Probiotics for Preventing Relapse in Ulcerative Colitis: A Systematic Review and Bayesian Network Meta-Analysis

Steven Alvianto, Virly Nanda Muzellina**, Nicolas Daniel Widjanarko*, Yeong Yeh Lee***, Olivia Wangidjaja**

*School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia
**Division of Gastroenterology, Pancreatobiliary, and Digestive Endoscopy, Department of Internal Medicine, Dr. Cipto Mangunkusumo National General Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia
***School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Malaysia

Corresponding author:
Steven Alvianto, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, Email : alvianto_steven@yahoo.com

ABSTRACT

Background: *Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by periods of relapse and remission. Preventing relapse is critical to improving long-term outcomes. This study aimed to compare the efficacy of probiotics, 5-aminosalicylic acid (5-ASA), probiotics combined with 5-ASA, and placebo in preventing relapse in UC.*

Methods: *A comprehensive search from PubMed, Cochrane Library, MEDLINE, ProQuest, ScienceDirect, Clinical Trials. gov and Google Scholar databases were conducted. The primary outcome was clinical relapse. A Bayesian random-effects model calculated pooled odds ratios (ORs) with 95% CIs and treatment ranks were assessed using the surface under the cumulative ranking curve (SUCRA).*

Results: *Of total 552 initial papers, 37 extracted, and 26 were removed due to exclusion criteria. Eleven RCTs involving 1,099 participants were eventually included for analysis. Probiotics combined with 5-ASA had the highest efficacy (OR = 0.23, 95% CI: 0.027–1.09; SUCRA = 71.43), followed by 5-ASA alone (OR = 0.25, 95% CI: 0.035–0.95; SUCRA = 66.90) and probiotics alone (OR = 0.275, 95% CI: 0.059–0.724; SUCRA = 59.69). Placebo ranked lowest (SUCRA = 1.98). The most commonly used probiotics included E. coli Nissle 1917, Lactobacillus GG, and Bifidobacterium species. The most frequently used 5-ASA preparation was mesalazine. Interventions were generally well-tolerated, with no significant adverse events reported.*

Conclusion: *With the Bayesian NMA, Probiotics plus 5-ASA demonstrates the highest efficacy in preventing relapses in UC. Further research is needed to standardize probiotic regimens and to assess long-term outcomes with the combination approach.*

Keywords: *5-ASA, probiotics, probiotics plus 5-ASA, relapse, ulcerative colitis*

ABSTRAK

Latar Belakang: *Kolitis Ulseratif (KU) adalah penyakit radang usus kronis dengan karakteristik periode kambuh dan remisi. Mencegah kekambuhan sangat penting untuk meningkatkan hasil jangka panjang. Studi ini bertujuan untuk membandingkan efikasi probiotik, asam 5-aminosalisilat (5-ASA), kombinasi probiotik dengan 5-ASA, dan plasebo dalam mencegah kekambuhan KU.*

Metode: *Pencarian komprehensif dilakukan pada database PubMed, Cochrane Library, MEDLINE, ProQuest, ScienceDirect, ClinicalTrials.gov, dan Google Scholar. Hasil utama yang diukur adalah kekambuhan klinis. Model efek acak Bayesian menghitung rasio odds (OR) gabungan dengan interval kepercayaan (CI) 95%, serta peringkat pengobatan dengan kurva peringkat kumulatif (SUCRA).*

Hasil: *Sebelas uji klinis acak (RCT) dengan 1.099 peserta dianalisis. Kombinasi probiotik dengan 5-ASA memiliki efikasi tertinggi (OR = 0,23, 95% CI: 0,027–1,09; SUCRA = 71,43), diikuti 5-ASA (OR = 0,25, 95% CI: 0,035–0,95; SUCRA = 66,90) dan probiotik (OR = 0,275, 95% CI: 0,059–0,724; SUCRA = 59,69). Plasebo memiliki peringkat terendah (SUCRA = 1,98). Probiotik yang sering digunakan meliputi E. coli Nissle 1917, Lactobacillus GG, dan Bifidobacterium. Preparat 5-ASA yang umum digunakan adalah mesalazine. Intervensi umumnya dapat ditoleransi dengan baik tanpa efek samping signifikan.*

Kesimpulan: *Kombinasi probiotik dan 5-ASA menunjukkan efikasi tertinggi dalam mencegah kekambuhan KU yang tidak aktif, meskipun tidak mencapai signifikansi statistik. Pengobatan ini lebih unggul dibandingkan terapi individu dan plasebo, mendukung potensinya dalam praktik klinis. Penelitian lebih lanjut diperlukan untuk menstandarisasi regimen probiotik dan mengevaluasi hasil jangka panjang.*

Kata kunci: *5-ASA, probiotik, probiotik plus 5-ASA, kekambuhan, kolitis ulseratif*

INTRODUCTION

Ulcerative Colitis (UC), a form of chronic inflammatory bowel disease (IBD), is characterized by recurring episodes of inflammation in the colonic mucosa, fluctuating between periods of remission and relapse.[1] While the exact cause remains unclear, UC is believed to result from a complicated interplay of environmental variables, immunological dysregulation, genetic susceptibility, and gut microbial imbalances.[2] The incidence of UC is increasing globally; for examples, in the Asian communities, rates ranged from 5.3 to 63.6 per 100,000, while in the North American populations, the incidence ranged from 37.5 to 238 per 100,000.[3–5] Conventional treatments primarily focus on reducing inflammation and maintaining long term remission, with mesalazine- or sulfasalazine-based therapies being the cornerstone for years.[6] Despite adherence to standard therapy, many patients still experienced relapses, highlighting the need for safer and more effective maintenance strategies, which has fueled interest in probiotic therapy as an alternative approach.[7]

Probiotics are living beneficial bacteria that improve gut barrier function, regulate immune responses, and maintain gut microbiota balance conferring health benefits.[8] Emerging evidence suggests that dysbiosis, or an imbalance in the gut microbiome, plays a crucial role in the UC pathogenesis, making probiotics a promising therapeutic option.[9] Probiotics are frequently prescribed by doctors as an adjuvant treatment since they are generally thought to be safe.[10] Different societies have different guidance on the use of probiotics in UC. For example, American Gastroenterological Association (AGA) 2020 stated currently there is no evidence to support the use of probiotics in UC patients.[11] However, the European Society for Parenteral and Enteral Nutrition supports the use of specific bacterial strains to induce remission in patients with mild-to-moderate ulcerative colitis, and in China, probiotics such as Bifidobacterium and Lactobacillus are recommended as adjuvant therapy to maintain UC remission.[12]

