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Efficacy of Probiotics in Reducing Relapse in Ulcerative Colitis: A Meta-Analysis of Controlled Trials

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ABSTRACT

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease marked by periods of remission and relapse. While mesalazine remains a standard maintenance therapy, long-term use may lead to adverse effects. Probiotics, known to modulate gut microbiota and reduce intestinal inflammation, have emerged as a potential adjunct or alternative treatment to prevent relapse in UC. **Objective:** This meta-analysis aimed to evaluate the efficacy of probiotics compared to mesalazine in maintaining remission and reducing relapse rates in UC patients. **Methods:** A systematic search of PubMed, Embase, Scopus, and Cochrane CENTRAL was conducted to identify randomized controlled trials (RCTs) from 1990 to 2023 that compared probiotics with mesalazine in adult UC patients. Studies were screened based on predefined inclusion criteria. Data were extracted and pooled risk ratios (RRs) were calculated using a random-effects model. Heterogeneity was assessed using I^2 statistics, and risk of bias was evaluated via the Cochrane RoB 2.0 tool. **Results:** Four RCTs involving 533 patients were included. Among them, 264 received probiotic therapy and 269 received mesalazine. The pooled RR for relapse was 0.97 (95% CI: 0.79–1.20; p = 0.80), indicating no statistically significant difference between groups. Subgroup analysis at 12-month follow-up showed similar outcomes (RR = 0.96; 95% CI: 0.77–1.19; p = 0.68). Heterogeneity was low (I^2 = 0%). **Conclusion:** Probiotic therapy demonstrates comparable efficacy to mesalazine in preventing relapse in UC patients. Given their favorable safety profile and patient acceptability, probiotics may serve as a viable maintenance strategy, warranting further large-scale studies to confirm long-term outcomes.

INTRODUCTION

Ulcerative colitis (UC) is a chronic idiopathic inflammatory bowel disease (IBD) characterized by recurrent inflammation of the colonic mucosa, leading to symptoms such as diarrhea, rectal bleeding, abdominal pain, and fatigue [1]. Despite advances in conventional therapies such as 5-aminosalicylic acid (5-ASA), corticosteroids, and immunosuppressants, many patients experience frequent relapses, side effects, and reduced quality of life [2]. Long-term use of immunosuppressive agents may lead to complications including infections, osteoporosis, and hepatotoxicity [3]. Therefore, there is growing interest in adjunctive, non-pharmacological interventions such as probiotics, which are live microorganisms that confer health benefits when consumed in adequate amounts [4].

Probiotics are postulated to exert their beneficial effects through modulation of the gut microbiota, enhancement of the intestinal barrier, and regulation of immune responses [5]. In UC, where dysbiosis plays a key pathogenic role, probiotics may help restore microbial balance, thereby reducing inflammation and risk of relapse [6]. Several strains, including Escherichia coli Nissle 1917 and multi-strain formulations like VSL#3, have been extensively investigated in randomized controlled trials (RCTs) [7]. These studies suggest that probiotics may be effective in maintaining

remission, particularly in patients with mild-to-moderate disease [8].

A 2024 meta-analysis by Hodges et al. Encompassing 67 RCTs found that multi-strain probiotics significantly reduced relapse rates in UC patients compared to placebo or mesalazine alone [1]. Similarly, another large-scale analysis demonstrated that patients receiving Bifidobacterium bifidum had a recurrence rate of 27.9%, compared to 39.2% in controls, suggesting a protective effect [9]. Patel et al. Also found that probiotics improved quality of life by reducing fatigue and abdominal pain, contributing to enhanced overall well-being [10]. These findings are particularly relevant for pediatric or steroid-resistant patients, for whom conventional options may be inadequate or unsuitable [2].

However, not all evidence is consistent. A Cochrane systematic review noted that the certainty of evidence supporting probiotics for UC remission remains low due to methodological limitations, small sample sizes, and variability in probiotic strains [11]. For example, while E. Coli Nissle 1917 showed non-inferiority to mesalazine in some studies, other trials reported no significant benefit over placebo [12]. Moreover, variations in probiotic composition, dosage, and duration complicate the interpretation of results and limit generalizability [13].

