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# Constipation targeted monostrain and multispecies probiotics: effects on symptoms and gut microbiota

Yanqing Zeng[1,2], Penglin He[1], Chenang Lyu[1], Yuwei Wu[2], Xinyu Zhao[2], Qihui Gu[2], Shi Wu[2], Youxiong Zhang[2], Xianhu Wei[2], Ran An[1]*, Qingping Wu[2]*

[1] *Department of Food Science & Technology, School of Agriculture and Biology, Shanghai Jiao Tong University, Shanghai 200240, China.*

[2] *National Health Commission Science and Technology Innovation Platform for Nutrition and Safety of Microbial Food, Guangdong Provincial Key Laboratory of Microbial Safety and Health, State Key Laboratory of Applied Microbiology Southern China, Institute of Microbiology, Guangdong Academy of Sciences, Guangzhou 510070, China.*

**ABSTRACT:** Probiotics, classified into monostrain, multistrain and multispecies formulations, have been suggested as effective interventions for alleviating constipation related symptoms by modulating gut motility and microbiota composition. However, the comparative efficacy of these probiotics has not been systematically evaluated. This study presents a systematic review and meta-analysis of randomized controlled trials (RCTs) to assess the effects of monostrain and multispecies probiotics on constipation symptoms and gut microbiota. Fifteen eligible RCTs were included in the analysis. Probiotic supplementation significantly improved spontaneous bowel movements (SMD = 0.60, 95% CI [0.27, 0.94], $P$ = 0.0005) and stool consistency (SMD = 0.25, 95% CI [0.03, 0.48], $P$ = 0.03), but had no significant effect on gut transit time (SMD = -0.04, 95% CI [-0.34, 0.27], $P$ = 0.82) or quality of life (QoL) scores ($P$ = 0.42). Importantly, no superior efficacy of multispecies probiotics over monostrain formulations was observed, except for a modest improvement in QoL ($P$ < 0.00001). Additionally, probiotics had a measurable impact on gut microbiota composition, although changes in microbial diversity were not consistently correlated with clinical outcomes. Collectively, these findings suggest that probiotics can be effective in alleviating specific constipation-related symptoms, but the choice between monostrain and multispecies formulations should be based on strain-specific characteristics rather than the number of strains or species included. Additionally, this study underscored the need for future research into optimizing strain combinations and understanding probiotic-host interactions to enhance therapeutic outcomes.

**Keywords**: probiotics; systematic; constipation; intestinal microbiota; meta-analysis.

## 1. Introduction

Probiotics are “live microorganisms that when administered in adequate amount confer health benefits to the host” [1]. Based on the composition of probiotics, probiotics can be classified into monostrain, multistrain and multispecies probiotics [2-4]. Specifically, monostrain probiotics consist of a single strain from a single species. Multistrain probiotics are composed of multiple strains of the same species. Multispecies probiotics, on the other hand, include strains from different species. In addition, as species specific effects of probiotics

***Corresponding author**
Ran An, ran.an@sjtu.edu.cn; Qingping Wu, wuqp203@163.com

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have been reported, the potential of multispecies probiotics to create a probiotic niche that promotes colonization and demonstrates greater efficacy than monostrain probiotics in improving health outcomes has been suggested [5,6]. Nevertheless, this hypothesis was based on the additive, synergistic or antagonistic potentials of multispecies probiotics (Figure 1), which could promote symbiosis and enhance overall gut health [6]. The empirical evidence, comparing the efficacy of monostrain, multistrain, and multispecies probiotics on alleviating health related symptoms, is still warranted.

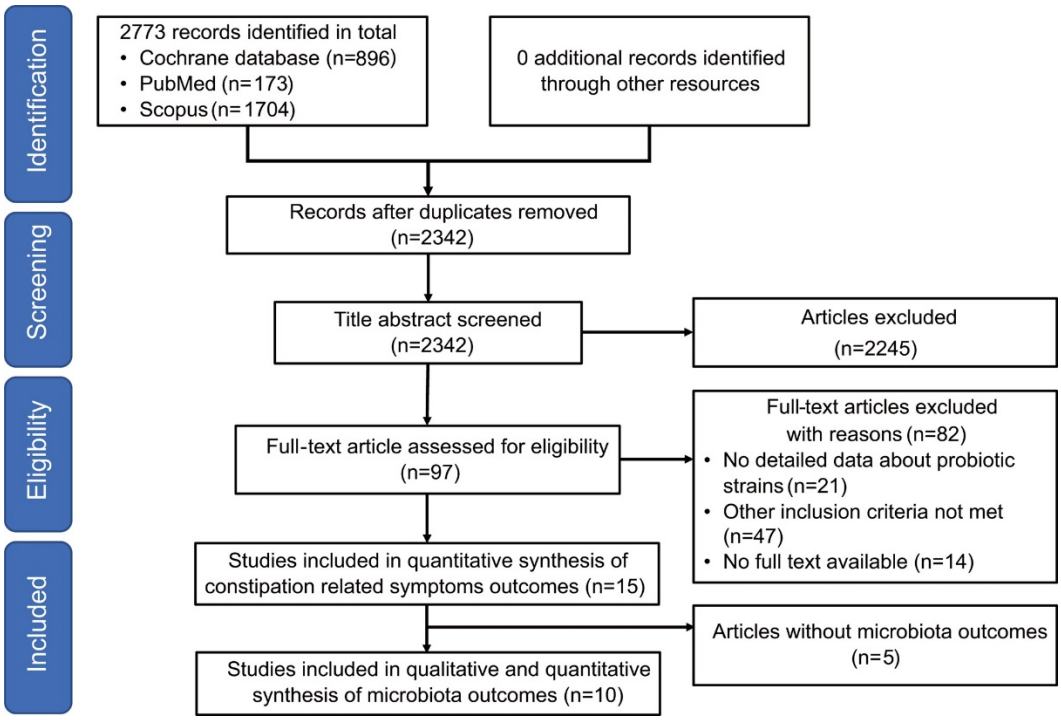


**Figure 1:** Background and potential mechanisms of probiotics involved in constipation amelioration via targeting gut microbiota. (i) Microbiota dysbiosis is common among constipation patients, characterized by reduced *Lactobacillus*[16,75], enhanced *Bifidobacterium*[15,76], methanogenic microorganisms[18], and potential pathogenic bacteria[16,17]. (ii) Supplemented probiotics may produce metabolites such as SCFAs and lactic acid to influence the intraluminal environment[77,78], as well as enzymes such as bile salt hydrolase[79]. Multistrain and multispecies probiotics have additive, synergistic and antagonistic potentials over monostrain probiotics and are expected to exert symbiotic functions to promote gut health. (iii) Probiotics may modify gut microbiota composition as well as microbial fermentations, which affect gut transit via various gut receptors, gut nervous system and immune system and the gut-brain axis, contributing to the amelioration of constipation[23,80]. SCFAs produced by probiotics and commensal microorganisms can stimulate gut transit by promoting intraluminal neurotransmitter 5-hydroxytryptamine (5-HT) production and subsequent activation of 5-hydroxytryptamine type 3 (5-HT3) receptor[81]. The activation of 5-HT receptors located on vagal nerves transmits bacterial signals to the central nervous system through gut-brain axis to enhance gut motility[82]. Nevertheless, SCFAs (especially butyrate acid) also increase electrolyte absorption and contribute to constipation pathogenesis[83]. Bacterial bile salt hydrolase deconjugate bile acid in the colon[14] to influence transit time and stool consistency[84]. Bile acid activates receptor TGR5 expressed by enteric neurons and endocrine cells and increase host 5-HT and calcitonin gene-related peptide secretion to stimulate peristalsis[85]. Other bacterial metabolites, including lipopolysaccharides, lipopeptides and peptidoglycans, tryptophan metabolites and indoles, *etc*. also regulate gut motility[86]. Some metabolites may further impact the host immune response through recognition by pattern recognition receptors such as toll-like receptors (TLR) to regulate inflammation, contributing to gastrointestinal homeostasis[23,87].