While exact mechanisms are unclear but probiotics have been shown to modulate inflammatory pathways, enhance mucosal healing, and restore microbial diversity, which are critical factors in UC management.[13] Wirya et al. stated that probiotics with specific strains can significantly enhance remission rates and lower relapse rates in IBD patients.[14] According to other studies, when compared to a placebo, probiotics may help induce clinical remission in active UC. However, when given alone, their efficacy seems comparable to that of 5-ASA, with little to no differences in clinical remission rates.[15] Probiotics may have little to no impact on clinical relapses or sustaining remission when compared to 5-ASA, and it's unclear if taking probiotics along with 5-ASA provides any further advantages over 5-ASA alone.[16]

Hence, by systematically reviewing and analyzing available clinical evidence, we seek to determine the efficacy of probiotics, 5-aminosalicylic acid (5-ASA), probiotics combined with 5-ASA, and placebo in preventing relapses in UC. This study uses a Bayesian network meta-analysis (NMA) to give a thorough evaluation on the efficacy of studied compounds and helps bridge the current knowledge gaps and to guide future clinical applications of probiotic-based therapies in UC management.

METHODS

The study adhered to the PRISMA 2020 guidelines for systematic reviews and meta-analysis methodology and registered with the International Prospective Register of Systematic Reviews (PROSPERO) (registration number CRD42025641731; February 2, 2025).

Primary Study Objective

Current study primarily aimed to compare the effectiveness of probiotics, 5-ASA, probiotics plus 5-ASA, and placebo in preventing UC relapses.

Search Strategy

A thorough literature search was performed using a number of electronic databases including Cochrane, ProQuest, MEDLINE, Google Scholar and ClinicalTrial.gov. SA, VNM, and NDW independentperformed the search using predefined keywords "Ulcerative Colitis" and "Probiotics" **(Table 1),** adhering to the PICOTS-SD criteria listed below:
Patients: Adult patients diagnosed with Ulcerative Colitis in remission

Intervention	: Probiotics alone, probiotic combined with 5-ASA
Comparator	: Placebo, 5-ASA alone
Outcomes	: Relapse rate (proportion of patients experiencing relapse)
Time	: No restriction of time
Setting	: Outpatient settings, including gastroenterology clinics, hospitals, and specialized IBD centers where patients with ulcerative colitis in remission are monitored.
Study Design	:All randomized controlled trials (RCTs)

Eligibility criteria

Type of Studies

We included all RCTs studies. We did not include observational studies, case series, case report, reviews, book chapters, commentaries/editorials, in vitro, and in-silico

Participants

UC adult patients (≥18 years old) in remission were included for this study. Pregnant or breastfeeding individuals were excluded.

Outcome of Interest

The primary focus of this study was the clinical relapse rate among UC patients after intervention using studied compounds as mentioned above. The safety profile (adverse events and major adverse events) was evaluated as secondary outcome.

Study Selection

The selection of pertinent studies was performed using a methodical screening procedure. Three researchers reviewed the titles and abstracts after deduplication using the Zotero software (version 7.0.15; Corporation for Digital Scholarship, Virginia, USA) on February 3, 2025. Studies that were judged unnecessary from preliminary assessments were excluded. The remaining full-text articles were then evaluated in accordance with predetermined eligibility standards. In order to guarantee thorough coverage, the reference lists of the included research were manually searched for other potentially eligible literatures. Achieving a majority agreement among the reviewers determined which literatures were chosen for final inclusion.

Table 1. Search Strategy Detailed

Database	Query
PubMed	"Colitis, Ulcerative"[MeSH Terms]
	“Probiotics”[MeSH Terms]
	#1 AND #2 Filters: Clinical Trial, Randomized Controlled Trial, Humans
Proquest	abstract([ulcerative colitis])
	abstract([Probiotics])
	#1 AND #2 Filters: Scholarly Journals, Article
Google Scholar	allintitle: ("Ulcerative Colitis") AND ("Probiotics”)
Cochrane	"Colitis, Ulcerative"[MeSH Terms]
	“Probiotics”[MeSH Terms]
	#1 AND #2
ClinicalTrial.gov	("Ulcerative Colitis") AND ("Probiotics”)

Data Collection Process

A standardized procedure for extracting data was used. The primary author's name, publication year, study design, sample size, and participant age, disease duration, definition of relapse, probiotic regimen, 5-ASA regimen, disease location (rectosigmoid/left-sided/pan-colitis), adverse events, and serious adverse events were all extracted from each included study by SA and VNM.

Summary Measures

Relapse rate statistics were presented as proportional data. The most suitable effect size metric was determined to be odds ratios (ORs).

Risk of Bias Assessment

NDW and OW assessed each study using the Cochrane Risk of Bias instrument 2 (RoB 2).[17] The entire review team discussed and eventually achieved a consensus on any differences in quality assessment.

Confidence in Cumulative Evidence

We used the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) system to evaluate the level of confidence in the cumulative body of evidence.[18] This system classified the evidence's overall certainty into four categories: high, moderate, low, and extremely low quality.

Synthesis of Results and Statistical Analysis

The NMA was conducted using the MetaInsight web-based tool (version 6.3.0), developed and maintained by the NIHR Complex Review Support Unit (CRSU). The platform, freely accessible at https://crsu.shinyapps.io/MetaInsight/, was accessed on February 5, 2025. The combined data were shown graphically using forest plots.[19] A bayesian random-effects model was employed because of possible differences in outcome evaluation techniques amongst studies. The discrepancy was evaluated using a deviation plot and node-splitting analysis. To evaluate the analysis's robustness, a sensitivity analysis was performed. The surface under the cumulative ranking (SUCRA) curve is used to rank the treatments. More effectiveness was indicated by a greater SUCRA.

RESULTS

Selection of Study

As seen in **Figure 1**, a flowchart representing the study selection procedure and the outcomes was created. Of total 552 papers from initial search, 37 papers were extracted in accordance with the selection criteria. Of the 37 papers, 26 including two evaluated in children and adolescents, sixteen in active UC, seven review studies, and one single arm trial—did not fit the inclusion criteria. Ultimately, 11 papers that qualified for data extraction were used in the network meta-analysis.

