Systematic Review

Evaluation of the Effect of Probiotic Supplementation on Intestinal Barrier Integrity and Epithelial Damage in Colitis Disease: A Systematic Review

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Context: *Previous reviews have focused on the effects of probiotics on colitis, but there is a need to understand their impact on barrier integrity and tight junction protein improvement in colitis.* ***Objective:*** *This study aimed to systematically examine the effects of probiotic use on barrier integrity in colitis disease. This study was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.* ***Data Sources:*** *A systematic search in PubMed, Web of Science, Scopus, and Cochrane databases identified 2537 articles.* ***Data Extraction:*** *As a result of the search, 2537 articles were accessed. Study results were summarized descriptively through discussions by intervention conditions, study population, measurement methods, and key findings. The included studies were independently reviewed and all authors reached consensus on the quality and major findings from the included articles. Forty-six studies that met the inclusion criteria were analyzed within the scope of the systematic review.* ***Results:*** *Although the study primarily utilized probiotics from the Lactobacillaceae family (notably, L casei, L reuteri, L rhamnosus, L plantarum, and L pentosus) and the Bifidobacteriaceae family (notably, B breve, B animalis, and B dentium), other probiotics also demonstrated positive effects on tight junction proteins. These effects are attributed to the production of bioactive and metabolic compounds, as well as short-chain fatty acids, which combat pathogens and reduce anti-inflammatory agents. However, it was observed that the effects of these probiotics on tight junction proteins varied depending on the strain and dose.* ***Conclusion:*** *The beneficial effects of probiotics on remission in inflammatory bowel disease are well documented. Studies show that probiotics generally improve intestinal barrier function, but factors such as dose, duration, and bacterial species combinations need further clarification. Additionally, comprehensive studies are needed to understand how improved barrier function affects absorption in individuals.*

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Key words: *colitis, tight junction proteins, probiotics, systematic review.*

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition with unclear etiology and pathophysiology that has been fully clarified, including Crohn's disease and ulcerative colitis.[1,2] While ulcerative colitis is mainly limited to the colon, Crohn's disease is characterized by skip lesions and transmural inflammation that can affect the entire gastrointestinal tract from the mouth to the anus, causing many symptoms such as abdominal pain, diarrhea, oral ulcers, malnutrition, and anemia, negatively affecting quality of life and general health.[3] As a result of a systematic review covering the years 1990–2019, approximately 4.9 million IBD cases were identified worldwide. The greatest number of cases are found in China and the United States.[4]

Genetic predisposition, environmental triggers, immune factors, and microbiota are thought to play a role in the pathogenesis of IBD.[5] As a result of the abnormal dysregulated immune response that develops under the influence of these factors, changes in mucosal barrier function and permeability and microbial clearance occur.[6] Although there is no definitive cure, current treatments are mainly focused on the initiation of remission, which is the period when the symptoms of the disease are alleviated, and the prolongation of the remission period. For this purpose, there are 2 steps in the management of the disease: treating the inflammatory process and related complications (eg, abscesses, fistulas, strictures, intestinal obstructions) and minimizing the side effects caused by the therapies used in the treatment process.[7] The treatment process varies according to the severity of the disease, the site of involvement, and the subtype of the disease. Treatments include drug therapy (corticosteroids, immunomodulators, anti–tumor necrosis factor [anti-TNF] agents), surgical intervention, enteral nutrition, and medical nutrition therapy to prevent nutritional deficiencies.[8]

Probiotics have many different strains and are defined as live microorganisms that positively affect host health when taken appropriately and sufficiently.[9] With their multiple effects, probiotics improve the impaired mucosal integrity and immune response, interact with pathogenic microorganisms, and maintain the existing healthy flora.[10]

Probiotics can affect host health through immunological pathways, such as activation of local macrophages, modulation of cytokines, and tolerance to food antigens and non-immunological pathways. They can also positively affect host health through non-immunological pathways such as food digestion and competition with pathogens, changes in ambient pH, bacteriocin production, and increased mucin production.[11] With all of these mechanisms, probiotics are essential in improving health by maintaining the immunological balance in the gastrointestinal system. However, their effectiveness varies according to probiotic type, disease type, microbial diversity, and dose.[12] In addition to gastrointestinal system diseases such as Crohn's disease, ulcerative colitis, diarrhea, and irritable bowel syndrome, probiotics can also show efficacy in many chronic and nonchronic diseases, such as cardiovascular diseases, cancer, mental problems, allergies, cold infections, obesity, and diabetes, due to improved microbiota.[13]

Dysbiosis, characterized by decreased mucin production, increased opportunistic pathogens, downregulation of anti-inflammatory bacteria in the intestinal lumen, and impaired epithelial integrity, is frequently seen as a cause or consequence of IBD.[14] In IBDs, including Crohn's disease, microbial diversity decreases, bacterial balance changes compared with healthy individuals, Firmicutes and Bacteroidetes species decrease, while Enterobacteriaceae species increase.[15] Considering these changes seen in IBD and the mechanisms of action of probiotics, the use of probiotics has become widespread to reduce inflammation, ensure healthy functioning of absorption and other functions by ensuring epithelial integrity, and improve the quality of life by normalizing the microbiota composition and managing the disease and providing remission.[16] In addition, the integrity of the intestinal barrier, which has nutrient and drug permeability, intestinal homeostasis, and immune roles, is disrupted and permeability increases; the expression of tight junction (TJ) proteins (occludin [OCLN], claudin [CLDN], zonula occludin [ZO]), cadherin 1/e-cadherin (CDH1), and junctional adhesion molecules (JAMs), which are indicators of barrier integrity, decreases.[17] However, there is still limited evidence on the effects of probiotic use on colitis. Therefore, this study aimed to systematically examine the effects of probiotic use on barrier integrity in colitis.

METHODS

Study Methods and Search Strategy

This study aimed to investigate the efficacy of probiotics in preventing and treating colitis. For this purpose, the effects of probiotics on intestinal barrier integrity and damage caused by colitis were determined.

The systematic review was conducted through 4 databases (PubMed, Web of Science, Scopus, and Cochrane). The following key words were searched: inflammatory bowel disease, Crohn's disease, Crohn's enteritis, ileitis, Lactobacilli, *Lactobacillus*, Bifidobacteria, *Bifidobacterium*, symbiotic, probiotics, *Saccharomyces*, VSL#3, dietary supplement therapies, diet, *Streptococcus salivarius*, *Escherichia coli* Nissle.