Constipation is a common gastrointestinal disorder that characterizes as “a variety of symptoms, including hard stools, excessive straining, infrequent bowel movements, bloating and abdominal pain”[7]. Approximately every one in seven adults (especially women and elderly) and one in three children suffered from constipation related symptoms[8-10]. With the high prevalence and demand in medical sources[11,12], studies investigating strategies to alleviate constipation related symptoms is warranted[13].

Although the pathophysiological reason of constipation remains obscure, factors such as genetic traits, lifestyle, dietary intake, physical activity, colonic motility dysfunction, psychological factors and intestinal microbiota, have been considered to make an impact thereof [14]. Earlier studies have shown that constipation is associated with a shift in the structure and function of the intestinal microbiota, as known as dysbiosis[15-17], indicating its involvement in the pathophysiology of constipation[18,19]. Regular therapeutic approaches to alleviate constipation related symptoms include lifestyle and dietary modifications, stool softeners, and laxatives[20]. The satisfaction rate with these traditional methods, however, is not ideal (*ca.* 50%)[21,22] with limited efficacy and concerns about safety[22]. To this end, there is an urgent need for alternatives with increased efficacy and satisfaction for constipated patients.

Probiotics were suggested to be a promising alternative to alleviate constipation related symptoms via increasing the abundance of beneficial microbes, production of beneficial metabolites, increasing gut motility, modulation of the gut-brain axis and the immune system [23]. Of note, probiotics play a pivotal role in modulation of the gut microbiota, which is important in gastrointestinal health and constipation related symptoms. Specifically, probiotic supplementation may restore microbial balance in individuals with constipation-related dysbiosis, promoting the growth of beneficial bacteria and enhancing microbial diversity [24,25]. These changes could lead to increased production of short-chain fatty acids (SCFAs), such as butyrate and acetate, which stimulate colonic motility and soften stools [26]. Additionally, probiotics may interact with the gut-brain axis, influencing neural pathways to improve gut motility and reduce abdominal discomfort [27]. This hypothesis forms the basis of our systematic comparison of monostrain and multispecies probiotics in alleviating constipation-related symptoms and impact on intestinal microbiota.

The efficacy of probiotics as an alternative to alleviate constipation related symptoms vary, with high heterogeneity [28] in probiotics usage [29] and efficacy [30], as well as in their impact on the intestinal microbiota composition [31]. Liu *et al*., systematically reviewed the efficacy of probiotics for functional constipation in children and concluded as no advocating use of probiotics in functional constipated children [32]. In contrast, a meta-analysis by Schoot *et al*. assessed the efficacy of probiotics in treating chronic constipation in adults and found that certain probiotics, particularly *Bifidobacterium lactis*, significantly improved stool frequency and integrative constipation symptoms [4]. This inconsistency may partly be attributed to differences in study populations, but variations in the types of included probiotics, *e.g.*, probiotics composition, could also play a critical role. For example, Zhang *et al.* conducted a meta-analysis on the effects of probiotics in adults with functional constipation and reported superior effects of multispecies probiotics [28]. This study, however, included dairy products, which inherently contain additional bioactive components, potentially confounding the results. These findings underscored the need for a focused meta-analysis that evaluates the efficacy of monostrain and multispecies probiotics specifically formulated for constipation management. Such an analysis would help delineate the role of strain-specific efficacy and provide clearer guidance for the targeted use of probiotics in alleviating constipation-related symptoms.

To this end, current study focused on the constipation and aimed to evaluate the efficacy of monostrain and multispecies probiotics on constipation related symptoms as well as their impact on intestinal microbiome. We hypothesized that supplementation of probiotics could alleviate constipation related symptoms and affect intestinal microbiota composition, and multistrain as well as multispecies probiotics have better efficacy over monostrain probiotics. Collectively, by systematically comparing these formulations, this study would address the heterogeneity in probiotic efficacy and provide actionable insights for clinical practice. In addition, current study would also offer practical recommendations for optimizing probiotic product design, bridging the gap between research findings and real-world applications.

## 2. Methods

### *2.1 Study protocol*

The systematic review was carried out according to the Cochrane handbook for systematic reviews of interventions[33] and reported in accordance with the updated Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA-S)[34]. Detailed search strategy, eligibility criteria, data extraction information has been registered on PROSPERO (CRD42023381848).

### *2.2 Study objectives*

The primary aim was to compare the efficacy of monostrain, multistrain and multispecies probiotics on constipation related symptoms and/or parameters. The secondary aim was to evaluate the role of supplemented probiotics on intestinal microbiota.

### *2.3 Searching strategy*

We performed the original literature search initially on 25$^{th}$ November 2022 and rerun on 4$^{th}$ June 2024 in the following databases: PubMed (includes MEDLINE), Scopus and Cochrane Library (includes EMBASE) using the following terms: 1. constipation; 2. functional constipation; 3. primary constipation; 4. chronic constipation; 5. idiopathic constipation; 6. Probiotics; 7. *Lactobacillus*; 8. *Bifidobacterium*; 9. *Lactococcus*; 10. *Streptococcus*; 11. *Propionibacterium*; 12. *Leuconostoc*; 13. *Pediococcus*; 14. Randomized controlled trial; 15. Clinical trial; specifically search databases using (1-5) AND (6-13) AND (14-15). The representative search strategy in PubMed was: [Ti&Ab] (constipation or functional constipation or primary constipation or chronic constipation or idiopathic constipation) & (Probiotics or *Lactobacillus* or *Bifidobacterium* or *Lactococcus* or *Streptococcus* or *Propionibacterium* or *Leuconostoc* or *Pediococcus*).

### *2.4 Study eligibility criteria*

Only studies written in English and conducted in human were included, with no limits in publication time. Nevertheless, we chose to exclude studies involving fermented foods to ensure that the meta-analysis reflects the direct effects of probiotic supplementation. This is because fermented foods like yogurt involved confounding variables, which inherently have additional bioactive components. These could independently influence gut microbiota and constipation-related symptoms, making it challenging to isolate the specific effects of probiotics. Specifically, during the search, we used filters for randomized controlled trials.

*2.5 Inclusion and exclusion criteria*

Only studies that met the following criteria were included:

- Studies based on a randomized controlled trial (RCT) design.
- Subjects of functional constipation, primary constipation, chronic constipation, or idiopathic constipation.
- Intervention in adults.

Studies were excluded if they bear any features below:

- Studies with no placebo control.
- Irritable bowel syndrome or drug induced constipation or constipation related to diseases other than constipation itself.
- Studies with no measurement of constipation relief (*i.e.*, stool form, spontaneous bowel movements, gut transit time, stool consistency, constipation severity score, quality of life related to constipation, and/or information about constipation symptoms).
- Studies with no detailed information about ingested probiotics (name of ingested bacterial strain and dosage).
- Probiotics supplemented together with prebiotics, in fermentation product form, or together with lactulose or any other laxatives or drugs.

*2.6 Study selection and data extraction*

Duplications were removed from the identified studies using the EndNote 20. Remaining studies were then screened for eligibility based on title and abstract. Qualified studies were further screened with full text reading. Throughout the screening process, two reviewers (YQZ and RA) made the decision independently. Disagreements between YQZ and RA were resolved by the third reviewer (PLH). Specifically, variables and indicators extracted from each included study are listed:

Primary outcomes:

1) Gut transit time: Measured as whole gut or colonic transit time.
2) Spontaneous bowel movements: Number of bowel movements per week or day.
3) Stool consistency: Evaluated using a scale such as the Bristol Stool Scale (BSS).