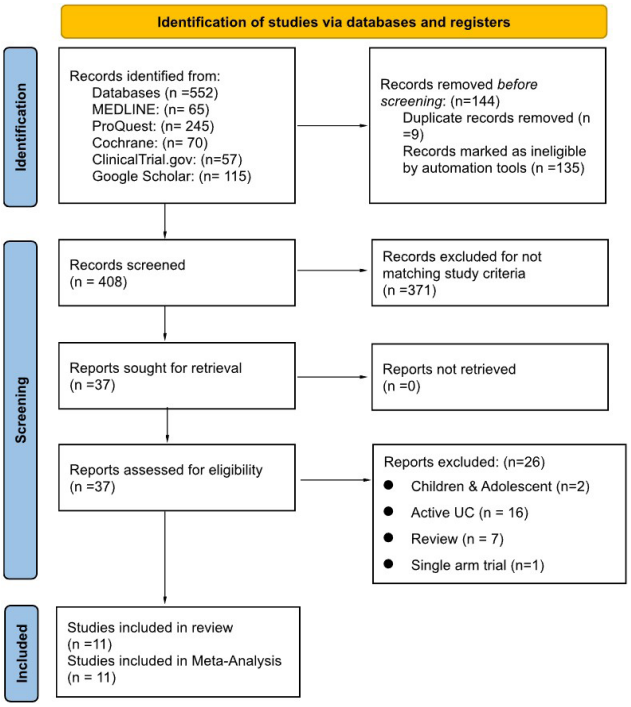


Figure 1. PRISMA Flowchart of Included Studies

Characteristics of the Included Studies

This study involved 1,099 participants with UC in remission with follow up duration ranging from 4 weeks to 52 weeks. Definitions of relapse were varied among studies because of differences in the evaluation tools used including clinical activity index (CAI) score, simple clinical colitis activity index (SCCAI), endoscopic index, Sutherland disease activity index (DAI), based on the appearance of UC clinical symptoms and endoscopic features and four studies like Copaci 2000, Cui 2004, Copaci 2014, and Bjanarson 2019 lack relapse information. The most commonly used probiotics included E. coli Nissle 1917, Lactobacillus GG, and Bifidobacterium species. The most frequently used 5-ASA preparation was mesalazine. There were no notable side effects observed, and the interventions were usually well tolerated. Most common adverse events reported included diarrhea, vomiting, nausea, flatulence, and abdominal pain. **Table 2** displayed further study characteristics.

NETWORK META-ANALYSIS RESULTS

Figure 2 shows the results of the NMA for relapse rates in UC. Probiotics plus 5-ASA (OR = 0.23, 95% CI: 0.027–1.09; SUCRA = 71.43) ranked highest. The 5-ASA alone ranked second (OR = 0.25, 95% CI: 0.035–0.95; SUCRA = 66.90), followed by probiotics alone (OR = 0.275, 95% CI: 0.059–0.724; SUCRA = 59.69) and placebo as the reference (SUCRA = 1.98). Further details of NMA result are shown in **Table 3 and 4.**

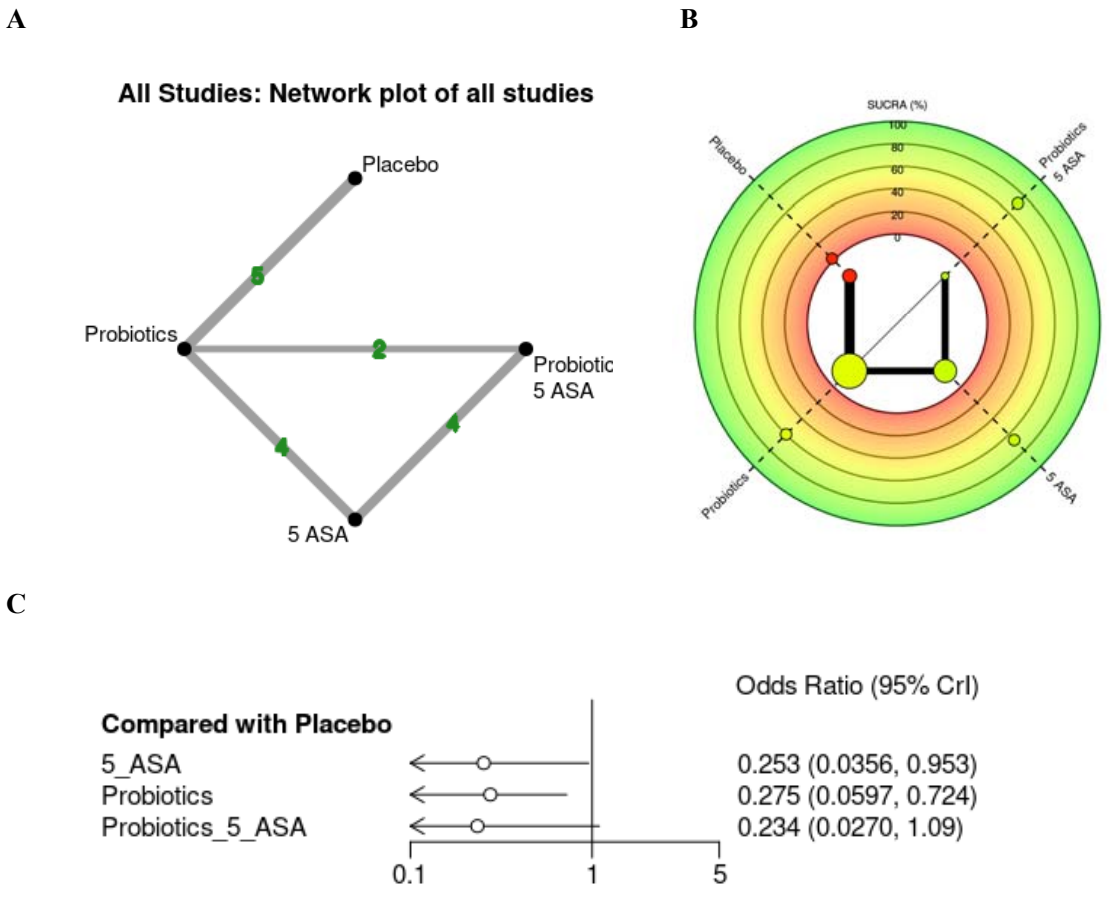


Figure 2. Network plot, forest plot, and SUCRA of efficacy. A: Network plot; B. SUCRA; C. Forest plot

