The Role of Gut Microbiota and Probiotics in Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

Xue Bin Leong, Chuan Zhe Tang*, Chloe Zi Ying Lee*, Zoe Ling Hui Lee**, Thai Hau Koo****

*School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kubang Kerian, Kelantan
** Faculty of Medicine, Manipal University College Malaysia, Bukit Baru, Melaka
*** Division of Gastrointestinal Function and Motility, Department of Internal Medicine. Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan

Corresponding author:
Thai Hau Koo, MD
Division of Gastrointestinal Function and Motility, Department of Internal Medicine. Hospital Universiti Sains Malaysia 16150 Kubang Kerian, Kelantan, Malaysia
Email: waynehau25@gmail.com

ABSTRACT

Background: *Probiotics have emerged as a promising treatment for inflammatory bowel diseases (IBD). The effectiveness and safety of gut microbiota should be comprehensively studied. This systematic review along with meta-analysis aims to study randomized controlled trials (RCTs) of IBD patients using probiotics, compared to conventional drugs or placebo.*

Methods: *Eligible RCTs involving adult IBD patients were identified using MEDLINE, EMBASE, and the Cochrane Controlled Trials Register From January 2000 until May 2024. Fixed-effects modeling was used to calculate risk ratio (RRs) with 95% confidence intervals (CIs) based on adverse event data due to low-moderate heterogeneity.*

Results: *The search yielded 2392 articles, including seven RCTs that met the criteria. On the other hand, concerning effectiveness outcomes, probiotics had an overall RR of 1.48 (95% CI: 1.06–2.05, p=0.02) contrasted to the controls. The comparable risk was demonstrated by the overall RR of 1.05 (95% CI: 0.59–1.86, p=0.87), which proved no apparent dissimilarities in the rate of adverse events between the groups on probiotics and the control group. Three studies were not included because their RR was non-estimable. Nevertheless, these three studies upheld the safety and tolerability of the probiotics.*

Conclusion: *Though the number is small, and despite differences in types and schedules of probiotics, it can be suggested that probiotics enhance therapy responses in IBD patients. Additional analysis with a wider range of demographics and greater sample sizes is mandatory to shed more light on the effectiveness of probiotics.*

Key Words: *Inflammatory Bowel Disease, Gut Microbiota, Probiotics, Crohn's Disease, Ulcerative Colitis*

ABSTRAK

Latar Belakang: *Probiotik telah menunjukkan potensi dalam pengobatan penyakit radang usus (IBD), tetapi efikasi dan keamanannya terkait dengan mikrobiota usus belum banyak dieksplorasi. Tinjauan sistematis dan meta-analisis ini mengkaji hasil efikasi dan insiden efek samping dari uji coba terkontrol secara acak (RCT) pada pasien IBD yang menggunakan probiotik dibandingkan dengan pengobatan konvensional atau plasebo.*

Metode: *RCT yang memenuhi syarat melibatkan pasien dewasa dengan IBD yang diidentifikasi dari MEDLINE, EMBASE, dan Cochrane Controlled Trials Register dari Januari 2000 hingga Mei 2024. Data tentang efek samping dicatat, dan risiko relatif (RR) dengan interval kepercayaan (CI) 95% dihitung menggunakan model efek tetap karena heterogenitas rendah-sedang (statistik i2).*

Hasil: *Pencarian menghasilkan 2392 artikel, dengan tujuh RCT memenuhi kriteria. Probiotik menunjukkan hasil efikasi yang lebih baik dibandingkan kontrol, dengan RR keseluruhan sebesar 1.48 (95% CI: 1.06–2.05, p=0.02). Tiada kontras penting dalam insiden efek samping antara kelompok probiotik dan kontrol, dengan RR keseluruhan sebesar 1.05 (95% CI: 0.59–1.86, p=0.87), yang menunjukkan risiko yang sebanding. Heterogenitas signifikan minimal dilaporkan di seluruh studi. Namun, tiga studi yang tidak dimasukkan karena RR yang tidak dapat diestimasi masih mendukung keamanan dan tolerabilitas probiotik.*