Secondary outcomes:

1) Constipation severity scores: Including scores like the Patient Assessment of Constipation-Symptoms (PAC-SYM) or other validated constipation scoring systems.
2) Quality of life (QoL): Assessed using scales such as PAC-QoL or other relevant QoL questionnaires.

3) Gut microbiota composition: Analyses at the genus, species, or family level, including changes in microbial diversity (α-diversity and β-diversity).

4) Short-chain fatty acids (SCFAs) and stool pH: Metabolite levels that may indicate the functional activity of gut microbiota.

*2.7 Risk assessment and meta-analysis*

The risk of bias for each study were assessed as follows: domains of risk include: random sequence generation and allocation concealment (selection bias), blinding of subjects and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other biases. These domains were documented as low risk, unclear risk, or high risk using the Cochrane risk of bias tool addressed in the Cochrane Handbook V.5.1.0 (Cochrane Collaboration; London, UK)[35].

The meta-analysis was performed using the RevMan 5.4 (The Nordic Cochrane Centre, The Cochrane Collaboration) referring to the methods mentioned in Cochrane Handbook for analysis[33]. Continuous variables of outcomes of the same scales were synthesized using the mean difference (MD) and 95% confidence interval (CI). In terms of different measurement scales, MD was replaced with the standardized mean difference (SMD) and 95% CI. $I^2$ was used to determine heterogeneity. When $I^2 > 50\%$ and $P < 0.05$, a random effects model was applied according to high heterogeneity. Otherwise, a fixed effects model was applied. When the number of studies included in an outcome ≥ 10, funnel plots were produced with RevMan 5.4 and publication bias was assessed through visual inspection and statistical analysis using Egger's test[36].

## 3. Results on the comparative analysis of monostrain and multispecies probiotics' efficacy

*3.1 Included studies*

Our literature search was carried out on 25th November 2022 and then rerun on 4th June 2024. In total, 2773 records were identified from Cochrane database (n = 896), PubMed (n = 173), and Scopus (n = 1704). After removing duplicates, titles and abstracts of 2342 studies were screened, and 2245 unsuitable studies were excluded. Full texts of 97 studies were assessed for eligibility, with 82 of them excluded with the following reasons: no detailed data about probiotic strains (n = 21), other inclusion criteria not met (n = 47), and no full text available (n = 14). In the end, fifteen studies were included for further systematic and qualitative analysis of constipation related symptoms, among which ten studies were included for analysis of microbiota outcomes (Figure 2).

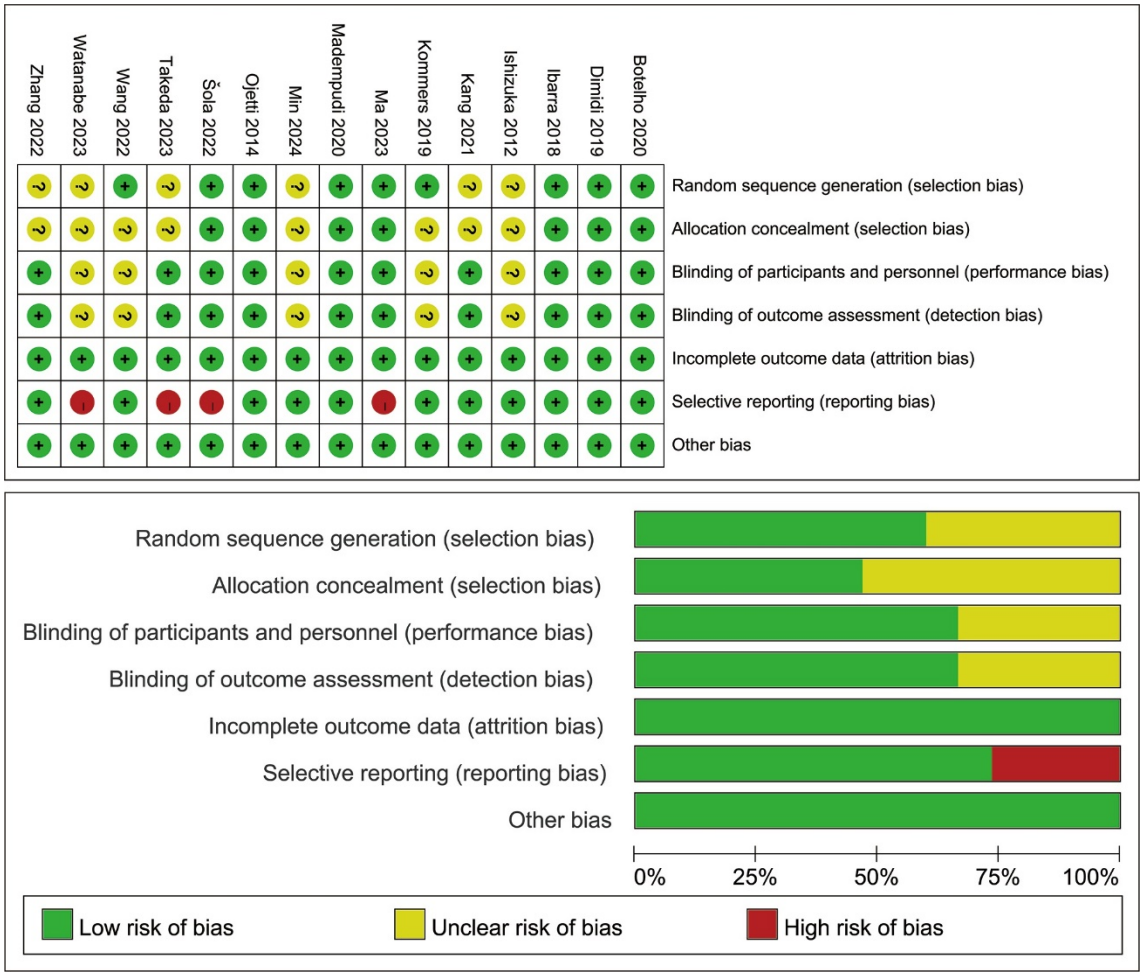


**Figure 2:** Flow diagram of study selection.

### *3.2 Characteristics of included studies*

Of the fifteen included studies, fourteen of them[37-50] were based on parallel design and one study[51] was based on a crossover design (Table 1). They were carried out in China (n = 3), Japan (n = 3), Korea (n = 2), Brazil (n = 2), India (n = 1), Italy (n = 1), France (n = 1), Croatia (n=1), and the UK (n = 1), published between 2012 and 2024. The involved probiotics were *Bifidobacterium animalis* subsp. *lactis*, *Bifidobacterium bifidum*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactiplantibacillus plantarum*, *Lacticaseibacillus rhamnosus*, *Lactococcus lactis*, *Lactococcus cremoris*, *Lactobacillus reuteri*, *Streptococcus thermophilus*, and *Bacillus coagulans.* They were supplied in the forms of (chewable) tablets, capsules, spray dried powder, milk powder-based formats and liquid oral formulations. Subjects were instructed to take the probiotics consecutively for different time periods, *i.e.*, from 7 days[41] to 12 weeks[47], with dosage ranging from $2.0\times10^{8}$ CFU[42] to $1.0\times10^{11}$ CFU[45] per day (Table 1).