Table 2. Characteristics of study

No	Author, Year, Study Design	Participants (N)	Age (years)	Disease Duration	Definition of Relapse	Follow up	Probiotic Regimen	5-ASA regimen	Disease Location (Proctosigmoid/ Left-sided/ Pancolitis)	Adverse Events	Serious Adverse Events
1	Kruis et al.,[20] 1997, RCT, multicenter	**N:**120 **Probiotic**:60 **5-ASA:**60	**Probiotics:** 43(20-88) **5-ASA:** 44(19-78)	**Probiotics**: 89 (6-276) months **5-ASA**: 109(1-516) months	CAI > 4	12 weeks	E. coli Nissle 1917, 2 capsules daily, each containing a concentration of 2.5 × 10^{10}	Mesalazine	**Probiotics:** 60/26/14 **5-ASA:** 71.7/11.3/17	**Probiotics**: 5/58 **5-ASA:**8/60 (Diarrhea, flatulence/ distension, nausea/vomiting)	NR
2	Copaci et al.,[21] 2000, RCT, single center	**N:**21 **Probiotics+5ASA** = 10 **5-ASA**: 11	NR	NR	NR	48 weeks	Saccharomyces boulardi	Mesalamine	NR	NR	NR
3	Zocco et al.,[22] 2003, RCT, single center	**N:**40 **Probiotics + 5-ASA**: 14 **5-ASA**: 14 **Probiotics:** 12	32	NR	characterized by endoscopic characteristics and clinical signs	48 weeks	Lactobacillus GG 18x10^{9} viable bacteria per day	Mesalazine	NR	**Probiotics**: NR **5-ASA:** NR **Probiotics + 5-ASA:** NR (Nausea, epigastric pain, constipation)	NR
4	Kruis et al.,[23] 2004, RCT, multicenter	**N:**327 **Probiotic:**162 **5-ASA**: 165	**Probiotics:** 43(19-69) **5-ASA:** 41(19-82)	**Probiotics:** ≤5 y: 43.8% >5 y: 56.2% **5-ASA:** ≤5 y: 50.9% >5 y: 49.1%	CAI >6; endoscopic index >4; histological evidence of acute inflammation; or a rise in CAI of at least 3 points concurrent with exceeding CAI = 4	52 weeks	In the first four days, take one tablet of E. Coli Nissle 1917 (2.5 25x10^{9} per capsule); starting on the fifth day, take two tablets daily.	Mesalazine	**Probiotics:** 63/16.7/16.1 **5-ASA:** 53.4/21.2/21.3	**Probiotics:** 68/162 **5-ASA:** 58/165 (Bloody stools, nausea, diarrhea, mucous secretion, abdominal pain)	**Probiotics:** 7 **5-ASA:** 6 Each SAEs occurred only once
5	Cui et al.,[24] 2004, RCT, single center	**N:**30 **Probiotic: 15** **Placebo:** 15	NR	NR	NR	8 weeks	1260 mg of E. faecalis, Bifidobacterium longum, and L. acidophilus (BTV), 2 pills, 3 times a day	-	NR	NR	NR
6	Zocco et al.,[25] 2006, RCT, single center	**N:** 187 **Probiotic**: 65 **5-ASA:**60 **Probiotic+5-ASA:** 62	**Probiotics:** 34±6 **5-ASA:** 33±4 **Probiotics + 5-ASA:** 33±7	**Probiotics:** 8±5 years **5-ASA:** 8±4 years **Probiotics + 5-ASA:** 8±7 years	A rise in CAI of > 4 points or the onset of UC symptoms	52 weeks	Lactobacillus GG (1.8x10^{10}viable bacteria/day)	Mesalazine	**Probiotics:** 18.4/12.3/69.3 **5-ASA:** 18.3/15/66.7 **Probiotics+ 5-ASA:** 19.3/12.9/67.8	No significant AEs reported	No significant SAEs reported
7	Wildt et al.,[26] 2011, RCT, single center	**N:**32 **Probiotic:** 20 **Placebo:** 12	**Probiotics:** 40.5(23-68) **Placebo:** 35.5(25-67)	**Probiotics:** 51.5(3-288) months **Placebo:** 33.5(2-194) months	SCCAI score >4 and/or grade 2–3 endoscopic alterations	52 weeks	Bifidobacterium animalis (Probio-TecAB-25), L. acidophilus, 6 capsules daily (1.5x1011CFU)	N/A	NR	**Probiotics:** 23 events/ 20 patients **Placebo:** 10 events/12 patients (Flatulence, abdominal pain, bloating, changes in faecal consistency, musculoskeletal, headache, dizziness, influenza, gastroenteritis, cystitis, pneumonial, various)	**Probiotics:** 0/20 **Placebo:** 0/12

No	Author, Year, Study Design	Participants (N)	Age (years)	Disease Duration	Definition of Relapse	Follow up	Probiotic Regimen	5-ASA regimen	Disease Location (Proctosigmoid/ Left-sided/ Pancolitis)	Adverse Events	Serious Adverse Events
8	Copaci et al.,[27] 2014, RCT, single center	**N:** 36 **Probiotic:** 10 **5-ASA:** 26	18-65 years	NR	NR	24 weeks	Bifidobacterium longum W11	Mesalamine	NR	NR	NR
9	Yoshimatsu et al.,[7] 2015, RCT,	**N**:60 **Probiotics+5ASA:** 30 **Placebo:** 30	**Probiotics:** 44.8±13.8 **Placebo:** 42.9±15.9	**Probiotics:** 8.0±6.3 years **Placebo:** 6.7±5.9 years	CAI ≤ 5	52 weeks	Bio□three (2mg Streptococcus faecalis,10 mg Clostridium butyricum,10 mg Bacillus mesentericus), 3 tablets 3 times daily	Pentasa	Probiotics:26/26/48 Placebo:21.7/ 39.1/39.2	no adverse changes were seen	NR
10	Matsuoka et al.,[28] 2018, RCT, multicenter	**N :** 195 **Probiotic:** 98 **Placebo**: 97	**Probiotics:** 41.3 (20-70) **Placebo:** 41.8(20-66)	NR	The start of remission induction therapy for worsening UC and/ or the persistence of a rectal bleeding score of > 2 on the Sutherland DAI score for three days in a row	48 weeks	a pack per day, 1 billion bacteria of Bifidobacterium breve + L. acidophilus	5-ASA (not mentioned the drug name)	Probiotics: NR/50.5/49.5/ Placebo:45.3/54.7/	**Probiotics:** 1/98 (Body odor) **Placebo:** 2/97 (abdominal pain, bloating)	**Probiotics:** 3/98 **Placebo:** 1/97 Causal relationship was ruled out
11	Bjanarson et al.,[29] 2019, RCT, single center	**N**: 81 **Probiotic:** 40 **Placebo :** 41	**Probiotics:** 47.3±14.4 **Placebo:** 43.4±12.1	NR	NR	4 weeks	10 billion bacteria each day (L. rhamnosus, L. plantarum, L. acidophilus, and E. fecium)	5-ASA (not mentioned the drug name)	**Probiotics:** 47.5/22.5/3 **Placebo:**51.2/ 24.3/ 24.4	No significant side effects were reported	**Probiotics:** 0/40 **Placebo:**0/41