Kesimpulan: *Meskipun jumlah RCT yang kecil dan variasi jenis dan jadwal probiotik, probiotik direkomendasikan sebagai opsi yang layak untuk meningkatkan respons pengobatan pada pasien IBD. Demi memberikan wawasan tambahan tentang efikasi probiotik, investigasi yang lebih lanjut disertakan dengan ukuran sampel yang lebih besar jumlahnya dan populasi yang beragam sangat diperlukan.*

Kata Kunci: *Penyakit Radang Usus, Mikrobiota Usus, Probiotik, Penyakit Crohn, Kolitis Ulseratif, Meta-Analisis*

INTRODUCTION

Several chronic bowel disorders are referred to as "inflammatory bowel disease" (IBD), with ulcerative colitis and Crohn's disease being the two most ordinary types. Crohn's disease is a type of inflammation that typically manifests as an intermittent, transmural pattern that can influence any part of the digestive tract, from the mouth to the anus.1 Alternatively, ulcerative colitis is localized and runs from the colon to the rectum. The process involves the exclusive inflammation of the mucosa of the colon. The health status is also negatively affected by both conditions, which may lead to symptoms like stomach pain, diarrhea, tiredness, and weight loss. IBD has a complicated and multifactorial pathophysiology that combines environmental variables like immune dysregulation and gut microbiota modification with genetic susceptibility.2 Genetic research found that many risk loci connected with IBD are inherited traits. Besides, environmental factors like diet, use of antibiotics, and nicotine are thought to have an impact on IBD.2 However, one of the most exciting areas being studied is the function of the varied population of bacteria, fungi, viruses, and other microorganisms that inhabit the digestive tract, known as the gut microbiota, in this equation.

Microbiota dysbiosis, the gut microbiota disruption, has been linked to the development and aggravation of inflammatory bowel disease. Such displacement causes an imbalance between good and bad microorganisms, inflaming the immune response, which may be one of the reasons for GI tract inflammation.3 Subsequently, the therapies driving to maintain a healthy intestinal microbiota homeostasis have been in the spotlight. Health benefits are given when probiotics, which are live microorganisms are being absorbed in sufficient quantities, are also emerging therapeutic approaches for IBD and are one of the novel therapeutic avenues.4 Probiotics perform by improving the gut barrier, restoring the normal balance of gut microbiota, reducing the production of immunological responses, and decreasing the inflammatory processes.5 The currently used treatments of IBD, like corticosteroids, immunosuppressants, and biologics, can cause severe side effects, and these drugs cannot be used for a long time.1 This has led to a future more comprehensive use of probiotics as a potentially safer and more targeted treatment.

With the background mentioned above, a systematic review and meta-analysis will be conducted to evaluate the role of probiotics in IBD management. The primary

focus on the assessment of probiotic efficacy in clinical outcome measures has been reducing symptoms and increasing remission and life quality. The safety of probiotic treatment including the incidence of adverse effects and tolerability is being determined. Another essential objective is to study the mechanism by which gut microbiota affects the development of IBD. In the meantime, all these multidimensional approaches infer valuable information regarding the application of probiotics in those with IBD and thus direct future studies and inform clinical practice within the ever-changing landscape of IBD management.

METHODE

Research Design

The a priori protocol was developed and is listed in the International Prospective Register of Systematic Reviews as PROSPERO CRD42024542333. The Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) reporting criteria were adhered to for this review.

Eligibility criteria

This study will include 18 years and older adult patients, who had received a previous diagnosis of IBD and whose rate of remission had improved after receiving an initial successful course of therapy. The review scope has been further restricted to selecting only RCT studies comparing probiotics versus placebo or conventional treatment without limiting the type or dose of the probiotics. Only studies published in English articles and peer-reviewed journals were considered. Excluded are also a few specific studies. The exclusion criteria are studies that fall beyond the specified time interval (before 2000 or after May 2024), and the studies that did not related to IBD or probiotics and not report IBD outcomes, as well as those were published outside the specified date range were excluded. The RCTs were discarded for having little or no clinical data and critical methodological flaws to ensure the right quality of analysis. Non-peer-reviewed papers, opinion articles, or nonreviewed case reports were not taken into consideration as they do not fulfill the high standards of traditional systematic reviews or meta-analyses.