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**Table 1** Study characteristics.

| Study | Country | Size (female %) | Age | BMI, kg/m$^2$ | Study design | Intervention | Control | Intervention period | Outcomes | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Constipation relief | Microbiota profile |
| [38] | UK | I: 37 (92)<br>C: 38 (92) | I: 35 ± 12<br>C: 31 ± 10 | I: 23.6 ± 3.1<br>C: 22.8 ± 2.6 | Parallel | *Bifidobacterium lactis NCC2818*, 1.5 × 10$^{10}$ CFU/d | Maltodextrin | 4 wks | Whole gut transit time; stool output; constipation symptoms and severity; PAC-SYM; PAC-QoL | Stool microbiota; fecal SCFAs; stool pH |
| [51] | Japan | 17 (100) | 20-23 | - | Parallel crossover | *Bifidobacterium lactis GCL2505* in milk-like drink, 10$^{10}$ CFU/d | Carrier materials without probiotics | 2 wks | Number of defecations; number of days with defecation; Stool quantity | Total number of bacteria; bifidobacteria |
| [39] | Korea | I: 40<br>C: 40 | I: 44.4 ± 2.2<br>C: 45.3 ± 1.8 | I: 22.2 ± 0.4<br>C: 23.2 ± 0.5 | Parallel | *Bacillus coagulans SNZ 1969*， 1.0 × 10$^9$ CFU/d | Maltodextrin | 8 wks | †Whole gut transit time; complete spontaneous bowel movements; bowel discomfort symptom scores | α-diversity; gut microbial dynamics; stool pH |
| [37] | Brazil | I: 21 (86)<br>C: 14 (86) | I: 25.71 ± 7.22<br>C: 31.00 ± 11.64 | I: 23.14 ± 3.57<br>C: 24.54 ± 5.00 | Parallel | *Lactobacillus acidophilus NCFM*, *Lactobacillus casei Lc-11*, *Lactococcus lactis Li-23*, *Bifidobacterium bifidum BB-06*, and *Bifidobacterium lactis HN019* in capsule, 5 × 10$^9$ CFU/d | Maltodextrin | 30 d | Evacuation frequency; stool consistency; gastrointestinal tract functional health (Rome IV criteria) | Relative abundance; α-diversity; β-diversity |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| [40] | China | I: 53 (79)<br>C: 50 (92) | I: 51.7 ± 12.8<br>C: 47.6 ± 13.6 | I: 23.1 ± 2.64<br>C: 23.9 ± 2.48 | Parallel | *Bifidobacterium bifidum CCFM16*, 2 × $10^9$ CFU/d | Maltodextrin | 4 wks | Stool frequency; stool consistency; PAC-SYM; PAC-QoL | α-diversity; β-diversity; *Bifidobacterium* composition; fecal SCFAs |
| [41] | China | I: 59 (73)<br>C: 58 (60) | I: 45.80 ± 12.03<br>C: 43.07 ± 9.36 | - | Parallel | *Lactiplantibacillus plantarum Lp3a*, 2 × $10^{10}$ CFU/d | Placebo (similar in appearance) | 7 d | Stool frequency; defecation condition; stool form | Microbiome composition |
| [44] | France | I (high): 76 (79)<br>I (low): 76 (80)<br>C: 76 (80) | I (high): 42.9 ± 13.8<br>I (low): 41.6 ± 15.3<br>C: 40.6 ± 12.8 | I (high): 24.1 ± 3.9<br>I (low): 24.2 ± 3.7<br>C: 24.8 ± 3.6 | Parallel | *Bifidobacterium lactis HN019* in capsules, 1 × $10^{10}$ CFU/d (high) or 1 × $10^9$ CFU/d (low) | Carrier material | 28 d | Colonic transit time; bowel movement frequency; stool consistency; PAC-SYM; PAC-QoL | - |
| [43] | Brazil | I: 52 (100)<br>C: 50 (100) | I: 27.15 ± 5.52<br>C: 24.38 ± 5.41 | I: 25.39 ± 3.87<br>C: 24.12 ± 4.39 | Parallel | *Bifidobacterium lactis BL- 04*, *Bifidobacterium bifidum Bb-06*, *Lactobacillus acidophilus La-14*, *Lactobacillus casei Lc-11,* and *Lactococcus lactis LL-23*, 1 × $10^9$ CFU/d | Maltodextrin | 15 d | PAC-QoL | - |
| [50] | India | I: 50 (32)<br>C: 50 (50) | I: 42.54 ± 12.16<br>C: 45.30 ± 11.33 | - | Parallel | *B. coagulans Unique IS2*, 2 × $10^9$ CFU/d | Placebo (unspecified) | 4 wks | Stool Frequency; stool consistency; constipation scoring system scale | - |
| [42] | Italy | I: 20 (55)<br>C: 20 (65) | I: 34.5±16<br>C: 36.7±14 | - | Parallel | *Lactobacillus reuteri DSM 17938*, 2 × $10^8$ CFU | Matching placebo (unspecified) | 4 wks | Bowel movements frequency; stool consistency | - |
| [46] | Korea | I: 14 (57)<br>C: 14 (57) | I: 43.7±12.8<br>C: 44.5±8.5 | - | Parallel | *Lactiplantibacillus plantarum PBS067*, *Lacticaseibacillus rhamnosus LRH020*, *Bifidobacterium animalis* subsp. *lactis BL050*, *Lactiplantibacillus* | Maltodextrin, contained the same number of excipients (corn starch and rice powder) as | 4 wks | Stool frequency; stool consistency | α-diversity; β-diversity; microbiome composition |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | *plantarum UALp-05*, *Lactobacillus acidophilus DDS-1*, and *Streptococcus thermophilus CKDB027*, altogether $1\times10^{10}$ CFU/d | the probiotic capsules | | | |
| [47] | Croatia | I: 28(75)<br>C: 32 (66) | I: 76 (66–82)<br>C: 79 (65–98) | I: 26.6 (15.2–35.0)<br>C: 28.3 (23.5–47.8) | Parallel | *Lactobacillus acidophilus LA3*, *Bifidobacterium animalis* subsp. *lactis BLC1*, and *Lactobacillus casei BGP93*, altogether $1 \times 10^9$ CFU/d | Medium-cha in triglyceride oil, fractionated oil with triglycerides of caprylic (C8) and capric acid (C10) and silicon dioxide | 12 wks | Cumulative numbers of stools | - |
| [45] | China | I: 78 (81)<br>C: 85 (80) | I: 22.68 ± 5.66<br>C: 21.59 ± 4.59 | - | Parallel | *Lactiplantibacillus plantarum P9*, $1 \times 10^{11}$ CFU/ d | Maltodextrin | 42 d | (Complete) spontaneous bowel movements; stool consistency; PAC-QOL | α-diversity; microbiome composition; fecal metabolites |
| [48] | Japan | I: 38 (46)<br>C: 41 (44) | I: 78.1 ± 6.4<br>C: 77.9 ± 6.2 | I: 22.8 ± 3.5<br>C: 22.8 ± 3.5 | Parallel | Sachets containing lyophilized powder of Bifidobacterium longum BB536, $5 \times 10^{10}$ CFU/d | Placebo (unspecified) | 4 wks | Constipation symptom score, including frequency of bowel movements | β-diversity; microbiome composition |
| [49] | Japan | I (low): 21 (71)<br>I (medium): 21 (81)<br>I (high): 21 (81)<br>C: 20 (80) | I (low): 42.7 ± 12.2<br>I (medium): 40.5 ± 12.1<br>I (high): 40.9 ± 11.4<br>C: 40.9 ± 12.6 | I (low): 21.8 ± 4.7<br>I (medium): 21.4 ± 2.9<br>I (high): 21.1 ± 3.3<br>C: 20.4 ± 2.6 | Parallel | *Lactococcus cremoris FC* ($1.0\times10^{10}$, $1.7\times10^{10}$ or $2.0\times10^{10}$ CFU/d), corn starch, sucrose fatty acid esters, vitamin D, micronized silicon dioxide, hydroxypropyl methylcellulose | Placebo (additional 100 mg corn starch instead of probiotic) | 4 wks | Defecation frequency, stool consistency (defined on a seven-point scale) | Bacteria concentration |

### 3.3 Risk of bias

Five studies were rated as low risk of bias[37,38,42,44,50], while ten studies were rated as unclear or high risk of bias due to incomplete reporting of information[39-41,43,51] (Figure 3). Specifically, six RCTs were incomplete with random sequence generation details[39,41,46,48,49,51], and eight RCTs didn't report convincible allocation concealment designs[39-41,43,46,48,49,51]. Five RCTs didn't provide information about the blinding of subjects and personnel as well as outcome assessment[40,43,46,49,51], and four RCTs had high risks of selective reporting[45,47-49].

