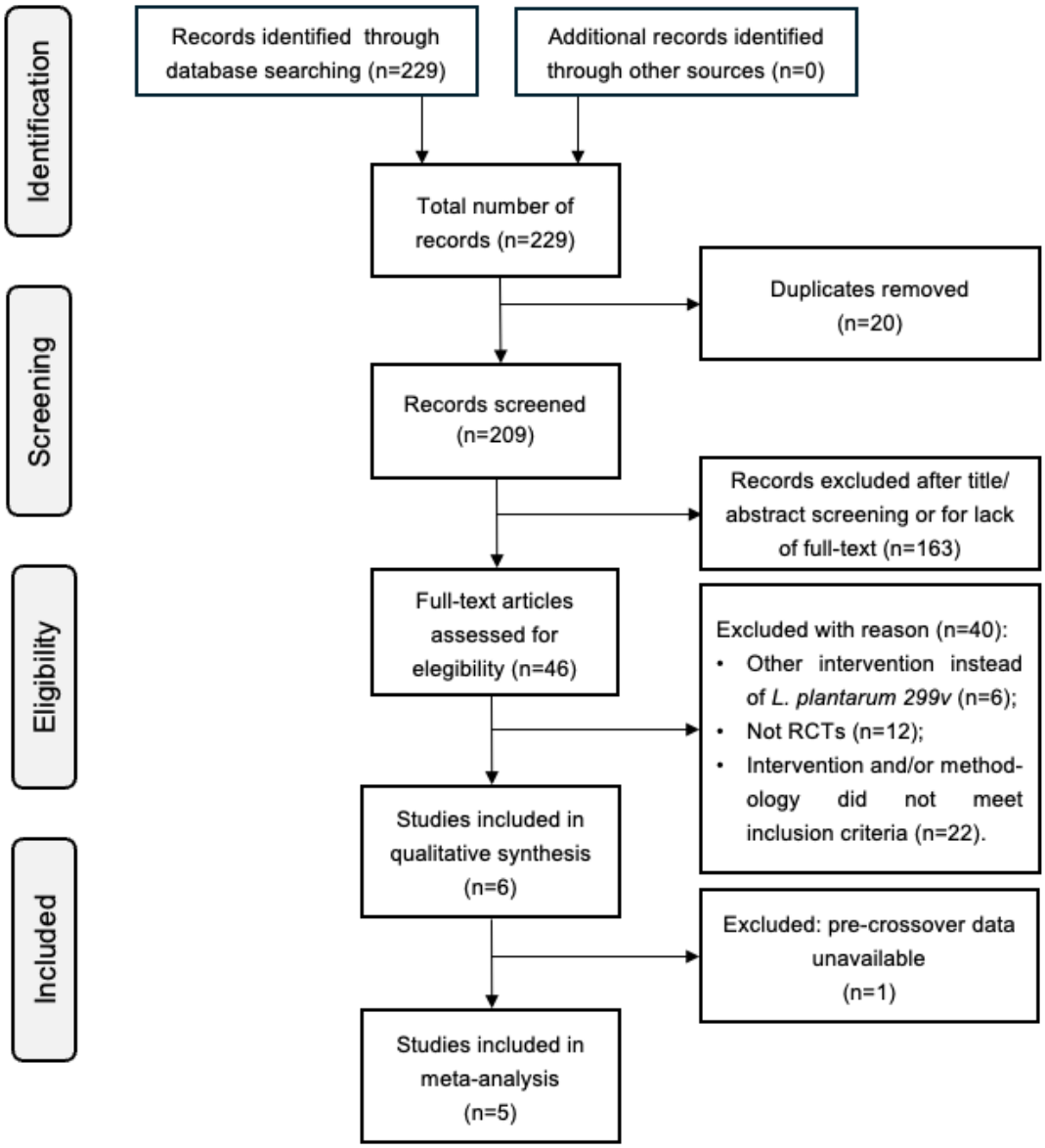
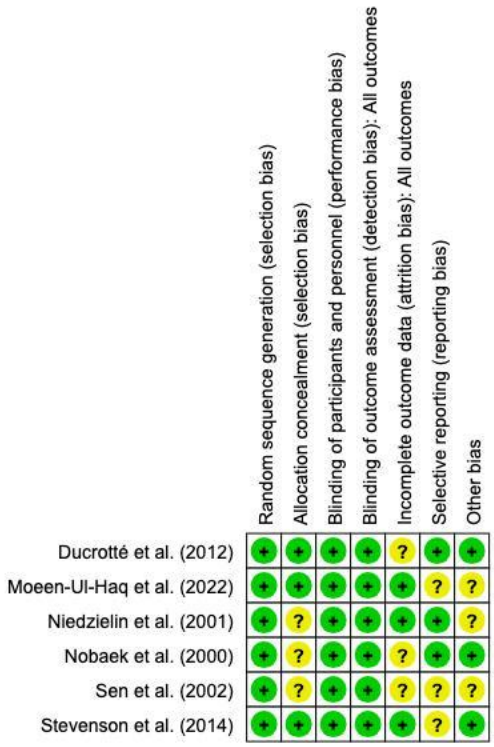