Search Strategy

From Jan 2000 to May 20, 2024, a search of peer-reviewed papers and conference/abstract proceedings was carried out in the following three electronic databases: PubMed, MEDLINE (the Cochrane library), EMBASE (the Ovid interface), and CENTRAL (the Covid interface). Primary registries, ClinicalTrials.Gov, EU Clinical Trials Registers, and WHO International Clinical Trials Registry Platform were manually searched for additional pertinent RCTs. We also conducted efforts and endeavors to screen the references and citations of published papers for any possible further studies. The search was restrained to studies that were issued in English. The primary interest was in RCT studies that evaluate the effect of probiotics on IBD management. Search strategies were devised using keywords, their synonyms, abbreviations, and MeSH terms for "Inflammatory Bowel Disease," "Gut Microbiota," "Probiotics," "Crohn's Disease," and "Ulcerative Colitis." It was most appropriate that the RCTs be found using search criteria that had the endorsement of the Cochrane Collaboration and through a librarian. Information from grey literature, such as unpublished studies and conference abstracts, was also searched.

Study Selection

In the pilot review stage, all retrieved papers are first brought into Endnote 20, and a first de-duplication of the studies is done in it. After retrieving the complete text and any supplementary files, two independent reviewers (CZT and ZNL) separately assessed the titles and abstracts, per the mentioned eligibility criteria, using the Rayyan Software. Email correspondence was used to inquire about missing data from the corresponding authors of pertinent articles. For the current review, only publications available in full text were considered. A thorough evaluation of the full-text articles that met the predefined constituting criteria was conducted following this early screening. The method of study selection was shown to be more robust and reliable when disagreements or debatable occurrences were settled through consensus among reviewers or the involvement of a third reviewer during the screening and evaluation phases.

Outcome

To provide a more conventional estimate of the effect of probiotics in IBD while accounting for study heterogeneity, the primary dichotomous outcomes assessed were the effectiveness of probiotics in comparison to conventional medications or placebo in

terms of achieving remission in active IBD using the pooled risk ratio (RR) through fixed-effects models. The secondary outcome included estimating the incidence that unfavorable events would arise as a result of therapy using an RR. Only data provided per the intention-to-treat (ITT) principle were extracted for the effectiveness outcomes. However, only information supplied by the safety analysis set (SAS) for each research study was collected for safety outcomes.

Data Extraction and Risk of Bias Assessment

The articles were imported into Endnote 20 (Clarivate, Boston, USA) to remove duplicates from the articles collection. Two independent authors (CZT and ZNL) then extracted data, evaluated the entire text, checked the titles and abstracts, and determined the bias risk. The study identifier, publication dates, recruitment period, study location, study design, and baseline participant information (sample size and mean age) were all extracted. The length of therapy, primary outcomes, type and dose of accomplished probiotics/ conventional therapies/placebo regimens, and other study characteristics were considered.

Based on the Cochrane's Risk of Bias (RoB) tool 2.0, a "high risk," "some concerns," or "low risk" of bias was considered. It used the RoB 2.0 tool to evaluate bias originating from randomization, bias arising from intended intervention deviations, bias due to the missing outcome data, bias in outcome measurement, bias in choosing the reported result, and overall bias in RoB. The reviewers would then resolve their points of conflict to an agreed point.