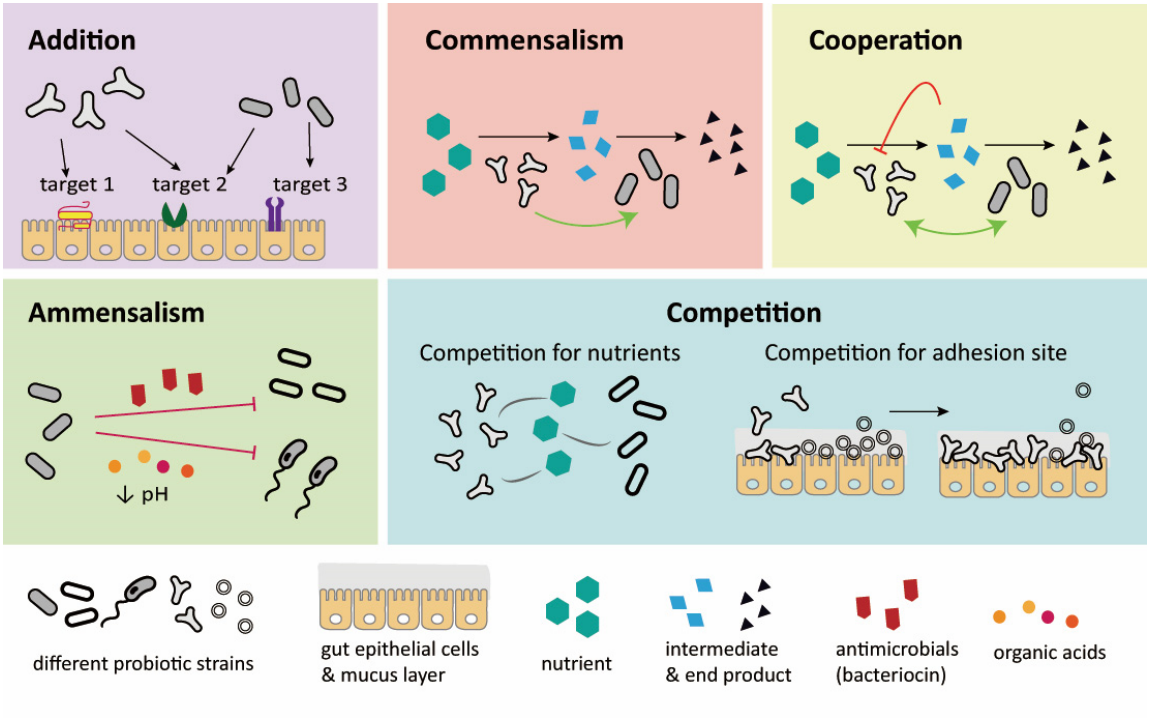


**Figure 3:** Risk of bias assessment summary and graph of the included studies.

### 3.4 Efficacy of monostrain and multispecies probiotics on constipation related symptoms or parameters

All included studies used different parameters to evaluate constipation relief, including gut transit time, spontaneous bowel movements, stool consistency, constipation severity score and quality of life (QoL).

#### 3.4.1 Gut transit time

Three studies based on monostrain probiotics involving 368 subjects (aged 21 to 57, 34%-92% female) from the UK, France, and Korea reported the influence of probiotics on whole gut transit time or colonic transit time. There was no significant reduction in gut transit time after probiotics supplementation (SMD = -0.04, 95% CI, [-0.34, 0.27], $P$ = 0.82) (Figure S1). Moderate heterogeneity was found among the studies ($I^2$ = 60%).

#### 3.4.2 Spontaneous bowel movements

Fourteen included studies evaluated changes in (complete) spontaneous bowel movements after probiotic treatment based on data from 1196 subjects (aged 18 to 98, 32%-100% female) from Brazil, the UK, India,

France, Italy, Korea, China, Japan, and Croatia[37-42,44-51]. Supplementation of probiotics could increase the spontaneous bowel movements significantly (SMD = 0.60, 95% CI, [0.27, 0.94], $P$ = 0.0005) (Figure S2). Of note, multispecies probiotics were less efficient than monostrain probiotics in increasing spontaneous bowel movements (95% CI, [-0.32, 0.42] vs. [0.33, 1.09]; test for subgroup differences: $P$ = 0.01). High heterogeneity was found among the studies ($I^2$ = 88%). Visual inspection of funnel plots and result of Egger's test showed no evidence of funnel plot asymmetry ($P$ = 0.27) (Figure S3).

*3.4.3 Stool consistency*

Ten randomized controlled trials (RCTs) assessed the effect of probiotic supplementation on stool consistency using a seven-score scale such as the Bristol Stool Scale (BSS) or by the number of subjects with BSS 1 or 2[37,38,40-42,44-46,49,50]. Probiotic interventions covered 972 subjects (aged 17 to 64, 32%-92% female) from Brazil, the UK, France, India, Italy, China, Japan, and Korea. Probiotics showed overall enhancement in stool consistency (SMD = 0.25, 95% CI, [0.03, 0.48], $P$ = 0.03) (**Figure S4**). However, multispecies probiotics were not significantly more efficient than monostrain probiotics in increasing stool consistency (95% CI, [-0.71, 0.94] vs. [0.03, 0.52]; test for subgroup differences: $P$ = 0.72). Considerable heterogeneity was found among the studies ($I^2$ = 68%). Visual inspection of funnel plots and result of Egger's test showed no evidence of funnel plot asymmetry ($P$ = 0.47) (Figure S5).

*3.4.4 Constipation severity score*

Six RCTs investigated the effect of probiotic supplementation on various constipation severity scores, including the Patient Assessment of Constipation-Symptoms (PAC-SYM) score, Constipation Scoring System score, bowel discomfort symptom score, and defecation condition scale, based on 591 subjects (aged 21 to 64, 60.3%-92% female) from the UK, Korea, France, China, and Japan[38-41,44,48]. Madempudi *et al.* and Min *et al.* reported subitem scores of symptom questionnaires without total scores, therefore were excluded from analysis[46,50]. Six monostrain probiotics significantly reduced the constipation severity score (SMD = -0.54, 95% CI, [-1.05, -0.02], $P$ = 0.04) (Figure S6). High heterogeneity was found among the studies ($I^2$ = 91%).

*3.4.5 Quality of Life*

Four RCTs investigated the effect of probiotic supplementation (including monostrain and multispecies probiotics) on QoL based on 456 subjects (aged 18 to 64, 78.9%-100% female) from the UK, France and China and revealed no significant impact thereof (MD = 0.10, 95% CI, [-0.14, 0.34], $P$ = 0.42) (Figure S7)[38,40,44] Ma *et al.* reported subitem scores of QoL without total scores, therefore were excluded from analysis[45]. Of note, multispecies probiotic formula was significantly more effective than monostrain probiotics in improving QoL scores ($P$ < 0.00001, Figure S7), although high heterogeneity was found among the studies ($I^2$ = 85%). In other words, probiotic supplementation did not significantly affect QoL scores overall. However, multispecies probiotics demonstrated significantly greater increase in QoL scores than monostrain probiotics.

### *3.5 Role of probiotics on intestinal microbiome*

#### *3.5.1 Microbiota composition*

Out of the seven studies that were included, three studies presented findings on the impact of probiotic supplementation (*Bifidobacterium lactis NCC2818*, *Bifidobacterium lactis GCL2505*, or *Lactococcus cremoris FC*) on the total count of bacteria per gram of feces or dry feces, which were based on a total of 121 subjects (aged 20 to 37, 92%-100% female) from the UK and Japan[38,49,51]. The supplementation of these three monostrain probiotics did not have significant impact on the total count of bacteria (SMD = 0.23, 95% CI, [-0.05, 0.51], $P$ = 0.11) (Figure S8).