Table 1. PICOS Criteria for Inclusion of Studies

Parameter	Inclusion criterion	Exclusion criterion
P (Participants)	The study included only randomized controlled trials and clinical trials, animal studies, and tissue-culture studies conducted between January 1, 2020, and April 30, 2023 using only live probiotic supplements, published in Turkish and English, and shown only in adults	Adults aged ≤18 y
I (Intervention)	Recipients of live probiotic supplementation and treatment	Studies in which postbiotic or probiotic food (kefir, etc) or heat-killed probiotics without live strains were evaluated
C (Comparison)	Human subjects with Crohn's disease and colitis model animals and cells, with and without probiotic supplementation, pre-post probiotic supplementation studies	Not applicable
O (Outcome)	The outcome of probiotic supplementation associated with change of intestinal barrier integrity parameters (ZO, CLDN, OCLN, TEER, etc)	Studies evaluating only inflammation parameters, prebiotics, supplements given in complex with probiotics (minerals, vitamins, prebiotics, dietary fiber, etc), studies that did not evaluate tight junction proteins and transepithelial electrical resistance (TEER) parameters
S (Study design)	Randomized or nonrandomized controlled trials, single-arm pre-post or experimental studies, animal experiments, tissue culture studies, clinical studies	Studies whose methods and results needed to be better explained, and whose full text could not be accessed and published before 2020 were excluded

Abbreviations: CLDN, claudin; OCLN, occluding; ZO, zonula occluding; TEER, transepithelial electrical resistance.

The study's criteria were prepared according to PICOS (Participants, Intervention, Comparison, Outcome, Study design) criteria (Table 1). The protocol and reporting of this systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria.[18]

Inclusion and Exclusion Criteria

The study included only randomized controlled trials and clinical trials, animal studies, and tissue-culture studies conducted between January 1, 2020, and April 30, 2023, using only live probiotic supplements, published in Turkish and English, and conducted only in adults. In the systematic review, studies conducted in the population under 18 years for research in humans, studies whose methods and results needed to be better explained, and whose full text could not be accessed and that were published before 2020 were excluded. In addition, postbiotic, probiotic food (kefir, etc) studies; studies using only heat-killed probiotics without live strains; studies evaluating only inflammation parameters, prebiotics, supplements given in complex with probiotics (minerals, vitamins, prebiotics, dietary fiber, etc); and studies that did not evaluate TJ proteins and transepithelial electrical resistance (TEER) parameters were excluded.

Selection Process

Three authors independently identified eligible studies (B.Ş., D.S., M.Ş.B.). Titles and abstracts of articles were screened for eligibility. Once potential studies were identified, the authors reviewed the full-text articles to assess and discuss their eligibility in case of inter-reviewer differences. If there was a disagreement between reviewers, the study was shared with the fourth author (M.G.K.), a consultant, and a solution was sought through discussion. The PRISMA 2020 flowchart for new systematic reviews involving databases and record searches is shown in Figure 1.

Protocol Registration

This review protocol was registered in the PROSPERO International Prospective Register of Systematic Reviews (registration no. CRD42023452774).

RESULTS

Figure 1 shows the literature search process used in this study, presented as a PRISMA flow chart. Altogether, 2647 articles were accessed from 4 databases searched. Of these, 110 were excluded for duplication and 9 for language requirements. A further 2127 were excluded for the following reasons: reviews ($n = 433$), different types of study ($n = 9$), studies outside of the subject area ($n = 1642$), studies in progress ($n = 26$), studies not meeting population requirement ($n = 107$), and studies that could not be accessed online ($n = 11$). After abstract reviews, 217 more articles that did not meet the methods and inclusion criteria were excluded from 263 articles, and 46 studies were included in the systematic review. Of the included studies, 6 were cell studies and