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(a)



(b)

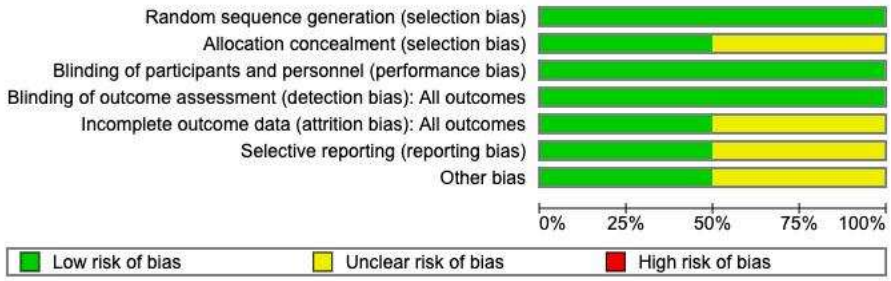


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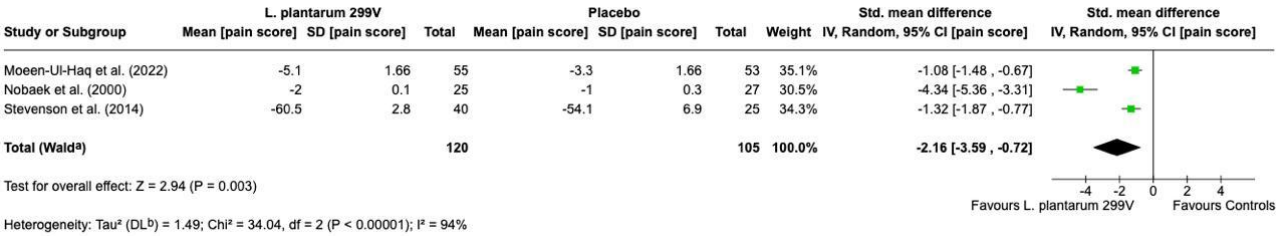


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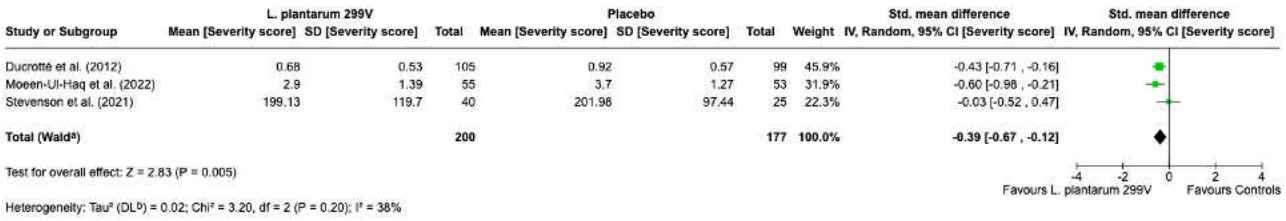