Out of the six studies that reported on changes in microbiota profile (β diversity) before and after probiotic supplementation[37,39-41,46,48], only one study showed significant changes in the microbiota profile following the intake of monostrain probiotics[40]. In contrast, the remaining five studies did not find any significant changes[37,39,41,46,48].

In terms of microbial α diversity (richness and evenness), the supplementation of probiotics showed no significant impact. These findings were based on six studies covering 526 subjects (aged 17 to 64, 57%-92% female) from Brazil, Korea, and China[37,39-41,45,46].

Information about microbiota composition at the genus level was provided in five RCTs (Table 2)[38-41,51]. Specifically, a large number of bacterial groups changes after the probiotic supplementation. Three RCTs observed a significant increase in the relative abundance of *Bifidobacterium* after the supplementation of probiotics[40,49,51]. Two studies found significant increase in the relative abundance of *Klebsiella* after the supplementation of *Bifidobacterium bifidum CCFM16* and *Bacillus coagulans SNZ 1969*[39,40]. The relative abundance of *Bacteriodetes* decreased after the supplementation of *Bifidobacterium bifidum CCFM16* and a multispecies probiotic formula[40,46]. Two RCTs reported no significant changes in microbial composition after corresponding probiotic intervention[38,41].

#### *3.5.2 Recovery of supplemented probiotics*

Six studies investigated the recovery of supplemented probiotics in feces (Table 3)[37,39,40,45,46,51]. Detected by quantitative real-time PCR, *Bifidobacterium lactis GCL2505* was successfully recovered from all twelve *GCL2025*-administrated subjects with an average amount of (9.9 ± 0.3) log per gram of feces, while undetected in the placebo period[51]. In addition, Ma *et al.* identified higher level of *Lactiplantibacillus plantarum P9* from probiotic group then placebo group using DNA shotgun metagenomic sequencing[45]. Kang *et al*. revealed a significant increase in the abundance of *Bacillus coagulans* after the supplementation of *Bacillus coagulans SNZ 1969* based on 16S rRNA gene sequencing[39]. Using the same approach, Wang *et al*. found that *Bifidobacterium bifidum CCFM16* significantly increased the relative abundance of *Bifidobacterium bifidum* in feces[40], and Min *et al.* successfully retrieved all six supplemented strains from feces[46]. Botelho *et al.*, however, failed in detecting any *Lactobacillus acidophilus NCFM*, *Lactobacillus casei Lc-11* and *Bifidobacterium lactis HN019*[37]. Neither did they observe a significant increase in the

relative abundance of *Lactobacillus lactis* and *Bifidobacterium bifidum*, indicating an unsatisfying recovery of the probiotic strains in these multispecies formula[37].

**Table 2** Probiotic effects on genus level.

| Study ID | Probiotic strains | Alteration in microbiota composition (on genus level) from baseline |
|---|---|---|
| †Ishizuka 2012 | *Bifidobacterium. lactis GCL2505* | ↑ ***Bifidobacterium*** |
| ‡Zhang 2022 | *Lactiplantibacillus plantarum Lp3a* | No significant changes were detected. |
| †Dimidi 2019 | *Bifidobacterium lactis NCC2818* | No significant changes were detected. |
| ‡Wang 2022 | *Bifidobacterium bifidum CCFM16* | ↑ ***Bifidobacterium***, *Escherichia-Shigella*, ***Klebsiella***, *Blautia*<br>↓ ***Bacteroides*** |
| †Kang 2021 | *Bacillus coagulans SNZ 1969* | ↑ *Streptococcus*, ***Klebsiella***, *Turicibacter*, *Peptoclostridium*, *Citrobacter*, *Eggerthelia*, *Gemella*, *Bacillus*, *Sellimonas*<br>↓ *Propionibacterium*, *Aeromonas*, *Cloacibacillus*, Lachnospiraceae UCG-003, *Eubacterium*, Clostridium sensu stricto 1 |
| †Min 2024 | *Lactiplantibacillus plantarum PBS067, Lacticaseibacillus rhamnosus LRH020, Bifidobacterium animalis subsp. lactis BL050, Lactiplantibacillus plantarum UALp-05, Lactobacillus acidophilus DDS-1, Streptococcus thermophilus CKDB027* | ↑ *Actinobacteria*, *Firmicutes*, *Verrucomicrobia*<br>↓ ***Bacteroidetes***, *Proteobacteria* |
| †Watanabe 2023 | *Lactococcus cremoris FC* | ↑ ***Bifidobacterium*** (only in low-dose group) |

↑: significantly increased, ↓: significantly decreased. †Compared with placebo group. ‡Comparison between pre- and post-intervention. The bold letters show the enriched or decreased genus identified in multiple studies.

**Table 3** Recovery of probiotics in feces.

| Study ID | Probiotic strain | Method | Recovery |
|---|---|---|---|
| Ishizuka 2012 | *Bifidobacterium lactis GCL2505* | Quantitative real-time PCR | (*Bifidobacterium lactis GCL2505*) (9.9 ± 0.3) log/g (12/12), experimental vs. n.d. (0/12), placebo |
| Kang 2021 | *Bacillus coagulans SNZ 1969* | 16S rRNA gene sequencing | (*Bacillus coagulans*) increased in treatment group comparing to placebo ($P < 0.05$) |
| Wang 2022 | *Bifidobacterium bifidum CCFM16* | 16S rRNA gene sequencing | Higher relative abundance of supplemented *Bifidobacterium bifidum* in treatment group than placebo group. |
| Botelho 2020 | *Lactobacillus acidophilus NCFM*, *Lactobacillus casei Lc-11*, *Lactococcus lactis Li-23*, *Bifidobacterium bifidum BB-06*, *Bifidobacterium lactis HN019* | 16S rRNA gene sequencing | Of the probiotic strains administered, only *Lactobacillus lactis* and *Bifidobacterium bifidum* were detected in feces, but without significant differences between the two treatment and placebo group. |
| Min 2024 | *Lactiplantibacillus plantarum PBS067*, *Lacticaseibacillus rhamnosus LRH020*, *Bifidobacterium animalis* subsp. *lactis BL050*, *Lactiplantibacillus plantarum UALp-05*, *Lactobacillus acidophilus DDS-1*, *Streptococcus thermophilus CKDB027* | 16S rRNA gene sequencing | The six strains of probiotics significantly increased in relative abundance after probiotics supplementation. |
| Ma 2023 | *Lactiplantibacillus plantarum P9* | Shotgun metagenomic sequencing | As the intervention proceeded, *Lactiplantibacillus plantarum P9* was detected only in subjects ingested the probiotic powder but not placebo material, especially at day 28. |

n.d.: not detectable.

### *3.5.3 Microbial metabolites*

Four studies based on 421 subjects (aged 17 to 58, 34%-92% female) from the UK, Korea and China investigated changes in the concentration of fecal SCFAs or stool pH before and after the intervention (Table 4)[38-40]. Two studies revealed no significant changes in stool pH after the probiotic supplementation[38,39]. Supplementation of *Bifidobacterium lactis NCC2818* or *Lactiplantibacillus plantarum P9* did not significantly change the level of SCFAs[38,45]. Wang *et al.*, however, observed an increase in the level of acetate acid and butyrate acid in feces, as well as higher total SCFAs[40].