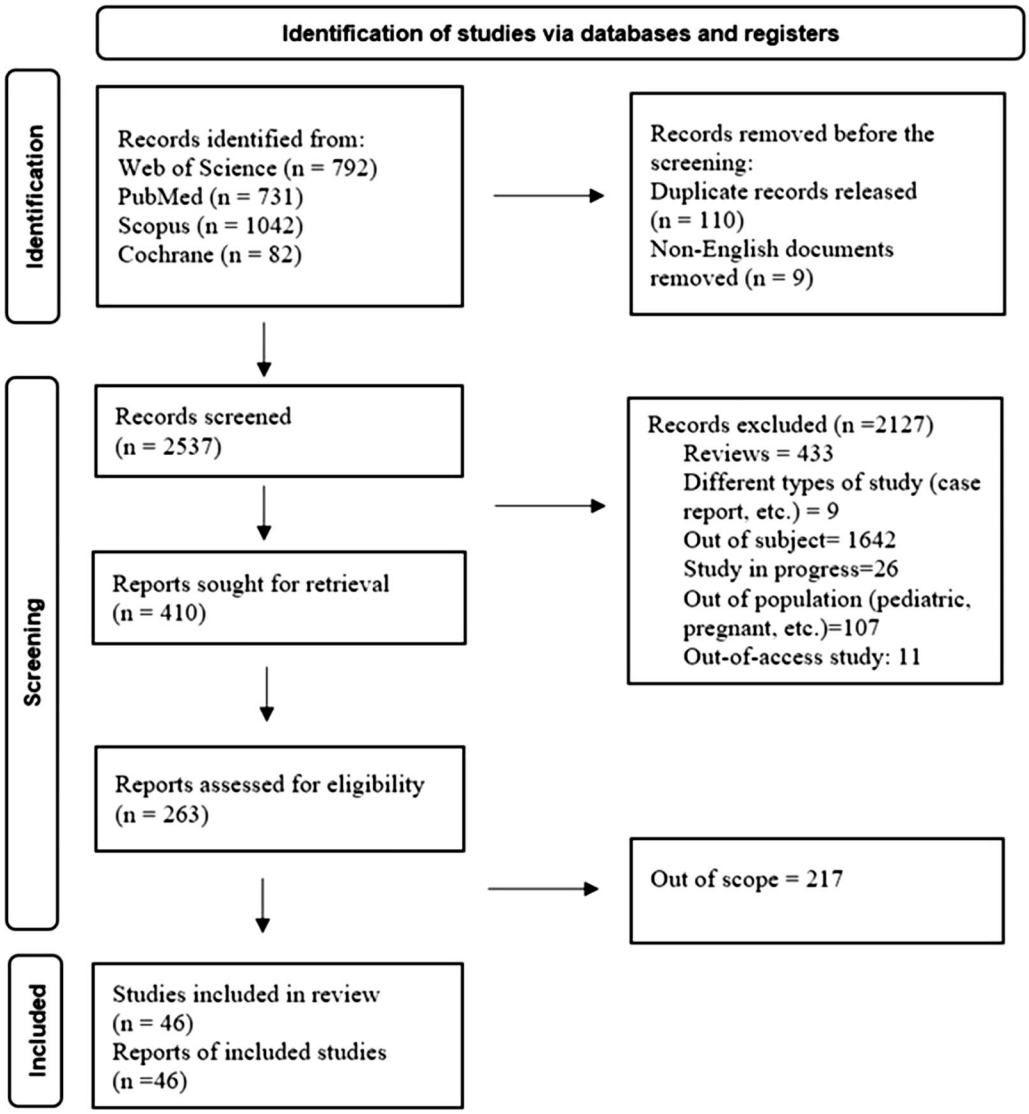

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 Flow Chart. The figure illustrates the literature search process used in this study. Altogether, 2647 articles were accessed from 4 databases searched. Of these, 119 were excluded because they did not meet the duplication and language requirements. In the ongoing review of studies, 433 were excluded as reviews, 9 for study type, 1642 for being off-topic, 26 as for study process, and 118 as being population and inaccessible studies. After abstract reviews, 217 more articles that did not meet the methods and inclusion criteria were excluded from 263 articles, and 46 studies were included in the systematic review. Of the included studies, 6 were cell studies and 40 were animal studies. No clinical research meeting the parameters was found.

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The characteristics of the cell and animal studies are described in Table 2[17,19–23] and Table 3,[24–63] which provide a detailed summary of the demographic data for the samples and study designs.

The cell studies included in the systematic review applied lipopolysaccharide (LPS), hydrogen peroxide (H_2O_2), and dextran sodium sulfate (DSS) models for colitis induction. Different strains and doses were preferred in these models. The TEER parameters used to evaluate TJ proteins and barrier integrity were assessed. The probiotic type, strain, dose, and results obtained in cell studies are given in Table 4.[17,19–23]

In 2 studies using *Lactobacillus rhamnosus*,[17,19] significant increases were observed in the probiotic group after colitis induction in the TJ proteins evaluated. In addition, different doses of the *L rhamnosus* strain were used, and it was determined that the effects of the parameters changed according to the doses.[19] In another study in which *L rhamnosus* was used, while it significantly increased TEER, an increase in TJ proteins

Table 2. Characteristics of Cell Studies

Reference no.	No. of samples	Study design
17	10 Groups	Caco-2/LPS
19	5 Groups	Caco-2/LPS
20	11 Groups	Caco-2/LPS
21	4 Groups	Caco-2/LPS
22	4 Groups	IBD/DSS
23	5 Groups	IBD/H_2O_2

Abbreviations: Caco-2, human colon epidermal adenocarcinoma cell line; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; H_2O_2, hydrogen peroxide; LPS, lipopolysaccharide.

Table 3. Characteristics of Animal Studies

Reference no.	No. of samples	Study design
24	4 Group[a]	Colitis/DSS
25	6 Groups × 8 rats	IBD/DSS
26	7 Groups × 8 rats	Colitis/DSS
27	5 Groups × 6 rats	IBD/DSS
28	6 Groups × 10 rats	Colitis/DSS
29	3 Groups × 8 rats	IBD/DSS
30	4 Groups × 6 rats	IBD/DSS
31	3 Groups × 8 rats	IBD/DSS
32	5 Groups × 8 rats	IBD/TNBS
33	5 Groups × 10 rats	IBD/DSS
34	5 Groups × 6 rats	Colitis/TNBS
35	3 Groups × 7-8 rats	Colitis/DSS
36	4 Groups × 10 rats	Colitis/DSS
37	3 Groups × 10 rats	Colitis/DSS
38	7 Groups × 6 rats	Colitis/DSS
39	4 Groups × 8 rats	Colitis/IBD/DSS
40	4 Groups × 4 rats	Colitis/DSS
41	7 Groups × 7 rats	UC/DSS
42	3 Groups × 6 rats	IBD/DSS
43	4 Groups × 3 rats	Colitis/DSS
44	11 Groups × 8 rats	IBD/colitis/DSS
45	5 Groups × 8 rats	DSS
46	5 Groups × 6 rats	Colitis/DSS
47	3 Groups × 15 rats	IBD/colitis/DSS
48	4 Groups × 10 rats	UC/DSS
49	8 Groups × 3 rats	Colitis/DSS
50	2 Groups × 4 rats	Colitis/TNBS
51	4 Groups × 10 rats	Colitis/DSS
52	4 Groups × 6-8 rats	IBD/DSS
53	10 Groups × 6 rats	CD/TNBS
54	9 Groups × 10 rats	IBD/DSS
55	2 Groups × 16 rats	UC/DSS
56	3 Groups × 6 rats	IBD/DSS
57	5 Groups × 10 rats	UC/DSS
58	5 Groups × 9 rats	Colitis/DSS
59	5 Groups × 8 rats	IBD/DSS
60	4 Groups × 8 rats	IBD/colitis/DSS
61	3 Groups × 7 rats	IBD/colitis/DSS
62	4 Groups[a]	Colitis/DSS
63	5 Groups × 8 rats	Colitis/DSS

[a]Number of mice not specified in the study.

Abbreviations: CD, Crohn's disease; DSS, dextran sodium sulfate; IBD, inflammatory bowel disease; LPS, lipopolysaccharide; TNBS, trinitrobenzenesulfonic acid; UC, ulcerative colitis.

was also found. *Weissella confusa* was also used in the same study, and it was stated that *W confusa* significantly increased TEER and improved TJ proteins more effectively than *L rhamnosus*, and its use with *W confusa* gave more effective results.[23]

The effects of *Bifidobacterium* strains, which have an important role in the intestinal microbiota, were also examined in colitis models: the N8 strain of *Bifidobacterium dentium* increased ZO-1, OCLN, and CLDN-1 protein expression and TEER.[20] In another study examining 2 different strains of *Bifidobacterium*, it was reported to increase TEER.[22] In 1 study, it was found that *Bifidobacterium longum* strains upregulated the mRNA expressions of ZO-1, OCLN, and CLDN-1 proteins.[21]

The effects of probiotic use in animal models of colitis are given in Table 5.[24–63] A study examining the effects of the *Bifidobacterium* strains showed a significant improvement in the expression of ZO-1, CLDN-3, and CDH1, which are TJ proteins.[61] In another study, it was reported that CJ238 and JSNJJJNM2 strains among the 4 selected substrains of *B bifidum* showed a significant improvement effect on ZO-1 levels; the other 2 substrains used were ineffective.[53] It was found that high doses of *B lactis* increased TJ protein expression.[64] *Bifidobacterium longum* significantly decreased the FITC (fluorescein isothiocyanate) index but did not cause a significant difference in TJ proteins.[60] *Bifidobacterium breve* was given at a high dose (5×10^9 CFU/mL), significantly increasing TJ protein expression.[63] In a different study in which 3 different strains of *Bifidobacterium* were used as a mixture, it was stated that no significant change was observed in TJ proteins.[62]