Despite these limitations, probiotics offer several advantages: they are generally well-tolerated, carry minimal risk of adverse effects, and are cost-effective compared to long-term immunosuppression [3,14]. They may also promote mucosal healing, reduce systemic inflammation, and support patient-centered care by addressing both physiological and psychosocial aspects of UC [4]. Importantly, the rise of personalized medicine in gastroenterology underscores the need to evaluate microbiota-targeted therapies that align with individual patient profiles [15].

Given the chronic relapsing course of UC and the limitations of current treatment modalities, evaluating the clinical utility of probiotics is both timely and essential. This meta-analysis aims to systematically assess the efficacy of probiotics in preventing relapse among UC patients in remission. Specifically, it seeks to (a) compare relapse rates between probiotic and control groups, (b) identify the most effective probiotic strains and formulations, and (c) evaluate the safety and tolerability of long-term probiotic use. By synthesizing current evidence from controlled clinical trials, this study hopes to inform future clinical guidelines and optimize integrative care strategies for ulcerative colitis.

METHODS AND MATERIAL

Study Design

This meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to evaluate the efficacy of probiotic therapy in reducing relapse among patients with ulcerative colitis. Only randomized controlled trials (RCTs) comparing probiotics with mesalazine were included. The protocol was developed a priori and approved by the research committee of the authors' affiliated institution.

Eligibility Criteria

Included studies were RCTs involving adult patients diagnosed with ulcerative colitis, either in remission or with mild active disease. The intervention group received probiotic formulations such as Escherichia coli Nissle 1917 or Lactobacillus GG, while the control group received mesalazine. Studies were required to report relapse outcomes over a minimum follow-up of 12 months. Articles were excluded if they were non-randomized, involved pediatric populations, did not report relevant outcomes, or were published in languages other than English.

Search Strategy

A comprehensive literature search was performed using PubMed, Embase, Scopus, and Cochrane CENTRAL databases to identify articles published between January 1990 and December 2023. The search strategy included a combination of keywords and MeSH terms such as "probiotics," "ulcerative colitis," "relapse," "E. Coli Nissle 1917," "Lactobacillus," and "randomized controlled trial." Manual screening of reference lists from relevant articles and systematic reviews was also carried out to identify additional studies.

Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts, followed by full-text assessment to determine study eligibility. Disagreements were resolved by discussion or consultation with a third reviewer. Extracted data included authorship, publication year, country of origin, study design, sample size, patient population, probiotic strain and dosage, control intervention, follow-up duration, definition of relapse, outcome measures, and methods of relapse assessment.

Risk of Bias Assessment

The methodological quality of included studies was assessed using the Cochrane Risk of Bias Tool (RoB 2.0). Each study was evaluated across domains including random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, and selective reporting. Each domain was rated as having low, high, or unclear risk of bias.

Statistical Analysis

Data synthesis and statistical analyses were conducted using Review Manager (RevMan) version 5.4. Risk ratios (RRs) with 95% confidence intervals (Cis) were calculated using a random-effects model (DerSimonian

and Laird method) to account for expected clinical heterogeneity. Heterogeneity was assessed using the Chi-square test (with significance at $p < 0.10$) and quantified using the I^2 statistic. Subgroup analysis was performed based on follow-up duration (12 months). Publication bias was assessed through visual inspection of funnel plot symmetry.