AE, adverse events; CAI, clinical activity index; NR, not reported; RCT, randomized controlled trial; ; SCCAI, simple clinical colitis activity index; Sutherland DAI, Sutherland disease activity index;

Table 3. Treatment effects for all studies: comparison of all treatment pairs

	5-ASA	Placebo	Probiotics	Probiotics + 5-ASA
5-ASA	5-ASA	3.95 (1.05, 28.12)	1.1 (0.38, 3.32)	0.93 (0.27, 3.1)
Placebo	0.25 (0.04, 0.95)	Placebo	0.28 (0.06, 0.72)	0.23 (0.03, 1.09)
Probiotics	0.91 (0.3, 2.66)	3.63 (1.38, 16.74)	Probiotics	0.84 (0.21, 3.3)
Probiotics + 5-ASA	1.08 (0.32, 3.66)	4.28 (0.91, 36.99)	1.19 (0.3, 4.74)	Probiotics + 5-ASA

Table 4. SUCRA rank

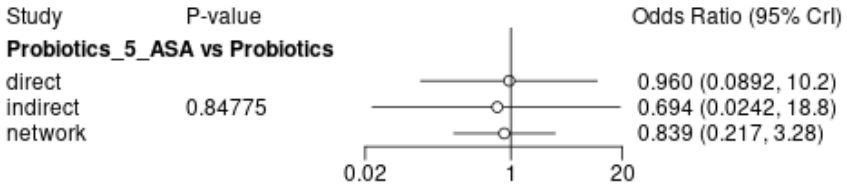
Treatment	Rank 1	Rank 2	Rank 3	Rank 4	SUCRA
5_ASA	0.30	0.41	0.27	0.02	66.90
Placebo	0.00	0.01	0.03	0.96	1.98
Probiotics	0.23	0.32	0.44	0.00	59.69
Probiotics_5_ASA	0.46	0.25	0.26	0.03	71.43

Inconsistency

We evaluated inconsistency in our NMA using both local and global methods. Node-splitting analysis allowed us to compare direct and indirect estimates for each treatment comparison. For probiotics plus 5-ASA vs. probiotics, the direct estimate was OR of 0.960 (95% CrI: 0.0892–10.2), while the indirect estimate was 0.694 (95% CrI: 0.0242–18.8). The overall network estimate was 0.839 (95% CrI: 0.217–3.28). With a p-value of 0.848, we found no meaningful difference between direct and indirect estimates, suggesting comparison consistency **(Figure 3.A).**

To assess inconsistency at a broader level, we used a deviance plot, which compared the fit of the standard NMA model against an unrelated mean effects (UME) inconsistency model. The fact that most points closely followed the diagonal line indicated that both local or global models provided similar fits, reinforcing the absence of major inconsistency in the network as illustrated in **Figure 3.B**. Together, above findings suggest that our network estimates are reliable and not affected by significant inconsistencies.

A.



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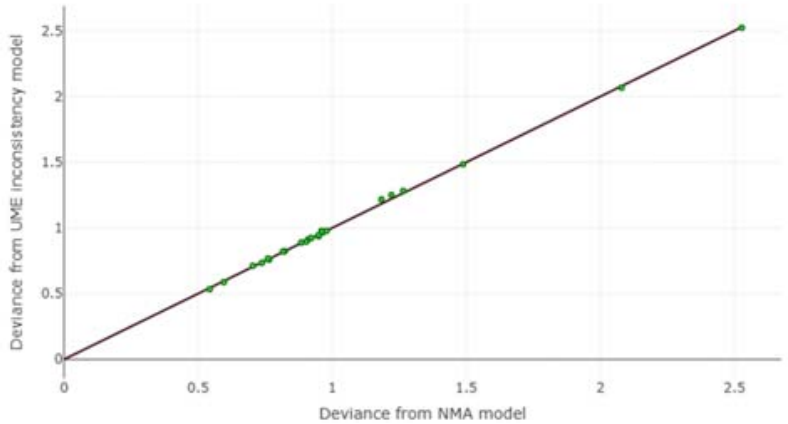

Figure 3. A. Node-splitting analysis for assessing inconsistency in NMA; B. Deviance plot comparing the NMA model and an inconsistency model.

Quality Assessment and Confidence in Cumulative Evidence

A total of 11 RCTs were evaluated based on the findings of the ROB2 quality assessment. The overall risk of bias for the studies was classified as moderate to high (**Table 5**). According to GRADE evidence, overall, the included studies had a moderate risk of bias (**Table 6**), primarily due to limitation with study design, such as unclear allocation of treatments and differences in probiotic strains used. The comparisons between 5-ASA, probiotics, and probiotics plus 5-ASA against placebo showed moderate certainty of evidence, with odds ratios (ORs) suggesting a potential benefit in reducing relapse (OR = 0.253, 95% CI: 0.035–0.95 for 5-ASA vs. Placebo; OR = 0.275, 95% CI: 0.059–0.724 for Probiotics vs. Placebo; OR = 0.234, 95% CI: 0.027–1.09 for Probiotics + 5-ASA vs. Placebo). However, for indirect comparisons, such as 5-ASA vs. probiotics plus 5-ASA (OR = 0.93, 95% CI: 0.27–3.1), 5-ASA vs. probiotics (OR = 1.1, 95% CI: 0.38–3.32), and probiotics vs. probiotics plus 5-ASA (OR = 0.84, 95% CI: 0.21–3.3), the evidence certainty was rated as low, primarily due to wide confidence intervals and potential indirectness. Although the risk of publication bias was minimal, the substantial uncertainty in effect sizes limits confidence in drawing definitive conclusions.