In the current systematic review, studies examined the effects of *Bacillus*, which is also used for different diseases in the intestinal system and shows probiotic effects with the spores and metabolites it produces, on colitis. It was found that *B subtilis* had positive effects on ZO-1, OCLN, and CLDN-1 proteins in colitis.[28,32] In another study in which supplementation was given for different periods, it was found that *B subtilis* given for a longer period of time increased ZO-1 and OCLN from TJ proteins, while short-term supplementation had no significant effect.[30] In other studies, using *Bacillus amyloliquefaciens*, *Bacillus cereus*, and *Bacillus coagulans* strains, significant improvements in the evaluated TJ protein parameters (ZO-1 and/or OCLN and/or CLDN-1) were reported.[29,33,34]

The effect of the *Bacteroides vulgatus* strain, which is expected to have beneficial effects as a probiotic, on the colitis model FITC index indicating permeability status decreased; ZO-1 and CLDN-1 expressions of TJ proteins increased. Still, no significant change was observed in OCLN.[28]

In a study examining the effect of the *Clostridium butyricum* strain, which is known to play a role in butyric acid production, a significant increase was observed in the ZO-1 level of the probiotic used compared with

Table 4. Results of Cell Studies in Colitis Disease

Reference no.	Probiotic strain and species	Dose; duration of use	Parameters evaluated	Core clinical outcomes
17	*Lactobacillus rhamnosus* LR 32, *Bifidobacterium lactis* BL 04, *B. longum* BB 536	10:1, 1:1, 1:10, 1:100 CFU/mL; 24 h	ZO-1, OCLN, CDH1, CLDN-1, CLDN-2	*Bifidobacterium longum* BL536 has been recognized as one of the most effective probiotic strains. Administration of the probiotic formulation containing selected *Lactobacillus* and *Bifidobacterium* genus strains modulated ZO-1, CLDN-1, and OCLN expression.
19	*Lactobacillus rhamnosus* (pre-processing)	10^7, 10^8, $10^{9,}$ CFU/mL; 24 h	CLDN, OCLN, ZO-1	While only 10^8-CFU/mL doses significantly increased the mRNA expressions of OCLN, all amounts significantly increased protein expression. Both mRNA and gene expressions were significantly increased in ZO-1. In CLDN, there was a significant increase in mRNA expressions at all doses, and doses of 10^7 CFU/mL and 10^8 CFU/mL were substantial in gene expression.
20	*Bifidobacterium dentium* N8, *Bifidobacterium dentium* E7	5×10^9 CFU/mL; 24 h	TEER, ZO-1, OCLN, CLDN-1	*Bifidobacterium dentium* N8 significantly increased the TEER value. Stimulated by LPS, paracellular permeability of Caco-2 cells decreased. *B dentium* N8 significantly increased ZO-1, OCLN, and CLDN-1 mRNA expression. *B dentium* N8 was found to have a better protective effect on the intestinal barrier than E7.
21	*Bifidobacterium longum* K5, *Bifidobacterium longum* K15, *B animalis* subsp. *laktis* BB-12	1.0×10^8 CFU/mL; 15 d	TEER	*Bifidobacterium longum* subsp. *longum* K5 (MOI 1:100) upregulated ZO-1, OCLN, and CLDN-1 mRNA expression.
22	*Bifidobacterium longum*, *Bifidobacterium breve*	5×10^8 CFU/mL; 48 h	TEER	Both probiotics increased TEER.
23	*Weissella confusa* (WC) F213, *Lactobacillus rhamnosus* (LR) FBB81	1×10^9 CFU/mL; 2 h	ZO-1, TEER	WC, LR, and their combinations reduced the negative effect of H_2O_2 on barrier resistance. WC was more effective than other probiotics. WC maintained ZO-1 protein stabilization compared with other groups.

Abbreviations: CFU, colony-forming units; CDH1, e-cadherin 1; CLDN, claudin; DSS, dextran sodium sulfate; FITC, fluorescein isothiocyanate; H_2O_2, hydrogen peroxide; OCLN, occludin; TEER, transepithelial electrical resistance; ZO, zonula occludin; MOI, Multiplicity of Infection.

Table 5. Results of Animal Studies in Colitis Disease

Reference no.	Probiotic strain and species	Type of intervention	Dose; duration of use	Parameters evaluated	Core clinical outcomes
24	*Lactobacillus acidophilus*, *Bacillus amyloliquefaciens*, *Bifidobacterium bifidum*	Therapeutic	1×10^{10} CFU/kg; 7 d DSS + 14 d probiotic	OCLN, ZO-1, JAM, FABP-2, CLDN-1	OCLN, JAM, ZO-1 expression increased significantly in the probiotic group, while CLDN-1 and FABP-2 did not increase significantly.
25	*Bifidobacterium bifidum* H3-R2, *Propionibacterium freudenreichii* B1, *Clostridium butyricum* C1-6	Preventive	10^9 CFU/mL; total 14 d (last 7 d DSS)	ZO-1, OCLN, CLDN-1	All three strains increased the expression of ZO-1, OCLN and CLDN-1. *P freudenreichii* B1 and *C butyricum* C1-6 increased TJ protein expression more than *B bifidum* H3-R.
26	*Lactobacillus acidophilus*, *L helveticus*, *L plantarum*	Preventive	1×10^9 CFU/mL; total 21 d (last 7 d DSS)	ZO-1, OCLN, CLDN-1, CDH1	The strains used were effective in increasing OCLN and ZO-1, but ineffective in CDH1 and CLDN-1. Mix of probiotics is effective in increasing CLDN-1 levels.
27	*Lactococcus lactis* mBD14, (with or without plasmid)	Preventive	1.0×10^{10} CFU/d; total 15 d, (last 7 d DSS)	CLDN-1, OCLN, ZO-2	Probiotic strains increased CLDN-1, OCLN, ZO-2 expression, but probiotics with plasmid increased TJ expression.
28	*Bacteroides vulgatus* FTJS7K1 (7K1)	Simultaneous	5×10^9 CFU/ mL; 7 d (probiotic and DSS)	FITC index, ZO-1, CLDN-1, OCLN,	FITC decreased significantly. ZO-1 and CLDN-1 mRNA expressions increased. No significant difference in OCLN.
29	*Bacillus cereus* HMPM18123	Preventive	2×10^8 CFU/mL; total 21 d (last 7 d DSS)	ZO-1, OCLN, CLDN-1	The strains ZO-1, OCLN, and CLDN-1 increased gene expression and mRNA expression.
30	*Bacillus subtilis*	Simultaneous	1×10^{10} CFU/d; first group: DSS + 6 wk probiotic + DSS; second group: DSS + 2 wk probiotic	ZO-1, OCLN	While ZO-1 and OCLN increased in the group given *B subtilis* for 6 wk, no difference was found in the group given *B subtilis* for 2 weeks.
31	*Bacillus subtilis* RZ001	Preventive	1×10^8 CFU/mL; total 14 d, last 7 d DSS	ZO-1, OCLN, CLDN-1	Probiotics significantly increased ZO-1, OCLN, and CLDN-1 expression.
32	*Bacillus subtilis* HH2	Therapeutic	1.0×10^8 CFU/mL; 3 d TNBS + 5 d probiotic	ZO-1, OCLN, CLDN-1	*B subtilis* HH2 improved intestinal epithelial barrier function through modulation of ZO-1, OCLN, CLDN-1, and their related mRNAs.
33	*Bacillus coagulans* MTCC 5856 spores	Preventive	2×10^9 CFU/d; 14 d probiotic, last 7 d DSS	ZO-1, OCLN, CLDN-1	ZO-1, OCLN, and CLDN-1 expression increased and mucosal damage decreased in the probiotic group.
34	*Bacillus amyloliquefaciens*	Preventive	$\geq 10^8$ CFU/g; 21 d + 7 d TNBS	OCLN	Probiotic-enriched yogurt increased OCLN and supported the maintenance of intestinal barrier integrity.
35	*Clostridium butyricum*	Preventive	10^8 CFU/g; 21 d + 7 d DSS	OCLN, CLDN-1, CLDN-2, CLDN-3, ZO-1	The mRNA-dependent ZO-1 level was significantly higher in the probiotic-supplemented group. No significant difference was found in OCLN expression and mRNA-dependent CLDN (1,2,3) levels.