**Table 4** Probiotic effects on fecal SCFAs and stool pH.

| Study ID | Probiotic strains | Alteration in SCFAs | | | | | | | Alteration in stool pH |
|---|---|---|---|---|---|---|---|---|---|
| | | Total | Acetate | Propionate | Butyrate | Iso-butyrate | Valerate | Isovalerate | |
| Dimidi 2019 | *Bifidobacterium lactis NCC2818* | ns | ns | ns | ns | ns | ns | ns | ns |
| Wang 2022 | *Bifidobacterium bifidum CCFM16* | ↑ | ↑ | ns | ↑ | ns | ns | ns | - |
| Kang 2021 | *Bacillus coagulans SNZ 1969* | - | - | - | - | - | - | - | ns |
| Ma 2023 | *Lactiplantibacillus plantarum P9* | - | ns | ns | ns | ns | ns | ns | - |

↑: increased; ns: no significant effects; -: not reported.

## 4. Discussion

In the current study, we investigated the impact of monostrain and multispecies probiotics on constipation related symptoms and intestinal microbiota, by systematically reviewing available constipation-targeting RCTs based on monostrain, multistrain and multispecies probiotics. Our hypothesis was that supplementation of probiotics could alleviate constipation related symptoms and affect intestinal microbiota composition, and multistrain as well as multispecies probiotics have better efficacy over monostrain probiotics. We found that supplementation of probiotics was effective in alleviating some constipation related symptoms and/or parameters (spontaneous bowel movements, stool consistency, and integrative symptom scores), but not gut transit time or QoL. Multispecies probiotics did not demonstrate superior effect on spontaneous bowel movements and stool consistency, but were more effective in reducing QoL, comparing to monostrain probiotics. Supplementation of probiotics did not significantly affect the total bacterial count or microbial diversity. Although not exclusively, supplemented of probiotics could be traced back and affect intestinal microbiota composition and functionality.

The present study systematically reviewed and analyzed the effects of monostrain and multispecies probiotics on constipation symptoms. While 97 studies were initially full text assessed, only 15 met the strict inclusion criteria. This relatively limited number of studies reflects our deliberate effort to minimize potential sources of bias and ensure the comparability of outcomes across studies. One major exclusion was studies involving fermented foods, such as yogurt containing probiotics. This exclusion was based on the potential

confounding effects of additional bioactive components in these foods, such as peptides, vitamins, or other metabolites, which may independently influence gut motility and microbiota composition. Including such studies would have introduced variability, making it difficult to isolate the effects of probiotics themselves. By focusing solely on studies involving pure probiotic supplementation, we aimed to provide a more accurate assessment of the direct effects of probiotics on constipation-related outcomes. Additionally, we acknowledge that the limited number of included studies may restrict the scope of our conclusion. However, the consistency of the observed effects across the selected studies strengthens the reliability of our findings. Future research could explore the potential combined effects of probiotics and other bioactive components in fermented foods to provide a broader understanding of their role in alleviating constipation, based on broader spectrum of database, such as Web of Science.

Supplementation of probiotics was effective in alleviating most constipation related symptoms. Specifically, consistent with earlier meta-analyses[28,29,52], the current study found that supplementation of probiotics was effective in improving spontaneous bowel movements and stool consistency; however, the current study presents disagreement with these publications on the efficacy of probiotics of reducing gut transit time and QoL scores. In terms of constipation severity scores, probiotics supplementation was effective as in line with one study[4], while contradicting to some several other studies[29,53-56]. Notably, this inconsistency could be partly attributed to differences in study population and in study in-/ex-clusion criteria, for instance, the matrix of supplemented probiotics. It is known that fermented foods such as yogurt could alter the gut microbiota and relieve constipation symptoms[57]. Moreover, prebiotic consumption could also stimulate specific bacterial genera and lead to the release of SCFAs, and affect stool formation and transit[58]. Therefore, trials using probiotic-derived fermented foods and with inclusion of prebiotics/symbiotics were excluded from this meta-analysis to reach a fair comparison between probiotic strains.

The current meta-analysis revealed distinct strain specificity in alleviating constipation related symptoms, which highlights the importance of probiotic choice and drives people to combine multiple probiotic species or strains for increased efficacy. The superior effect of multispecies over monostrain probiotics, with respect to alleviating constipation related symptoms, was however not observed based on findings of current study. Multispecies or multistrain probiotics were thought to combine the property of each probiotic strain or even having superior effect over the combined effect, demonstrating broader functional coverage or better efficacy[3,6]. Indeed, as evaluated in the current systematic review, a multispecies probiotic formula was significantly more effective than monostrain probiotics in reducing QoL scores. However, although probiotic strains like *Bifidobacterium lactis HN019* and *Lactobacillus acidophilus NCFM* could ameliorate constipation related symptoms by themselves[59-62], a superior effect of their combination on increasing spontaneous bowel movements and stool consistency was not observed[37]. This finding is in line with another meta-analysis reported a limited impact of multispecies probiotics on spontaneous bowel movements [4]. Furthermore, another study even found that fewer number of probiotic strains was related to

shorter intestinal transit time, ruling against increasing probiotic strain/species numbers for better functionality[2].

The efficacy of multistrain/multispecies probiotics could be attributed to the interaction modes between strains[63]. Although none of the studies using multispecies probiotics in this meta-analysis tested the compatibility among probiotic strains, different interaction modes between probiotic strains have been found in a variety of multistrain or multispecies probiotics and could contribute to enhanced or weakened functionality (Figure 4). On one hand, synergy effects could exist between probiotic species. For instance, among the combination of amylolytic *Bifidobacterium breve 46* and nonamylolytic *Lactobacillus paracasei F8*, *Bifidobacterium breve 46* supports *Lactobacillus paracasei F8* with intermediate metabolites to grow together on starch[64]. Furthermore, *Lactobacillus rhamnosus GG* or *Lactobacillus bulgaricus* could promote the adhesion of *Bifidobacterium lactis Bb12* to the intestinal mucus[65], providing a better chance of colonization. On the other hand, competition and/or inhibition could exist between probiotic species and/or strains. For instance, interspecies inhibition and self-inhibition were found within the probiotic composing *Lactiplantibacillus plantarum, Lactobacillus rhamnosus, Lactobacillus acidophilus* and *Enterococcus faecium*[66]. Moreover, *Lactobacillus johnsonii NCC533* coexisted with *Lactobacillus paracasei* but excluded *Bifidobacterium longum NCC2705* from the colon of gnotobiotic mice gut. Further supplementation with *Escherichia coli Nissle* allowed increased growth of *Bifidobacterium longum NCC2705* and eliminated *Lactobacillus johnsonii NCC533*[67]. Among common probiotic species (e.g. bifidobacteria and others), lactobacilli seem to show stronger inhibition against other probiotic species, possibly attributable to lactobacilli's higher secretion of bacteriocin (antagonistic towards closely-related strains) and/or organic acids which serves as antimicrobial agents[68], as well as greater metabolic efficacy towards nutritional substrates, *e.g.* fructose, inulin, *etc*.[68,69]. To this end, interaction among probiotic strains should be evaluated while designing multispecies or multistrain probiotics.