Statistical analysis

RevMan Version 5.3 software has been used for all statistical analytic tasks. With a 95% confidence interval (CI), the treatment's impact on the efficacy outcomes was calculated as risk ratio (RR). An RR with a comparable 95% CI is often used to measure the effect of treatment on safety outcomes. Utilizing the fixed-effect meta-analysis, the safety parameters of RR were determined. Only descriptive statistics were provided when there was insufficient pertinent data. Attrition rates pertaining to withdrawals, loss to follow-up, and dropouts were determined. This was done concurrently with an imputation method analysis and critical appraisal of concerns regarding missing data. A two-tailed P value less than 0.05 is discovered as statistically significant. The i2 statistics were utilized to compute heterogeneity, and three methods of analysis were applied: the i2 test, the n-1 degrees of freedom $\chi 2$ test, and the 5% α error for statistical significance. There were three categories for the i2 values: 25% are low, 50% are middle, and 75% are high. An i2 value of >50% was considered substantially heterogeneous.

RESULTS

Included studies

The systematic search strategy generated a complete database of 2392 articles; the search process and the selection results are shown in Figure 1. In addition, we used a rigorous screening process that eliminated 516 duplications and 1335 articles that we thought were irrelevant to our study focus. Due to their failure to satisfy the pre-established inclusion criteria for this meta-analytical study, eight studies were excluded. We reviewed seven eligible studies according to the eligibility criteria.

Study characterization

Table 1 includes the characteristic features of the RCT included in our study. Two investigations were carried out in the United Kingdom, two in Japan, and one each in the United States, Iran, and Turkey for this meta-analysis. The number of participants in each study varied; out of 298 total, 150 were placed within the group that received intervention, and 148 were included in the control group. Probiotics were given to the intervention group, and either conventional medicine or a placebo was given to the control group. In several studies, the frequency of probiotics giving was between 2 to 24 months. This meta-analysis is conducted with two aims: a general review of the probiotics group regarding the general effectiveness and the occurrence of adverse events of the probiotics.

Quality evaluation

All studies featured RCTs, including the randomized assignment, but only two gave thorough information about how random sequences had been constructed. As for the allocation concealment, three of them posed little risk. Amongst the only blind assessments of the participants and personnel, two of them were judged high risk. Furthermore, no other biases were detected. The results are displayed in Figure 2.