(continued)

Table 5. Continued

Reference no.	Probiotic strain and species	Type of intervention	Dose; duration of use	Parameters evaluated	Core clinical outcomes
36	*Clostridium butyricum Prazmowski* (ATCC 19398)	Preventive	10^9 CFU/0.2 mL; 10 d probiotic (last 5 d DSS)	ZO-1, CLDN-3, OCLN	There was no significant difference in ZO-1, CLDN-3 expression and mRNA-dependent levels of ZO-1, CLDN-3, and OCLN before and after DSS in the strain group.
37	*Coprococcus eutactus*	Preventive	1×10^8 CFU/d; 14 d probiotics (last 7 d DSS)	OCLN, CLDN-1 ZO-1	Regional density of OCLN, CLDN-1, ZO-1, and mRNA expression of OCLN and CLDN-1 increased in the probiotic group.
38	*Lactobacillus rhamnosus*, *L plantarum* SS-128, AB-1	Simultaneous	$1x10^9$ CFU/mL; 7 d (DSS and probiotic)	CLDN-4, OCLN	The probiotic partially reversed DSS-induced decrease in CLDN-4 and OCLN.
39	*Lactobacillus rhamnosus*, *L plantarum karışım*	Therapeutic	2×10^9 CFU/d; 14 d DSS, last 7 d probiotic	ZO-1, CLDN-1	ZO-1 and CLDN-1 were significantly increased in the probiotic group.
40	*Lactobacillus salivarius*	Preventive	1×10^9 CFU/d; 1 wk probiotics + 6 d DSS	TEER, FITC, ZO-1 ZO-2, CLDN-1–4, CLDN-15, OCLN	There was no significant change in FITC index and TJ protein parameters. TEER increased significantly at 4 and 6 hours.
41	*Lactobacillus pentosus* A14-6, CMY46	Preventive	1×10^9 CFU/d; 21 d probiotic (last 7 d DSS)	ZO-1, OCLN, CLDN-1	ZO-1 and OCLN levels were significantly increased in both strains. CLDN-1 level was increased considerably in strain A14-6, with no significant difference in the other strain.
42	*Lactobacillus brevis* Bmb6	Simultaneous	10^9 CFU/mL; 14 d (DSS and probiotic)	ZO-1, CLDN-1	ZO-1 expression increased in the probiotic strain group, while no significant difference was found in CLDN-1 expression.
59	*Lactobacillus plantarum* Y44, *L plantarum* AKS-WS9	Preventive	3×10^8 CFU/mL; 14 days (last 7 d DSS)	ZO-1, OCLN	ZO-1 and OCLN expression increased and intestinal epithelial damage decreased in the probiotic group.
44	*Lactobacillus plantarum*, *L casei*	Therapeutic	1×10^9 CFU/d; days 1–7 DSS and days 5–14 probiotic	FITC index, ZO-1, CDH1, CLDN-3	FITC index was significantly decreased in both strains; ZO-1, CDH1, and CLDN-3 were significantly increased.
27, 58	*Lactobacillus reuteri*	Preventive	1×10^9 CFU/mL; 21 d probiotic + 6 d DSS	OCLN, CLDN-1	OCLN and CLDN-1 expression levels increased in the probiotic group compared with the DSS group.
46	*Lactobacillus reuteri* (FYNDL13 and FCQHC8L)	Preventive	1×10^9 CFU/mL; total 28 d (last 7 d DSS)	ZO-1, ZO-2, CLDN-3, OCLN	Preventive intervention with both strains significantly increased ZO-1, ZO-2, CLDN-3, and OCLN compared with DSS.
47	*Lactobacillus acidophilus*, *L reuteri*, *L rhamnosus*, *Bifidobacterium lactis*, *Streptococcus thermophilus*	Preventive	*L acidophilus*, *B lactis*: 12.5×10^7 CFU/d *L reuteri*, *L rhamnosus*, and *S thermophilus*: 5×10^7 CFU/d 28 d probiotic + 7 d DSS	OCLN	Increased OCLN expression was observed in both models after treatment.