Table 5. Assessment of the risk of bias using the Cochrane Collaboration tool

Author, Year	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Kruis, 1997	Unclear risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Copaci, 2000	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Unclear risk
Zocco, 2003	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Kruis, 2004	Low risk	Unclear risk	Low risk	Low risk	Low risk	Low risk	Low risk
Cui, 2004	Unclear	Unclear	Unclear	Unclear	High	Unclear	Unclear
Zocco, 2006	Unclear risk	Unclear risk	High risk	High risk	Low risk	Low risk	Low risk
Wild, 2021	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	High risk
Copaci, 2014	Unclear risk	Unclear risk	High risk	High risk	Unclear risk	Unclear risk	Unclear risk
Yoshimatsu, 2015	Low risk	Unclear risk	Low risk	Unclear risk	Low risk	Low risk	Low risk
Matsuoka, 2018	Unclear risk	Low risk	Low risk	Unclear risk	Low risk	High risk	High risk
Bjanarson, 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	High risk

Table 6. Grade Evidence

Comparison	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty	Effect Estimate (OR, 95% CI)
5-ASA vs Placebo	Serious[a]	Serious[b]	Not serious	Not serious	Not serious[d]	Moderate	0.253 (0.035–0.95)
Probiotics vs Placebo	Serious[a]	Serious[b]	Not serious	Not serious	Not serious[d]	Moderate	0.275 (0.059–0.724)
Probiotics + 5-ASA vs Placebo	Serious[a]	Serious[b]	Not serious	Not serious	Not serious[d]	Moderate	0.234 (0.027–1.09)
5-ASA vs Probiotics + 5-ASA	Serious[a]	Serious[b]	Not Serious	Serious[c]	Not serious[d]	Low	0.93(0.27-3.1)
5-ASA vs Probiotics	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious[d]	Low	1.1 (0.38-3.32)
Probiotics + 5-ASA vs Probiotics	Serious[a]	Serious[b]	Not serious	Serious[c]	Not serious[d]	Low	0.84 (0.21-3.3)

OR: odds ratio; CI: Confidence Interval.
[a]There are some studies having unclear and high risk in components of ROB2 including unclear allocation concealment and blinding issues.
[b] Variability in follow up duration and probiotic strains used.
[c] Large CI reduces certainty
[d]The qualitative assessment of publication bias found no evidence of unpublished papers during the literature search, indicating that publication bias was not influenced

DISCUSSION

The current study shows that probiotics plus 5-ASA was ranked highest in preventing relapse. UC is a condition that involves multiple pathogenesis including chronic inflammation and altered microbiome, hence combining the two compounds with different mechanisms of action is a rational therapeutic strategy. would make sense and it is shown in the current NMA to provide the most benefits. In this NMA, although not statistically significant, the adjunctive use of probiotics with 5-ASA provided the greatest benefits, likely through a synergistic effect: 5-ASA primarily targets inflammatory pathways, while probiotics modulate gut microbiota, strengthen mucosal barrier integrity and exert anti-inflammatory effects.[30,31]

Studied probiotic strains, including *Escherichia coli* (Nissle 1917), VSL#3, and *Bifidobacterium longum* (in combination with a prebiotic fructo-oligosaccharide/inulin mixture or fermented milk containing *Bifidobacteria*), have shown modest effectiveness in reducing disease activity in IBD.[32] NMA by Zhang et al. (2025) has shown that multi-strain probiotics formulations containing *Lactobacillus* and *Bifidobacterium* demonstrated significant efficacy and ranked highest in reducing clinical relapse of UC.[33] In the presentHence on its own, the current NMA, however, ranked probiotics alone ranked third, after 5-ASA on its ownmonotherapy, since controlling inflammation remains paramount toin preventing relapses. Furthermore, specific probiotic combinations, including *Bifidobacterium longum*, *Bifidobacterium breve*, and *Bifidobacterium bifidum* with *Lactobacillus* species, as well as Yakult (containing *Bifidobacterium breve* and *Bifidobacterium longum* with *Lactobacillus* could help sustain remission in patients with mild to moderate UC when combined with standard treatment.[34–36] The efficacy of these interventions has been assessed using various comparators and clinical outcome measures.[29]

Probiotics alone may exhibit weaker anti-inflammatory effects than 5-ASA alone because their mechanisms are largely indirect, relying on modulation of the intestinal microbiota and enhancement of mucosal barrier integrity rather than directly inhibiting pro-inflammatory mediators. This mode of action often results in a slower onset of therapeutic benefit, as microbiota remodeling occurs gradually over time. Furthermore, the efficacy of probiotics can vary substantially depending on the specific bacterial strains used and the host's baseline microbiome composition, leading to inconsistent outcomes. Their effects are also predominantly localized to the intestinal lumen and superficial mucosal layers, with limited penetration into deeper inflamed tissue, unlike 5-ASA, which can directly access and modulate local inflammatory pathways. Collectively, these factors contribute to the generally lower and less predictable anti-inflammatory potency of probiotics compared to 5-ASA.[37] Nevertheless, evidence from a meta-analysis by Jiang et al. (2016) indicated that probiotics may reduce the recurrence of UC and could have a comparable effect to 5-ASA in maintenance therapy. The included trials did not demonstrate statistically significant differences in maintenance efficacy between probiotic and control groups; however, the relatively small sample size in the pooled analysis limits the ability to draw definitive conclusions about their clinical impact.[38]

Through gut barrier restoration, immune regulation and restoring microbial balance, probiotics may help in regulating inflammatory responses although not to the same degree seen with 5-ASA. It is well established that the transcription factor NF-κB plays a crucial role in the expression of inflammatory mediators induced by lipopolysaccharides (LPS).[39] Because NF-κB activation drives the increased production of proinflammatory cytokines, chemokines, inflammatory enzymes like inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), along with adhesion molecules and inflammatory receptors, inhibiting NF-κB signaling could provide a targeted approach to suppress inflammatory pathways.[40] Probiotics have the potential to suppress the NF-κB-mediated production of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β), while also promoting the mRNA expression of the anti-inflammatory cytokine interleukin-10 (IL-10).[24] Moreover, oral administration of non-pathogenic *E. coli* strain Nissle 1917 has been shown to trigger a serologic antibody response, while also demonstrating immunomodulatory effects on macrophages via enhanced phagocytic capacity, increased secretion of TNF, and elevated production of spontaneous oxygen radicals.[41]

Sulfasalazine, mesalazine, and immunomodulators contribute to the maintenance of remission in IBD; however, their effectiveness remains suboptimal.[42] Consequently, integrating probiotics as an adjunctive therapy plus 5-ASA may enhance therapeutic efficacy of 5-ASA, supported by our study findings. Several comprehensive Cochrane reviews on clinical studies back up these findings too, recommending probiotics

or synbiotics combined with standard medications as a reliable and safe treatment for patients with UC. Mallon et al. and Naidoo et al. emphasize that while probiotics on their own are not effective in inducing remission, they can play a significant role in maintaining remission when paired with conventional therapies.[43,44] Similarly, a meta-analysis by Sang et al. found that although probiotics provide only a slight, non-significant benefit in inducing remission, they play a significant role in sustaining it.[45]

The Bayesian approach used in the current study offers significant advantages by providing a more reliable and comprehensive assessment of treatment effects across different interventions. Bayesian NMA enables the comparison of multiple interventions within a unified statistical framework, even when direct head-to-head trials are limited. In this study, it allowed for a comprehensive evaluation of probiotics, 5-ASA, their combination, and placebo by incorporating both direct and indirect evidence. This approach made it possible to estimate the relative efficacy of each treatment with greater precision. The use of SUCRA rankings provided a clear and interpretable hierarchy of treatment options, supporting clinical decision-making. Additionally, the Bayesian model's ability to accommodate small sample sizes and variations in study design enhanced the strength of the findings, despite the constrained number of available studies.[46,47] However, several limitations must be acknowledged. First, the heterogeneity arising from variations in the definition of relapse across studies limits our ability to achieve a fully homogeneous comparison of outcomes. Second, we were unable to identify and rank the most effective probiotic strains because we lacked the data necessary to perform a subgroup analysis based on particular strains.