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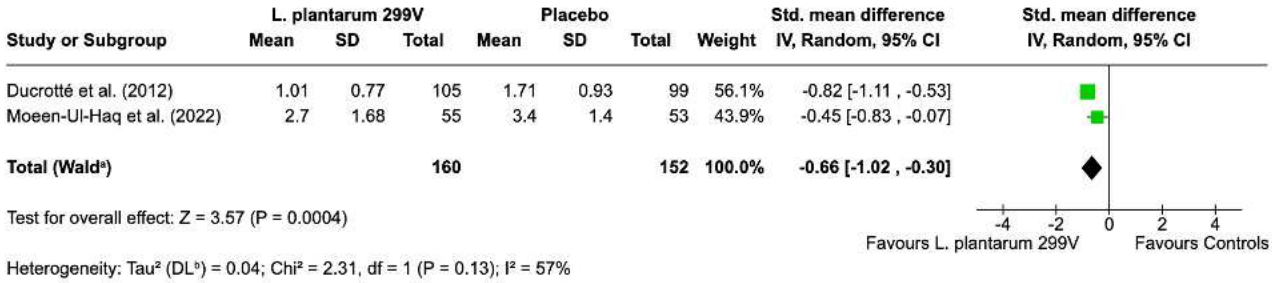


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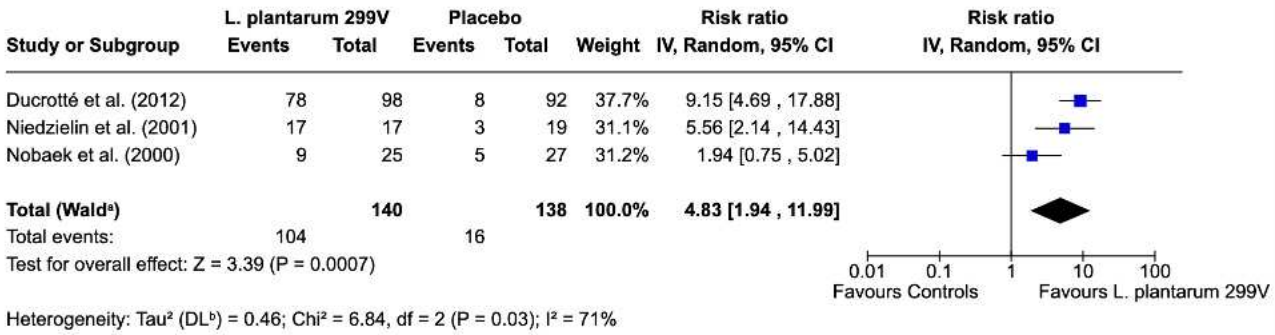


Figure 7. Forest plot comparing the effect of *Lactiplantibacillus plantarum* 299v versus placebo groups on bloating/flatulence improvement rate. The pooled estimate (black diamond) shows a significant effect favoring *L. plantarum* 299v (RR = 1.96; 95% CI: [1.06, 3.61]; *P* = 0.03). No heterogeneity was observed (I^2 = 0%)