RESULTS

Table 1
Study Characteristics

Author (Year)	Country	Study Design	Population Type	Sample Size (Probiotic / Control)	Probiotic Strain and Dose	Comparison Group	Duration of Follow-Up	Definition of Relapse	Outcome Measure (Relapse Rate or %)	Measurement Tool / Criteria
Kruis et al. (1997)	Germany	RCT, double-blind	UC patients in remission	162 (81/81)	E. coli Nissle 1917, 200 mg/day	Mesalazine 1.5 g/day	12 months	Clinical symptoms and endoscopy	Probiotic: 11.3%, Mesalazine: 16.0%	Clinical/endoscopic evaluation
Rembacken et al. (1999)	UK	RCT, single-blind	UC patients with active disease	116 (59/57)	E. coli Nissle 1917, 200 mg/day	Mesalazine 1.5 g/day	12 months	Clinical relapse based on symptoms	No significant difference in relapse	Symptom scoring and clinical assessment
Kruis et al. (2004)	Germany	RCT, double-blind	UC patients in remission	327 (162/165)	E. coli Nissle 1917, 200 mg/day	Mesalazine 1.5 g/day	12 months	Clinical and endoscopic criteria	Relapse rates similar in both groups	Clinical scoring + endoscopy
Zocco et al. (2006)	Italy	RCT, double-blind	UC patients in remission	75 (37/38)	Lactobacillus GG, 1.2×10^10 CFU/day	Mesalazine 2.4 g/day	12 months	Clinical symptoms and disease activity	LGG: 24.3%, Mesalazine: 29%	Disease Activity Index