The safety and tolerability of treatment are of particular importance. The use of non-pathogenic *E. coli* in the management of UC remains experimental and raises ethical concerns when considered as an alternative to established standard therapies. Therefore, future research should thoroughly assess these ethical considerations while optimizing treatment duration to minimize potential adverse effects. Correspondingly, stratifying analyses based on probiotic strains could help identify the most effective formulations for UC treatment. Ultimately, incorporating prebiotics alongside probiotic agents in future studies may provide deeper insights into their efficacy in managing UC and other forms of IBD.

CONCLUSION

In UC relapse prevention, the combination of probiotics plus 5-ASA was the most effective as evidenced by the lower odds ratio and highest SUCRA rank. However, the relative efficacy of such approach is not certain due to a lack of statistical significance and moderate evidence certainty. A customized approach with probiotics added to conventional therapies may hold potential for augmenting long-term disease control.

REFERENCES

1. McDowell C, Farooq U, Haseeb M. Inflammatory Bowel Disease. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Aug 11]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470312/
2. Colombel JF, Shin A, Gibson PR. AGA Clinical Practice Update on Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: Expert Review. Clin Gastroenterol Hepatol. 2019 Feb;17(3):380-390.e1.
3. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011 May;140(6):1785–94.
4. Niriella MA, De Silva AP, Dayaratne AHGK, Ariyasinghe MHADP, Navarathne MMN, Peiris RSK, et al. Prevalence of inflammatory bowel disease in two districts of Sri Lanka: a hospital based survey. BMC Gastroenterol. 2010 Mar 19;10:32.
5. Asakura K, Nishiwaki Y, Inoue N, Hibi T, Watanabe M, Takebayashi T. Prevalence of ulcerative colitis and Crohn's disease in Japan. J Gastroenterol. 2009;44(7):659–65.
6. Muzammil MA, Fariha F, Patel T, Sohail R, Kumar M, Khan E, et al. Advancements in Inflammatory Bowel Disease: A Narrative Review of Diagnostics, Management, Epidemiology, Prevalence, Patient Outcomes, Quality of Life, and Clinical Presentation. Cureus. 2023 Jun;15(6):e41120.
7. Yoshimatsu Y, Yamada A, Furukawa R, Sono K, Osamura A, Nakamura K, et al. Effectiveness of probiotic therapy for the prevention of relapse in patients with inactive ulcerative colitis. World J Gastroenterol. 2015 May 21;21(19):5985–94.
8. Mazziotta C, Tognon M, Martini F, Torreggiani E, Rotondo JC. Probiotics Mechanism of Action on Immune Cells and Beneficial Effects on Human Health. Cells. 2023 Jan 2;12(1):184.
9. Hsu CY, Mustafa MA, Moath Omar T, Taher SG, Ubaid M, Gilmanova NS, et al. Gut instinct: harnessing the power of probiotics to tame pathogenic signaling pathways in ulcerative colitis. Front Med (Lausanne). 2024;11:1396789.
10. Abraham BP, Quigley EMM. Probiotics in Inflammatory Bowel Disease. Gastroenterol Clin North Am. 2017 Dec;46(4):769–82.
11. Su GL, Ko CW, Bercik P, Falck-Ytter Y, Sultan S, Weizman AV, et al. AGA Clinical Practice Guidelines on the Role of Probiotics in the Management of Gastrointestinal Disorders. Gastroenterology. 2020 Aug;159(2):697–705.
12. Bischoff SC, Escher J, Hébuterne X, Kłęk S, Krznaric Z, Schneider S, et al. ESPEN practical guideline: Clinical Nutrition in inflammatory bowel disease. Clin Nutr. 2020 Mar;39(3):632–53.