(continued)

Table 5. Continued

Reference no.	Probiotic strain and species	Type of intervention	Dose; duration of use	Parameters evaluated	Core clinical outcomes
48	*Lactobacillus casei* ATCC 393	Preventive	1×10^{10} CFU/mL; 14 d probiotic +7 d DSS	OCLN, CLDN-1, ZO-1	OCLN, CLDN-1, and ZO-1 expression increased significantly.
49	*Lactobacillus casei shirota*	Simultaneous	1×10^{10} CFU/d; 7 d (DSS and probiotic)	OCLN	OCLN expression increased significantly.
50	*Escherichia coli* Nissle 1917	Preventive	10^9 CFU/mL; 14 d (last 7 d DSS)	ZO-1	There was a significant increase in ZO-1/B-actin in normal probiotics (not encapsulated). ZO-1 expression was higher compared with the TNBS group.
51	*Escherichia coli* Nissle 1917	Preventive	10^8 CFU/d; 15 d probiotic, days 6–12 DSS	ZO-1, CLDN-1, OCLN	Increased expression of ZO-1, CLDN-1, and OCLN compared with DSS.
52	*Escherichia coli* Nissle 1917	Simultaneous	10^9 CFU/d; total 42 d; days 1–7/ 15–21/29–35 DSS	ZO-1, OCLN, CLDN-1, CLDN-2	Probiotic strain increased ZO-1 expression; no significant difference in the expression of OCLN, CLDN-1, and CLDN-2.
53	*Bifidobacterium bifidum* CJ238, JSNJJNM2, FXJWS17M4, FBJ1M4	Preventive	10^9 CFU/g; 12 d (last 5 d DSS)	ZO-1	Among the live strains of BB, CJ238 and JSNJJJNM2 strains showed an improvement effect on ZO-1, while the other 2 strains were ineffective.
54	*Enterococcus faecalis*, *Bifidobacterium bifidum*, *Lactobacillus rhamnosus*, *L fermentum*	Preventive	1×10^9 CFU/mL; days 8–22 probiotic and days 15–22 DSS	OCLN, ZO-1, CLDN-4	*E faecalis* and *L rhamnosus* FN518 did not significantly change ZO-1 expression, whereas OCLN and CLDN-4 increased in all groups.
55	*Enterococcus faecium*	Simultaneous	10^9 CFU/mL; 7 d (DSS and probiotic)	ZO-1, CLDN	ZO-1 and CLDNs increased with probiotic treatment compared with DSS.
56	*Pediococcus pentosaceus* CECT 8330	Preventive	5×10^8 CFU/d; 5 d probiotic + 7 d DSS	ZO-1, OCLN	The given strain increased ZO-1 and OCLN expression and modulated intestinal function.
57	*Saccharomyces cerevisiae* I4	Simultaneous	1×10^7 CFU/mL; 7 d (DSS and probiotic)	CLDN-1, OCLN, ZO–1	CLDN-1, OCLN, and ZO-1 expression increased in the probiotic strain group.

(continued)

Table 5. Continued

Reference no.	Probiotic strain and species	Type of intervention	Dose; duration of use	Parameters evaluated	Core clinical outcomes
58	*Saccharomyces cerevisiae* 28-7	Preventive	1.0×10^8 CFU/mL; 20 d, 14 d only probiotic	ZO-1, OCLN	ZO-1 and OCLN expression increased in the probiotic group.
64	*Bifidobacterium animalis* subsp, *lactis* XLTG11	Preventive	1×10^7 CFU/d, 1×10^8 CFU/d; 21 d (days 15 and 20 DSS)	CLDN-1, OCLN, ZO-1	High doses of *B lactis* XLTG11 significantly upregulated the expression of TJ proteins
60	*Bifidobacterium longum*	Preventive	1×10^8 CFU/d; 14 d probiotic (last 7 d DSS)	FITC, ZO-1, OCLN	FITC index has significantly decreased. No significant difference was found in ZO-1 and OCLN.
61	*Bifidobacterium bifidum* ATCC 29521	Preventive	10^9 CFU/mL; 27 d probiotic (last 7 d DSS)	ZO-1, CLDN-3 CDH1	The expression of ZO-1, CLDN-3, and CDH1 was significantly improved. Also, the distribution of ZO-1 was improved.
62	*Bifidobacterium bifidum*, *B breve*, *B longum*	Simultaneous	1×10^9 CFU/mL; 2 d before and 4 d post–DSS administration and continued up to 9 d, 7 d DSS	ZO-1, CLDN-1, CLDN-2	BB1 treatment had no significant effect on ZO-1, CLDN-1, and CLDN-2 expression.
63	*Bifidobacterium breve* H4-2, *B breve* H9-4	Simultaneous	5×10^9 CFU/mL; 7 d (DSS and probiotic)	OCLN, CLDN-1, ZO-1	OCLN, CLDN-1, and ZO-1 expression was significantly increased in the probiotic groups.

Abbreviations: CFU, colony-forming units; CDH1, e-cadherin 1; CLDN, claudin; DSS, dextran sodium sulfate; FITC, fluorescein isothiocyanate; JAM, junctional adhesion molecule; OCLN, occludin; TEER, transepithelial electrical resistance; TNBS, trinitrobenzenesulfonic acid; TJ, tight junction; ZO, zonula occludin; FABP-2, fatty acid binding protein.

DSS, while no significant result was found in other evaluated parameters using the same strain.[35,36]

In a study in which the effects of the *Coprococcus eutactus* strain, a strong probiotic, were examined, it was reported that there were significant improvements in the evaluated TJ proteins.[37]

Regular intake of *Enterococcus faecium*, a type of probiotic that lives in the gastrointestinal tract, can reduce DSS-induced colitis damage in rats.[65] Although the role of *E faecium* in colitis and the potential mechanism of its protective effect are still unknown, in the study[55] ZO-1 and CLDNs increased with probiotic treatment compared with DSS. The present results suggest that *E faecium* administration may prevent DSS-induced intestinal inflammation and flora imbalance.

Lactobacillus reuteri,[46,58] *Lactobacillus casei*,[48,49] and other *Lactobacillus* strains[42,44] significantly increased the expression of some TJ proteins in colitis. Similarly, *Lactobacillus* strain mixtures significantly increased the expression of TJ proteins[26,38,39,59]; *Lactobacillus pentosus* subspecies showed a positive/no effect on the expression of TJ proteins.[41] It was stated that the *Lactobacillus salivarius* strain did not cause significant changes in FITC and TJ protein parameters.[40] *Pediococcus pentosaceus* CECT 8330, a sub-strain of *Pediococcus*, a lactic acid bacterium, has been shown to increase ZO-1 and OCLN expression and modulate intestinal function.[56]

Lactococcus lactis, a safe probiotic for humans, is widely used in food fermentation and can survive and remain viable in the gastrointestinal system for several days. *Lactococcus lactis* mBD14 has been reported to increase TJ protein expression.[27]

Although many studies examined the effect of bacteria on colitis, there are limited studies on yeasts. It has been stated that *Saccharomyces cerevisiae* increases TJ protein expressions in colitis.[45,57]

Escherichia coli Nissle 1917 is a well-established bacterium in terms of genetic modification and is considered a safe probiotic for human use.[66,67] Although *E coli* Nissle has made some progress in the therapy for IBD, low overall efficacy and high relapse rates have limited its application as first-line therapy for IBD.[68] However, recent studies have reported that *E coli* Nissle increases the expression of TJ proteins such as ZO-1, CLDN-1, and OCLN and has positive effects on the therapy for IBD.[50–52]

Although many studies[25,47] have shown that probiotics provide remission by improving the impaired barrier integrity caused by colitis, there are studies that have shown no effect.[24,54]

The effects of probiotics on TJ proteins according to their families are shown in Figure 2. Lactobacillaceae and Bifidobacteriaceae are the most commonly used probiotic families in the studies included in the present study. The effects on TJ proteins according to the strains of Lactobacillaceae and Bifidobacteriaceae families are shown in Figures 3 and 4, respectively. It is seen that the most studied strains are *L casei* and *L reuteri* in Lactobacillaceae strains, and these strains were effective in the studies. In Bifidobacteriaceae strains, the most studied strains were *B bifidum* and *B longum*, but the number of significant studies showing the effect of these strains on TJ proteins is low.