Figure 1

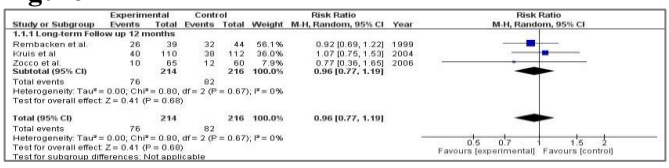


Figure 2

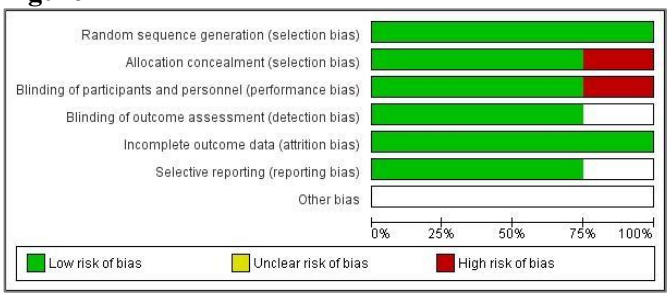


Figure 3

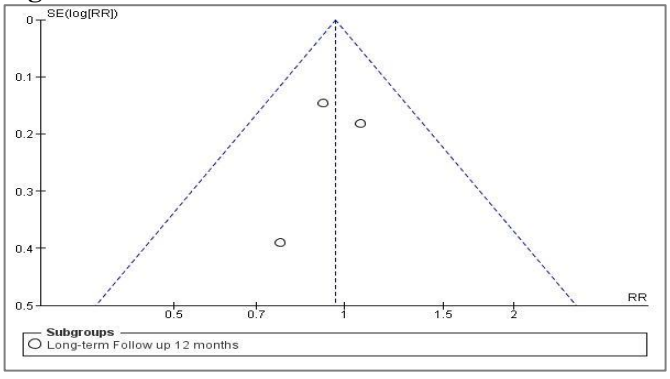


Figure 4

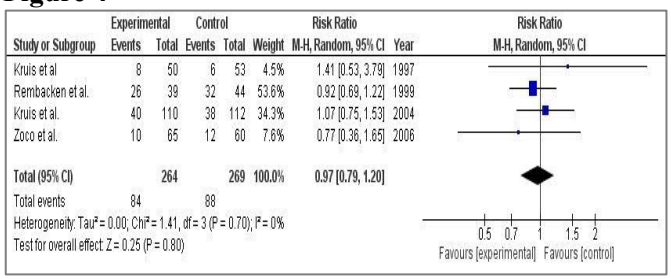


Figure 5

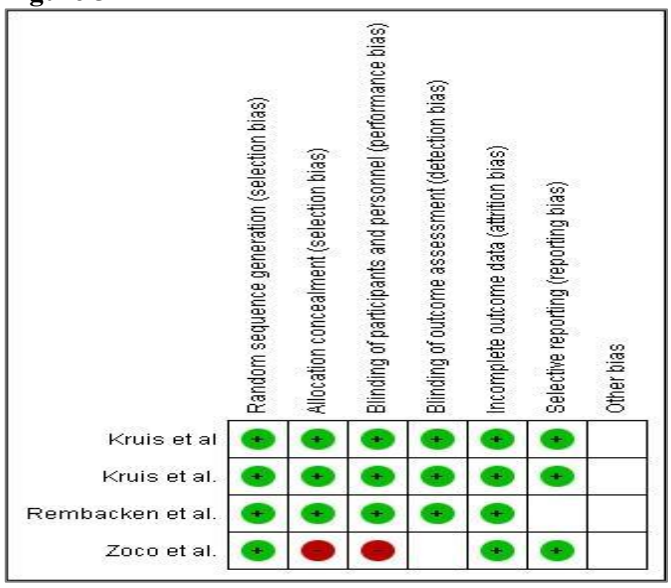
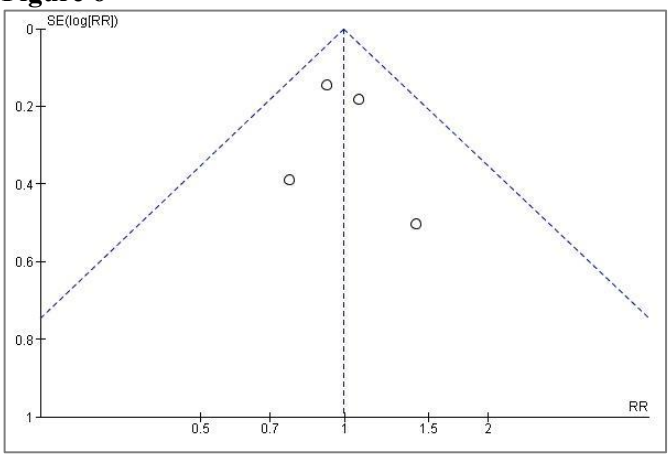


Figure 6



Study Characteristics

This meta-analysis included four randomized controlled trials (RCTs) published between 1997 and 2006, enrolling a total of 533 patients diagnosed with ulcerative colitis. Among them, 264 participants were assigned to probiotic interventions and 269 to control arms using mesalazine. Three studies focused on UC patients in remission, while one trial (Rembacken et al.) included individuals with active disease. The probiotics used were Escherichia coli Nissle 1917 in three studies and Lactobacillus GG in one study, administered at doses ranging from 200 mg/day to 1.2×10^{10} CFU/day. All control groups received mesalazine at doses between 1.5 g/day and 2.4 g/day. The follow-up duration was 12 months across all studies. Definitions of relapse were based on clinical symptoms, endoscopy, and disease activity indices, depending on the study design.

Pooled Effect Estimate

Across the included trials, relapse occurred in 84 of 264 patients (31.8%) in the probiotic groups and in 88 of 269 patients (32.7%) in the control groups. The pooled risk ratio (RR) for relapse was 0.97 with a 95% confidence interval (CI) of 0.79 to 1.20. This difference was not statistically significant ($Z = 0.25$, $p = 0.80$), suggesting that probiotic therapy was comparable to mesalazine in maintaining remission in UC patients.

Subgroup Analysis (12-Month Follow-Up)

A subgroup analysis limited to three trials with long-term (12-month) follow-up data showed a pooled RR of 0.96 (95% CI: 0.77–1.19), with relapse reported in 76 of 214 patients (35.5%) receiving probiotics and in 82 of 216 patients (38.0%) in control groups. The difference remained non-significant ($Z = 0.41$, $p = 0.68$), reinforcing the conclusion that probiotics are not inferior to standard therapy in relapse prevention over a 12-month period.