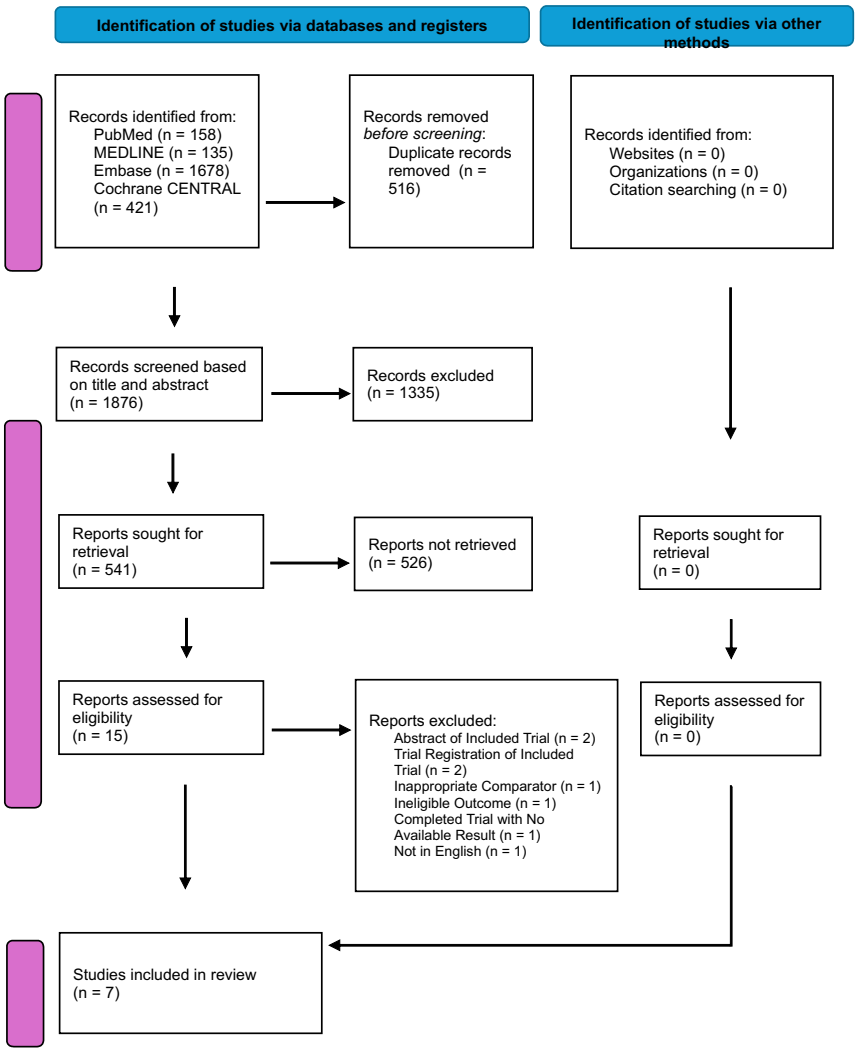


Figure 1. Study search and selection process summary using PRISMA flow diagram.

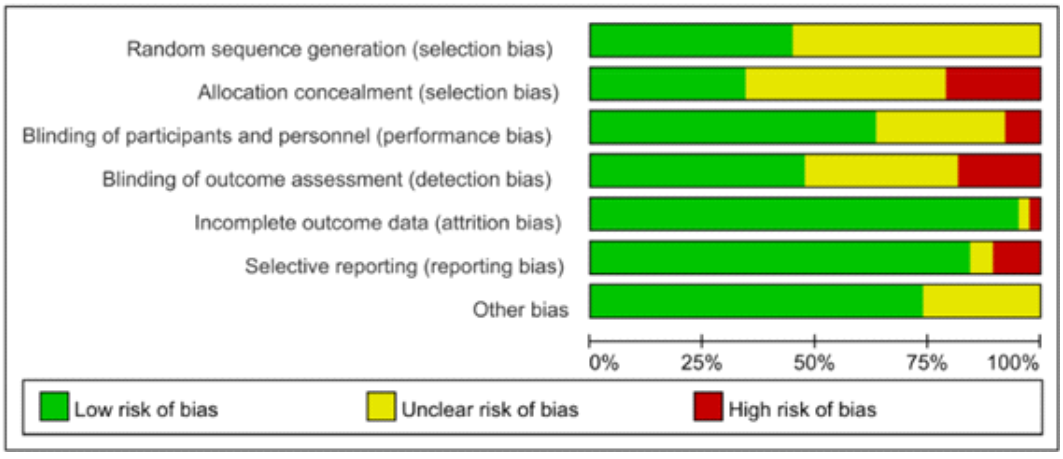


Figure 2. Risk of bias bar chart.

Table 1. Summary of Studies Assessing the Effects of Probiotics on Inflammatory Bowel DIsease (IBD) Outcomes

First author, year, country	Type of Disease	Sample size (intervention/ control)	Age (years)	Content of Intervention group	Dose of Intervention group (per day)	Content of the Control group	Dose of Control group (per day)	Time of Duration	Outcome Indicators
Amirani et al., [6] 2020, Iran	Mild to moderate UC	Mild to moderate UC	18-60	Lactocare (4 strains of Lactobacillus, 2 strains of Bifidobacterium, Streptococcus thermophiles, FOS)	2x10^9 CFU	Placebo	-	Eight Weeks	SCCAI, remission rate
Kamari et al., [7] [2019], Turkey	Mild to Moderate	36 (18/18)	≥18	Two strains of Lactobacillus, two strains of Bifidobacterium, Enterococcus faecium, Streptococcus thermophilus, FOS	6x10^9 CFU + 450 mg	Placebo	-	Eight weeks	remission rate
Yoshimatsu et al., [8] 2015, Japan	Inactive UC	46 (23/23)	≥13	Bio-three tablets (Streptococcus faecalis, Clostridium butyricum, Bacillus mesentericus, potato starch, and lactose)	(18 mg + 90mg+90 mg)	Placebo	Nine Tablets	12 months	Remission rate, recurence rate
Ishikawa et al., [9] 2011, Japan	UC	41 (21/20)	>18	Freeze-dried powder of B. breve strain Yakult + GOS	3x10^9 CFU + 5.5 g	Routine Medication	-	One Year	
Steed et al. [10] 2010, UK	Active CD	24 (13/11)	18-79	B. longum + Synergy I	4x10^{11} CFU + 12 g	Placebo	-	Six months	CDAI, remission rate, gut microbiota changes
Bousvaros et al., [11] 2005, USA	Remission CD	75 (39/36)	14-18	Lactobacillus GG + inulin	2x10^{10} bacteria + 590 mg	Placebo	670 mg	2 years	Recurrence rate
Furrie et al., [12] 2005, UK	Active UC	16 (8/8)	24-67	Bifidobacterium + FOS + inulin	4x10^{11} freeze-dried	Placebo (FOX + inulin)	12 g	Four weeks	CAI