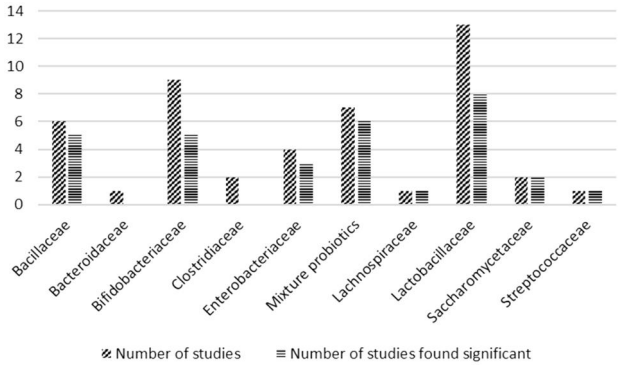

Figure 2. Effects of Probiotics on Tight Junction Proteins by Family

DISCUSSION

The present study aimed to investigate the effect of probiotics on intestinal barrier function in colitis. For this purpose, studies evaluating the effects of probiotic treatment on TJ proteins were systematically reviewed.

The systematic review examined probiotic treatment in 46 colitis studies. Positive results were observed in 32 of these studies, while the remaining studies did not show significant effects (Table S1). Probiotics can positively affect host health through immunological pathways, such as activation of local macrophages, modulation of cytokines, and tolerance to food antigens, as well as non-immunological pathways, such as food digestion and competition with pathogens, changes in ambient pH, bacteriocin production, and increased mucin production.[11] With all of these mechanisms, probiotics play an essential role in improving health by maintaining the immunological balance in the gastrointestinal system. However, their effectiveness varies according to probiotic type, disease type, microbial diversity, and dose.[12]

Research interest in the role of the gut microbiome on IBD and the use of probiotics to modulate and treat intestinal inflammation has increased considerably in recent years.[25,36,46] The beneficial effects of probiotics in IBD treatment are relatively moderate and primarily limited to pouchitis. The estimated mechanisms of action of probiotics on colitis are shown in Figure 5. Studies on identifying and using probiotic bacteria strains that can target and maintain intestinal epithelial TJ barrier function

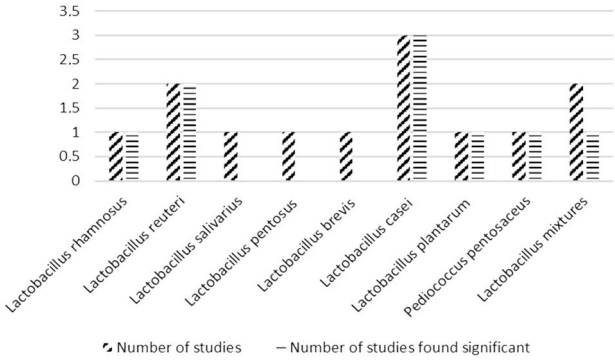

Figure 3. Effects on Tight Junction Proteins According to Lactobacillaceae Species

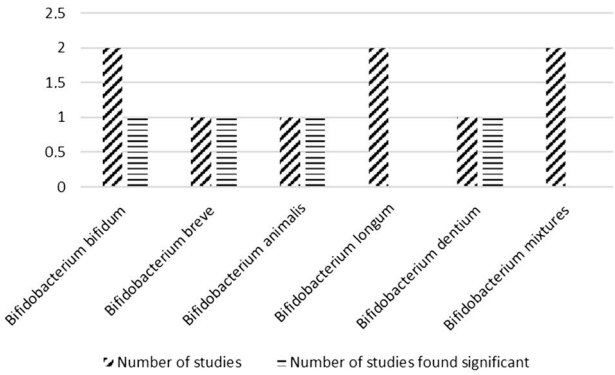

Figure 4. Effects on Tight Junction Proteins According to Bifidobacteriaceae Species

and prevent and treat intestinal inflammation are very limited.[69] Some probiotics have the same therapeutic effect as 5-aminosalicylic acid used in IBD treatment and are recommended by the European Society for Clinical Nutrition and Metabolism (ESPEN) for IBD treatment.[70]

The intestinal barrier function regulates the transport of nutrients, water, and electrolytes in the intestine and acts as an essential line of defense against pathogenic bacteria from the external environment.[71] An alteration or disruption in the expression of TJ proteins is associated with a rapid deterioration in intestinal barrier functions.[72] In addition, damage to the intestinal barrier function caused by pathogens also leads to the release of proinflammatory cytokines and disruption of TJs, causing abnormal intestinal inflammation and the development of chronic inflammatory diseases such as IBD.[73] Therefore, preservation of intestinal epithelial barrier integrity plays a crucial role in IBDs, and has become a therapeutic and preventive target for IBD.[19,74]

The intestinal mucosal barrier is the first line of defense against enteric pathogen invasion. Intestinal mucosal barrier integrity and functional maturation of the intestine are required to prevent intestinal infectious and inflammatory diseases such as IBD.[75] Tight junction proteins located between cells in the luminal wall prevent the activation of abnormal immune responses by effectively blocking the invasion of bacteria and toxins.[38,76] Dysfunction of TJ proteins leads to increased intercellular permeability of the intestinal epithelium and the entry of bacteria, endotoxins, and macromolecules into the circulation, related to the occurrence and development of various diseases. OCLN, CLDN-1 and ZO-1 are 3 important proteins that play an essential role in TJs.[77,78] The intestinal epithelium is continuously stimulated by various bioactive molecules, such as antigens, metabolites, and even psychological stress from nutrients and microorganisms. Therefore, proper control of immune responses is key to maintaining normal gut function.[79]

In the cell studies included in the systematic review, it was found that probiotics increased the levels of TEER and TJ proteins, and this increase was dose-dependent and had positive effects (Table 4[17,19–23]). In studies conducted in animal models, there were positive effects on the FITC index and intestinal integrity parameters, as well as studies with no effect. At the same time, no studies reported negative effects (Table 5[24–63]).