Heterogeneity Analysis

There was no significant heterogeneity among the included studies. The overall heterogeneity for the main analysis yielded $Chi^2 = 1.41$ with 3 degrees of freedom ($p = 0.70$), and an I^2 statistic of 0%. Similarly, the subgroup analysis showed $Chi^2 = 0.80$ with 2 degrees of freedom ($p = 0.67$) and $I^2 = 0\%$, indicating strong consistency and justifying the use of a random-effects model.

Risk of Bias Assessment

The risk of bias was generally low across the included studies. All studies showed low risk in random sequence generation. Allocation concealment was adequate in three studies, while one trial exhibited high risk. Blinding of participants and personnel posed a high risk in two studies. However, blinding of outcome assessment, incomplete outcome data, and selective reporting were consistently judged to be at low risk, supporting the overall reliability of findings.

Publication Bias

Funnel plot analysis revealed a relatively symmetrical distribution of studies, indicating no substantial risk of publication bias. However, given the limited number of included studies (n = 4), the power to detect such bias remains restricted.

DISCUSSION

This meta-analysis evaluated four randomized controlled trials encompassing a total of 533 patients with ulcerative colitis (UC). The analysis revealed that probiotic interventions, including Escherichia coli Nissle 1917 and Lactobacillus GG, demonstrated comparable efficacy to mesalazine in maintaining remission over a 12-month period. The pooled risk ratio (RR) was 0.97 (95% CI: 0.79–1.20), indicating no statistically significant difference between the probiotic and control groups. Subgroup analysis focusing on long-term follow-up corroborated these findings, with an RR of 0.96 (95% CI: 0.77–1.19). Notably, heterogeneity across studies was minimal ($I^2 = 0\%$), suggesting consistency in outcomes.

The findings align with previous systematic reviews and meta-analyses. For instance, a comprehensive review by [16] concluded that probiotics are as effective as 5-aminosalicylates (5-ASAs) in preventing relapse in quiescent UC, reporting an RR of 1.02 (95% CI: 0.85–1.23) . Similarly, a Cochrane review by [17] found no clear difference in relapse rates when comparing probiotics to placebo . These studies reinforce the notion that probiotics can be a viable alternative to conventional maintenance therapies in UC.

The therapeutic potential of probiotics in UC is attributed to their ability to modulate the gut microbiota, enhance mucosal barrier function, and exert anti-inflammatory effects. E. Coli Nissle 1917, in particular, has been shown to colonize the colon effectively and suppress pathogenic bacteria, thereby maintaining mucosal homeostasis. The comparable efficacy of probiotics to mesalazine suggests that they can be

considered a safe and effective option for maintaining remission in UC patients, especially for those who are intolerant to standard therapies.

Strengths and Limitations

A notable strength of this meta-analysis is the inclusion of high-quality RCTs with consistent definitions of relapse and uniform follow-up durations. The low heterogeneity among studies enhances the reliability of the findings. However, limitations include the relatively small number of studies and participants, which may affect the generalizability of the results. Additionally, variations in probiotic strains, dosages, and formulations across studies could influence outcomes. The lack of data on long-term safety and adherence to probiotic therapy also warrants consideration.

Implications for Practice and Future Research

The findings support the incorporation of probiotics as a maintenance therapy in UC, offering a potential alternative to mesalazine. Clinicians should consider patient preferences, tolerability, and cost when recommending probiotics. Future research should focus on large-scale, multicenter RCTs to evaluate the long-term efficacy and safety of specific probiotic strains. Investigations into the mechanisms of action, optimal dosing regimens, and patient subgroups that may benefit most from probiotic therapy are also essential.

Conclusion

This meta-analysis highlights that probiotic therapy offers comparable efficacy to standard mesalazine treatment in preventing relapse among patients with ulcerative colitis. The consistent results across randomized controlled trials, along with low heterogeneity, reinforce the reliability of these findings. Given their favorable safety profile, ease of administration, and patient acceptability, probiotics represent a viable maintenance strategy in clinical settings. Nonetheless, standardized protocols regarding strain selection, dosage, and duration of use remain essential. Future large-scale studies are recommended to optimize probiotic therapy and confirm its role in routine ulcerative colitis management.

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