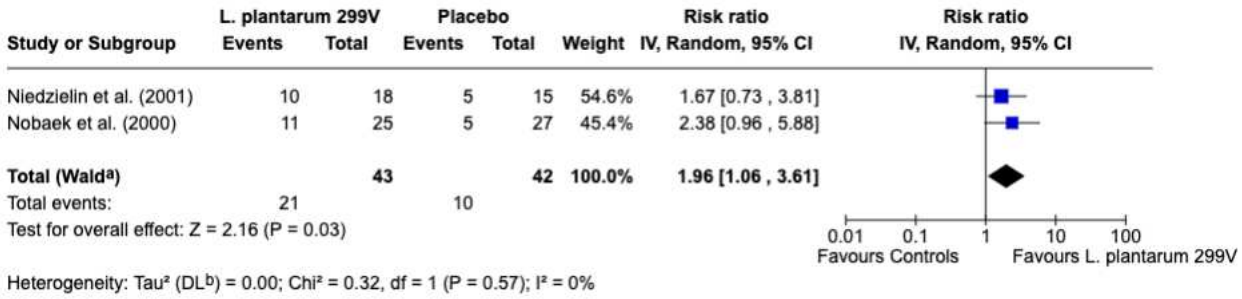


Figure 8. Forest plot comparing the effect of *Lactiplantibacillus plantarum* 299v versus placebo groups on constipation improvement rate. The pooled estimate (black diamond) shows no significant difference between the groups (RR = 1.39; 95% CI: [0.32, 6.11]; $P = 0.66$). High heterogeneity was observed ($I^2 = 72\%$)

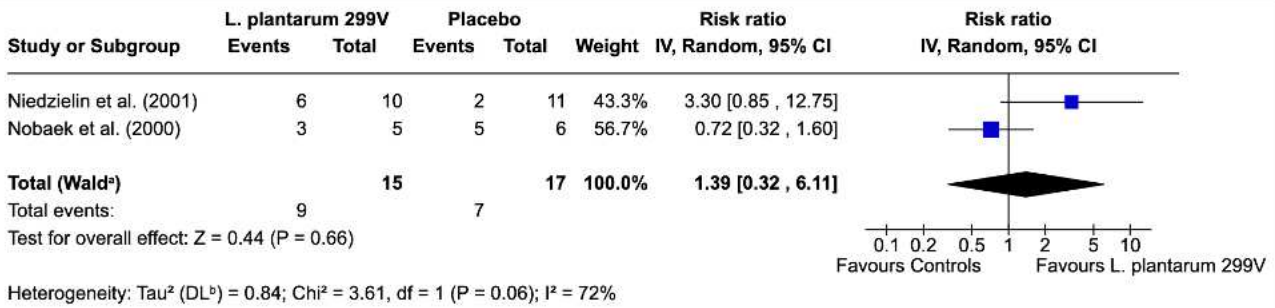
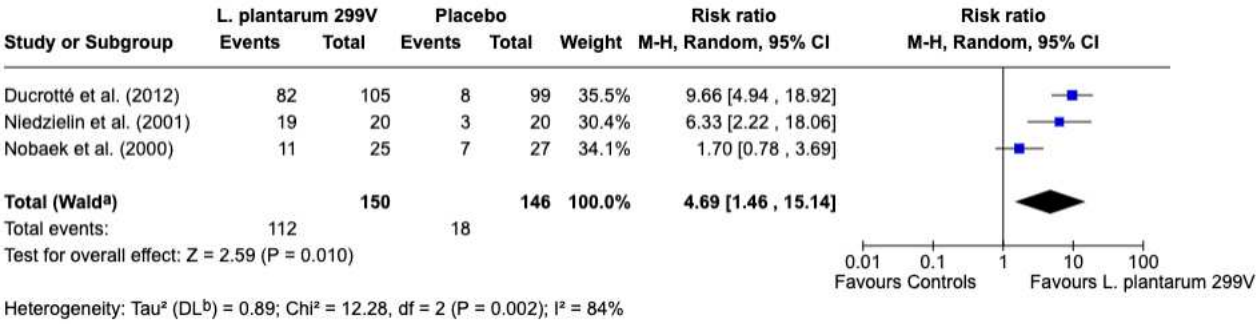


Figure 9. Forest plot comparing the rate of global improvement of digestive symptoms in irritable bowel syndrome between *Lactiplantibacillus plantarum* 299v and placebo groups. The pooled estimate (black diamond) shows a significant effect favoring *L. plantarum* 299v (RR = 4.69; 95% CI: [1.46, 15.14]; *P* = 0.010). High heterogeneity was observed (I^2 = 84%)



Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Supplementarymaterial15.07.docx