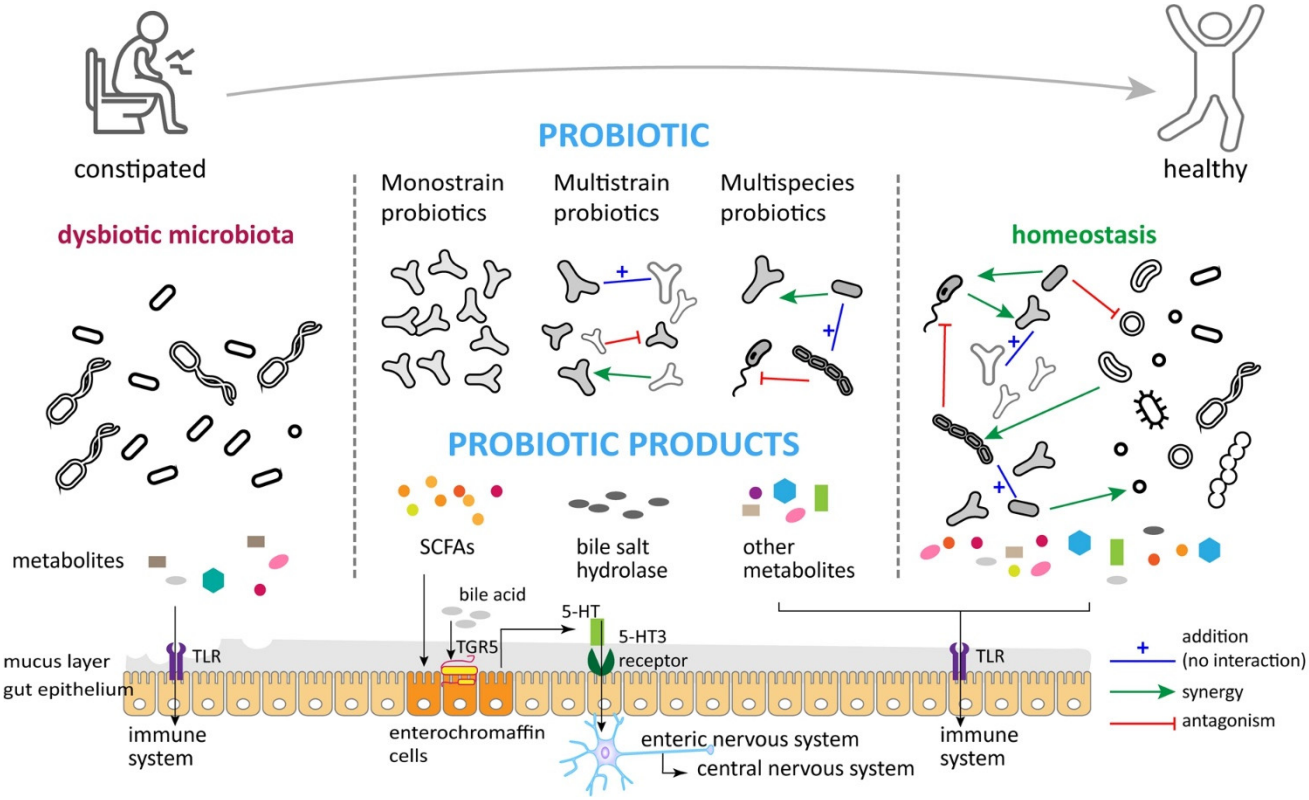


**Figure 4:** Modes of probiotic-probiotic interactions. Green and red arrows refer to stimulating and inhibitory affects respectively. Unidirectional or bidirectional metabolic cross-feeding of nutrients and microbial metabolites can promote synergy, while the production of inhibitory molecules contribute to ammenalism. These interactions as well as competition for resources between probiotic strains are expected to affect their viability and functionality rather than mere addition in the intestinal mucus.

Considering the complex microbial system nature in the human gastrointestinal tract, attention should also be paid to investigate the interaction between probiotic species/strains and intestinal commensal microbiota. In the current study, supplementation of probiotics did not significantly affect the microbiota alpha diversity and had varying effects on beta diversity. Moreover, changes in microbiota composition triggered by ingested probiotics varied, with several studies found no significant microbial shift in genus level. To better understand the impact of probiotics on intestinal microbes, recovery from fecal samples is often evaluated for clues of the viability, retention and growth of the ingested strain in the gut. In this study, not all included studies succeeded in retrieving the supplemented probiotic strains. Notably, the abundance of *Bifidobacterium lactis GCL2505* peaked in feces two days after the administration, then dropped quickly till not detectable seven days after the administration[51], suggesting that the ingested strain failed to colonize existing intestinal microbes. Therefore, the function and the mechanism of probiotics should be reconsidered according to their viability and colonization abilities when developing probiotics supplements in the future.

Supplementation of probiotics could also have an impact on intestinal microbial metabolites. Certain fermentation products such as SCFAs and lactic acid are known to lower fecal pH[70], modify intestinal motility[71] and manipulate the gut microbiota[72]. SCFAs produced in the colon[73], reflected in part as fecal pH, play a role in constipation management[40] and indicate microbial metabolic activity[74]. In our study, four monostrain probiotics presented divergent influences on fecal SCFAs or pH. Specifically, *Bifidobacterium*

*lactis NCC2818* and *Lactiplantibacillus plantarum P9* failed to alter the level of fecal SCFAs, in line with little or no impact on intestinal microbiota and constipation related symptoms[38,45]. However, fecal acetate and butyrate acid level were increased after *Bifidobacterium bifidum CCFM16* supplementation[40]. This difference could in part represent the net effect of acetate producing microorganisms: elevated abundance of *Bifidobacterium* and *Clostridia* (butyrate producers), but simultaneously with decreased abundance of *Bacteroides*. Wang *et al*. thus speculated that *Bifidobacterium bifidum CCFM16* achieved constipation relieving effects through SCFAs produced by above mentioned bacterial taxa[40]. Interestingly, some other probiotic strains, *i.e*., *Bacillus coagulans SNZ 1969* could modulate microbiota composition and alleviate overall symptoms without altering fecal SCFAs or pH[39]. These findings indicated that probiotics influence microbial composition and induce microbiota metabolites in a strain-specific manner and through different mechanisms, where further research is warranted.

Moreover, this study did not identify a single species as universally superior, certain species demonstrated specific benefits. For instance, *Bifidobacterium lactis* (*e.g., NCC2818, HN019*) consistently improved spontaneous bowel movements and stool consistency in multiple studies; *Lactobacillus plantarum* strains were also effective in improving stool frequency and consistency; *Bifidobacterium bifidum* (*e.g., CCFM16*) showed promising effects in increasing short-chain fatty acid (SCFA) production, which may contribute to symptom alleviation. In addition, this study did not observe a consistent pattern of superiority when comparing multispecies probiotics to monostrain probiotics, as their efficacy varied depending on the specific strains and study conditions. This variability highlights the importance of strain selection and tailoring probiotic formulations to targeted outcomes.

Our findings highlight the need for a shift in probiotic prescription practices, moving from the assumption that multispecies probiotics are inherently superior to a more evidence-based approach focusing on strain-specific efficacy. Clinicians can leverage these findings to adopt a more targeted approach in probiotic prescription, selecting strains with proven effectiveness for specific symptoms.

From a product development perspective, results of current study emphasized the necessity of designing probiotic formulations that leverage complementary mechanisms of action among strains. Rather than maximizing strain diversity, formulations should prioritize strains with proven efficacy in promoting gut motility and microbial balance. At a public health level, findings of current study can guide the development of recommendations for probiotic use in managing functional gastrointestinal disorders, providing an alternative to long-term reliance on laxatives and improving patient quality of life.

## 5. Conclusion

Current study provided critical insights into the efficacy of probiotics in constipation management, advocating for a targeted approach to probiotic selection. Specifically, this study illustrated that probiotics could increase spontaneous bowel movements and stool consistency, as well as alleviate overall symptoms. Additionally, some probiotics could modulate the composition and functionality of the intestinal microbial community. Nevertheless, the superior effect of multispecies over monostrain probiotics, with respect to

alleviating constipation related symptoms, was not observed in the current study. This highlighted the need in rational design of multispecies probiotics products to maximize their joint force. Future studies are warranted to investigate the relationship between probiotic species/strains, their interaction with existing intestinal microbes, as well as their impact on intestinal microbiota functionality. Together, this knowledge would hold significant potential for improving clinical practice, guiding product design, and shaping future research in the field.

## CRediT authorship contribution statement

The authors' responsibilities were as follows: RA and QPW designed research; YQZ, PLH, and RA conducted research; YQZ analyzed data, performed statistical analysis, and wrote the manuscript. RA, CAL, YW, XZ, QG, SW, YXZ, XHW, and QPW reviewed and edited the manuscript. All authors have read and approved the final manuscript.

## Declaration of competing interest

The authors declare no conflict of interest.

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