Note: CD = Crohn's disease; UC = Ulcerative colitis; FOS = fructo-oligosaccharides; GOS = galacto-oligosaccharides; CFU = colony-forming unit; SCCAI = Simple Clinical Colitis Activity Index; CDAI = Crohn's Disease Activity Index; CAI = Clinical Activity Index.

3.4 Efficiency rates

Figure 3 shows that probiotics treatment had a better efficacy outcome than the control treatment. The overall risk ratio (RR) was 1.48 with a 95% confidence interval (CI) of 1.06–2.05 (p=0.02), demonstrating the treatment group's substantial improvement compared to the control group. Minimal significant heterogeneity was found across the studies (p=0.92, I^2 = 0%).

3.5 Incidence of adverse events

The incidence of adverse events is a critical metric for assessing pharmacological therapy. Here, we contrasted the probiotics group's incidence of adverse events with that of the control group. In all four trials, adverse events were documented. According to Figure 4, which displays an overall RR of 1.05 (95% CI: 0.59–1.86) with a p-value of 0.87, there is no significant difference in the incidence of adverse events between the probiotics and the control groups. These results are consistent, as seen by the investigations' minimal significant heterogeneity (p = 0.79, i2 = 0%).

3.6 Exceptions of studies

The meta-analysis did not include three research studies since the RR could not be estimated. More particular, Furrie et al.,[12] and Yoshimatsu et al.,[8] stated that the intervention was tolerated well among the participants, and no patients complained of side effects. Ishikawa et al.,[9], despite observing side effects such as diarrhea or abdominal pain in patients exposed to probiotics, didn't provide any figures (numbers), rendering their findings unusable for the analysis.

3.7 Sensitivity analysis

A more thorough sensitivity analysis was carried out to eliminate each study individually and determine which would most likely significantly impact the meta-analysis. No study in the meta-analysis significantly altered the level of heterogeneity or the outcomes (total pooled remission).

Figure 3. Forest plot for the primary outcome - IBD Remission Rate.