13. Guo N, Lv LL. Mechanistic insights into the role of probiotics in modulating immune cells in ulcerative colitis. Immun Inflamm Dis. 2023 Oct;11(10):e1045.
14. Wirya LE, Schoeck HPG, Simatupang EP. The effect of probiotics on inflammatory bowel disease Remission and relaps rate: A systematic review and meta-analysis. Jurnal Penyakit Dalam Udayana. 2024 May 5;8(1):12–8.
15. Kaur L, Gordon M, Baines PA, Iheozor-Ejiofor Z, Sinopoulou V, Akobeng AK. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020 Mar 4;3(3):CD005573.
16. Iheozor-Ejiofor Z, Kaur L, Gordon M, Baines PA, Sinopoulou V, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2020 Mar 4;3(3):CD007443.
17. RoB 2: A revised Cochrane risk-of-bias tool for randomized trials | Cochrane Bias [Internet]. [cited 2025 Aug 11]. Available from: https://methods.cochrane.org/bias/resources/rob-2-revised-cochrane-risk-bias-tool-randomized-trials
18. Izcovich A, Chu DK, Mustafa RA, Guyatt G, Brignardello-Petersen R. A guide and pragmatic considerations for applying GRADE to network meta-analysis. BMJ. 2023 Jun 27;381:e074495.
19. Owen RK, Bradbury N, Xin Y, Cooper N, Sutton A. MetaInsight: An interactive web-based tool for analyzing, interrogating, and visualizing network meta-analyses using R-shiny and netmeta. Res Synth Methods. 2019 Dec;10(4):569–81.
20. Kruis W, Schütz E, Fric P, Fixa B, Judmaier G, Stolte M. Double-blind comparison of an oral Escherichia coli preparation and mesalazine in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 1997 Oct;11(5):853–8.
21. Copaci I, Chira C, Rovinaru I, Micu L. Maintenance of remission of ulcerative colitis (UC): Mesalamine, dietary fiber, S. Boulardi. Digestive and Liver Disease. 2000 May 1;32:A24.
22. Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 2006 Jun 1;23(11):1567–74.
23. Kruis W, Fric P, Pokrotnieks J, Lukás M, Fixa B, Kascák M, et al. Maintaining remission of ulcerative colitis with the probiotic Escherichia coli Nissle 1917 is as effective as with standard mesalazine. Gut. 2004 Nov;53(11):1617–23.
24. Cui HH, Chen CL, Wang JD, Yang YJ, Cun Y, Wu JB, et al. Effects of probiotic on intestinal mucosa of patients with ulcerative colitis. World J Gastroenterol. 2004 May 15;10(10):1521–5.
25. Zocco MA, dal Verme LZ, Cremonini F, Piscaglia AC, Nista EC, Candelli M, et al. Efficacy of Lactobacillus GG in maintaining remission of ulcerative colitis. Aliment Pharmacol Ther. 2006 Jun 1;23(11):1567–74.
26. Wildt S, Nordgaard I, Hansen U, Brockmann E, Rumessen JJ. A randomised double-blind placebo-controlled trial with Lactobacillus acidophilus La-5 and Bifidobacterium animalis subsp. lactis BB-12 for maintenance of remission in ulcerative colitis. J Crohns Colitis. 2011 Apr;5(2):115–21.
27. Copaci I, Chiriac G. MAINTENANCE OF REMISSION OF ULCERATIVE COLITIS: PREBIOTICS AND DIETARY FIBER. United European Gastroenterology Journal 2(1S). 2014;132–605.
28. Matsuoka K, Uemura Y, Kanai T, Kunisaki R, Suzuki Y, Yokoyama K, et al. Efficacy of Bifidobacterium breve Fermented Milk in Maintaining Remission of Ulcerative Colitis. Dig Dis Sci. 2018 Jul;63(7):1910–9.
29. Bjarnason I, Sission G, Hayee B. A randomised, double-blind, placebo-controlled trial of a multi-strain probiotic in patients with asymptomatic ulcerative colitis and Crohn's disease. Inflammopharmacology. 2019 Jun;27(3):465–73.
30. Hassan WU, Somaraj M, Nipu AP, Nadeem N, Zahra A, Mariam B, et al. Efficacy of Probiotics in Reducing Relapse in Ulcerative Colitis: A Meta-Analysis of Controlled Trials. Indus Journal of Bioscience Research. 2025 May 18;3(5):47–52.
31. Wang J, Wang X, Jiang M, Lang T, Wan L, Dai J. 5-aminosalicylic acid alleviates colitis and protects intestinal barrier function by modulating gut microbiota in mice. Naunyn-Schmiedeberg's Arch Pharmacol. 2025 Apr 1;398(4):3681–95.
32. Akutko K, Stawarski A. Probiotics, Prebiotics and Synbiotics in Inflammatory Bowel Diseases. J Clin Med. 2021 Jun 2;10(11):2466.
33. Zhang T, Li X, Li J, Sun F, Duan L. Gut microbiome-targeted therapies as adjuvant treatments in inflammatory bowel diseases: a systematic review and network meta-analysis. Journal of Gastroenterology and Hepatology. 2025;40(1):78–88.
34. Yao S, Zhao Z, Wang W, Liu X. Bifidobacterium Longum: Protection against Inflammatory Bowel Disease. J Immunol Res. 2021;2021:8030297.
35. Park IS, Kim JH, Yu J, Shin Y, Kim K, Kim TI, et al. Bifidobacterium breve CBT BR3 is effective at relieving intestinal inflammation by augmenting goblet cell regeneration. J Gastroenterol Hepatol. 2023 Aug;38(8):1346–54.
36. Wang W, Chen L, Zhou R, Wang X, Song L, Huang S, et al. Increased proportions of Bifidobacterium and the Lactobacillus group and loss of butyrate-producing bacteria in inflammatory bowel disease. J Clin Microbiol. 2014 Feb;52(2):398–406.
37. Tian C, Huang Y, Wu X, Xu C, Bu H, Wang H. The Efficacy and Safety of Mesalamine and Probiotics in Mild-to-Moderate Ulcerative Colitis: A Systematic Review and Meta-Analysis. Evid Based Complement Alternat Med. 2020 Mar 28;2020:6923609.
38. Jiang Y, Zhang ZG, Qi FX, Zhang Y, Han T. Comparison of maintenance effect of probiotics and aminosalicylates on ulcerative colitis: A meta-analysis of randomized controlled trials. Chronic Diseases and Translational Medicine. 2016 Mar 1;2(1):34–41.
39. Bhattacharyya S, Borthakur A, Dudeja PK, Tobacman JK. Lipopolysaccharide-induced activation of NF-κB non-canonical pathway requires BCL10 serine 138 and NIK phosphorylations. Exp Cell Res. 2010 Nov 15;316(19):3317–27.
40. Natarajan K, Abraham P, Kota R, Isaac B. NF-κB-iNOS-COX2-TNF α inflammatory signaling pathway plays an important role in methotrexate induced small intestinal injury in rats. Food Chem Toxicol. 2018 Aug;118:766–83.
41. Zhao Z, Xu S, Zhang W, Wu D, Yang G. Probiotic Escherichia coli NISSLE 1917 for inflammatory bowel disease applications. Food Funct. 2022 Jun 6;13(11):5914–24.
42. Kozuch PL, Hanauer SB. Treatment of inflammatory bowel disease: a review of medical therapy. World J Gastroenterol. 2008 Jan 21;14(3):354–77.

43. Mallon P, McKay D, Kirk S, Gardiner K. Probiotics for induction of remission in ulcerative colitis. Cochrane Database Syst Rev. 2007 Oct 17;(4):CD005573.
44. Naidoo K, Gordon M, Fagbemi AO, Thomas AG, Akobeng AK. Probiotics for maintenance of remission in ulcerative colitis. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD007443.
45. Sang LX, Chang B, Zhang WL, Wu XM, Li XH, Jiang M. Remission induction and maintenance effect of probiotics on ulcerative colitis: a meta-analysis. World J Gastroenterol. 2010 Apr 21;16(15):1908–15.
46. Sadeghirad B, Foroutan F, Zoratti MJ, Busse JW, Brignardello-Petersen R, Guyatt G, et al. Theory and practice of Bayesian and frequentist frameworks for network meta-analysis. BMJ Evid Based Med. 2023 Jun;28(3):204–9.
47. Greco T, Biondi-Zoccai G, Saleh O, Pasin L, Cabrini L, Zangrillo A, et al. The attractiveness of network meta-analysis: a comprehensive systematic and narrative review. Heart Lung Vessel. 2015;7(2):133–42.