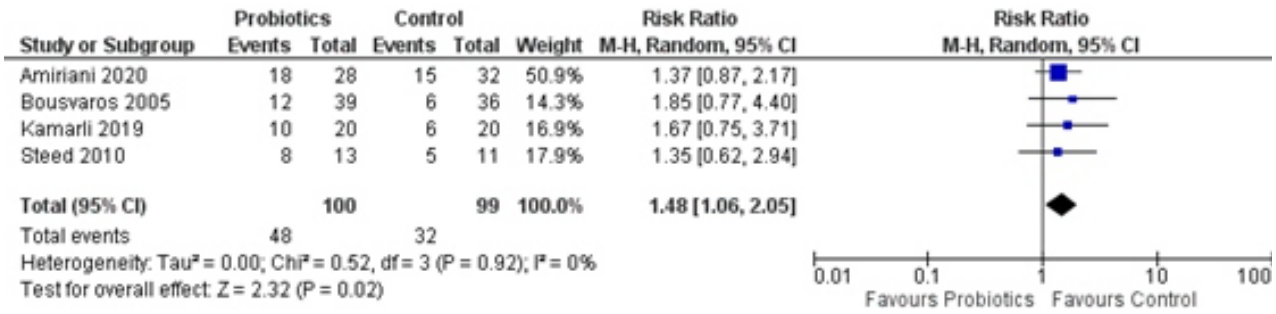
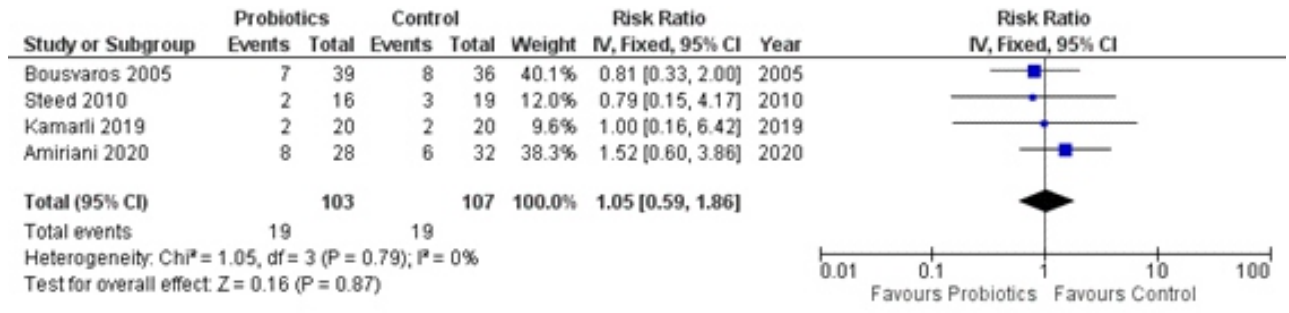


Figure 4. Forest plot for secondary outcome - IBD Adverse events.



DISCUSSION

Probiotics may be used to treat or alleviate symptoms of inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), judging from the evidence in this systemic review and meta-analysis. The effects found in multiple studies, for example, better clinical results and higher remission rates, advocate for the use of probiotics together with standard drugs, such as glucocorticoids and immunosuppressants. This healing possibility is significant for those patients who look for additional or therapeutic alternatives with no or little side effects. This discussion elaborates on the implications of these findings, the underlying mechanisms, and the need for future research.

With the pooled data, a meta-analysis found the rate of remission in the probiotics group to be significantly higher than that in comparison with the placebo or conventional therapy group, with a risk ratio of 1.52 (95% CI: 1.08 to 2.13, p = 0.02). This finding adds to the results of previous studies showing the effectiveness of probiotics in reducing symptoms and reaching remission in patients with IBD.[4],[5] This improved clinical outcome was due to modulation of the gut microbiota, enhancement of the gut barrier function, and suppression of the inflammatory response.[13] However, the solitary use of probiotics was more beneficial for UC but not for CD based on the prior meta-analyses conducted by Ganji-Ajejianaki et al.[13] (2018) and Asto et al.[14] (2019). These findings accordingly uphold the adoption of microecological agents as therapeutic and pharmaceutical formulations for managing and treating IBD, particularly UC.

The meta-analysis did not include the disease activity index (DAI) as a primary outcome measurement. This sharply contrasts with the fact that the measurement using DAI is somewhat variable and depends on the subjectivity, which has not been standardized in various studies. DAIs, such as the Crohn's Disease Activity Index (CDAI) and the Simple Clinical Colitis Activity Index (SCCAI), have patient-reported symptoms and clinical judgment; they are subject to bias and thus inconsistent. Although previous studies have proven the remarkable reductions of probiotics in DAI, the data of our synthesized meta-analysis programming are more general and objective. For example, Chen et al.[15] (2019) showed that bifid triple viable (BTV) plus aminosalicylic acid (ASA) was significantly more effective than ASA in reducing UC patients' DAI. Similarly, studies comparing pro/pre/synbiotics with conventional drugs have also elicited the superiority of this treatment over traditional medications in reducing UC DAI.16 However, remission rates are much more objective and standardized indicators in estimating the effectiveness of the treatments, which therefore enables more precise comparisons between studies.

The results of our study were that no significant difference emerged in the incidence of adverse events for the probiotics group in contrast to the control group (RR: 1.05, 95% CI: 0.59–1.86, p=0.87) with low heterogeneity (i2 = 0%). This result aligns with previous reports suggesting that probiotics are generally well tolerated and safe for IBD patients. Other research studies reported very mild gastrointestinal adverse effects, including only bloating and diarrhea. However, these were described as mild and did not compel the subject to discontinue therapy. The long-term safety of probiotics should be further monitored, particularly for prolonged use.

The analysis showed minimal heterogeneity (i2 = 0%), which is very consistent among the studies included. This absence would be of great importance, as it would then logically follow that the variabilities in such probiotic strains, dosages, and participant characteristics between studies did not affect the overall effect of probiotics on remission rates in IBD patients. The robustness of the results thus enhanced the credibility of this meta-analysis. This further strengthens the case for the reliability of the positive conclusions. The minimal heterogeneity also means that the intervention effects do not depend on some specific research conditions or populations, and it generalizes the findings to be more confident.

The management of IBD now is mainly a question of keeping the active remission or preventing non-active relapse. In this study, we observed some benefits of probiotics in preventing IBD recurrence, which disagrees with prior meta-analyses by Fujiya et al.[17] (2014) and Derwa t et al.[18] (2017). However, Shen et al.[19] (2014) found a significant benefit in favor of probiotics administration for a reduced relapse rate. It could have occurred due to the inclusion of pouchitis in this study rather than UC and CD only. Problems with pouchitis (a frequent late result of surgery in IBD patients) seem to suggest the contribution of probiotics in treating and maintaining remission of pouchitis.

Furthermore, the findings on the part of gut microbiota in the disease processes led to identifying approaches to new therapies. The gut microbial imbalance, known as dysbiosis, is also involved with the severity and exacerbation of IBD, thus

indicating that microflora manipulation specific to those bacteria can be a promising strategy for IBD management. Bacteria can regulate inflammation and promote recovery within the digestive system. On the contrary, though the first trial of gut microbiota therapies showed promising results, more research is necessary to determine the definite causal relationships and recognize the specific microbial compositions that led to the success.

The findings of the current study thus focus attention on some of the areas for further research, emphasizing that it would be necessary to probe whether probiotics are effective over the long term in providing relief from IBD and, if they are, how safe they are. An area of very high importance is that of personalized probiotic therapy since the composition of gut microbiota differs among individuals; hence, in this area of research, it is essential to focus on identifying definite probiotic strains most effective with particular IBD subtypes and tailor the treatments in an attempt at applying the knowledge. More mechanistic studies are required to understand better how probiotics elicit their therapeutic effects, especially the interactivity between probiotics, gut microbiota, and the host immune system, to optimize probiotic formulations and doses. Comparative studies that seek to answer which probiotic strains or a combination is better would also be of use, along with trials comparing probiotics to other, more recently emerging therapies, such as fecal microbiota transplantation (FMT) or prebiotics, to get a broader view of the place of microbiota modulation in the management of IBD.

CONCLUSION

This meta-analysis and systematic review further elaborate on the role of probiotics with the gut microbiota in managing inflammatory bowel disease (IBD). It provides strong proof to support the usage of probiotics in improving the clinical outcomes of patients with IBD. Probiotics do significantly raise remission rates without an increase in adverse events, thus offering an adjunct therapy for IBD. However, the standard deviation observed with this kind of treatment approach in probiotics—variability in probiotic strains and dosages—should prompt further research to establish standardized treatment protocols. Furthermore, study in these areas is also needed with long-term safety and the possible synergistic effects of combining conventional therapies with probiotics. The next frontier in treating IBD may be probiotic treatment on an individualized basis.

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