In the included studies, *Lactobacillus* and *Bifidobacterium* strains were most frequently used. *Bifidobacterium* has many positive effects in the gastrointestinal system, including IBDs.[80] One of these effects is prolonging remission and reducing attack symptoms by improving the impaired barrier integrity caused by colitis using many different strains. In the studies included in the systematic review, *Bifidobacterium* strains generally enhanced the decrease in the expression of TJ proteins caused by colitis, and there are studies in which no effect is observed depending on the strains and dose. *Lactobacillus*, one of the critical components of intestinal microbiota, has a potential and influential role in providing intestinal barrier function, T-cell–mediated immune effects, and improvement in intestinal flora, and is widely used in the protection and treatment of intestinal health.[81] In the current systematic review, the effect of *Lactobacillus* species on TJ proteins, one of the indicators of intestinal barrier integrity, was examined and it was determined that there were studies in which no effect was observed. However, primarily positive effects were observed (Table 5[24–63]).

Bacteroides, an essential part of intestinal bacteria, play an important role in maintaining the ecological balance and nutrient cycling in the intestine, with many functions.[82] *Bacteroides* are known to have antimicrobial, anticancer, immunomodulatory, short-chain fatty acid production, beneficial, and commensal effects on the immune system, and pathogenic effects in some cases.[83] In the current study, there was 1 study on

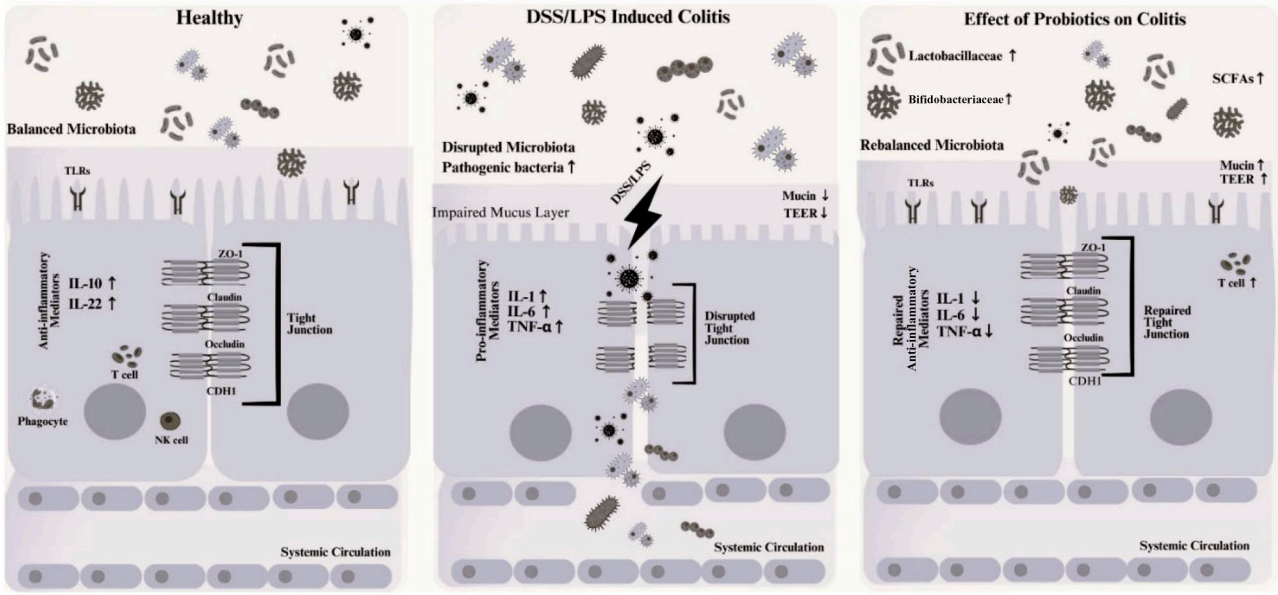

Figure 5. Effect of Probiotics in DSS/LPS-Induced Colitis. The figure illustrates the conditions of a healthy gut, DSS/LPS-induced colitis, and the effects of probiotic administration in colitis. Colitis disrupts the microbiota, leading to an increase in pathogenic bacteria, proinflammatory mediators, and intestinal permeability by reducing mucin production and TEER in a healthy microbiota. Probiotic administration in colitis can help restore balance by increasing SCFAs, enhancing T-cell activity, regulating TLRs, and promoting mucin and TEER levels. Additionally, probiotics reduce proinflammatory mediators such as IL-1, IL-6, and TNF-α, while restoring anti-inflammatory mediators, thereby improving both intestinal permeability and microbiota composition. ↑: Increase; ↓: decrease. Abbreviations: CDH1, cadherin-1/e-cadherin; DSS, dextran sodium sulfate; IL, interleukin; LPS, lipopolysaccharide, NK, natural killer; SCFA, short-chain fatty acid; TEER, transepithelial electrical resistance; TLR, Toll-like receptor; TNF-α, tumor necrosis factor α; ZO-1, zonula occludin-1

Bacteroides, and positive results were reported in the evaluated research.

The mechanisms underlying the protective effect of lactic acid bacteria (LAB) in the gut are hypothesized to be multifactorial, involving fermentation products, production of bioactive/metabolic compounds, and competition for mucosal sites. However, few studies have evaluated the synchronous communication between LAB and gut flora and the effect of regulating bacterial quorum sensing behavior on gut inflammation healing.[38]

The efficacy of different probiotic strains in colitis is controversial. One of the problems is that the definition of high-quality probiotics is not clear, and it is necessary to use sufficient numbers of live probiotics with a good measure of safety. In general, it is suggested that a mixture of probiotics may be a superior approach to using single-strain probiotics, as successful colonization and health-promoting effects are more pronounced. Simultaneous administration of different strains with various properties has increased colonization, probiotic effects, and biological activities. This can be explained by the dynamics of synergistic positive relationships between strains.[60] Mixtures of probiotic strains ameliorated the decrease in TJ protein expression, which is mainly caused by colitis (Table 5[24–63]).

Short-chain fatty acids, especially butyric acid, have many effects on the intestinal barrier and other intestinal functions. They increase barrier integrity by increasing TJ proteins.[84] In addition, short-chain fatty acids can regulate intestinal pH, increase mucin gene expression, increase mucus production, and prevent adhesion of pathogenic bacteria.[85] Probiotics are thought to increase TJ proteins by increasing short-chain fatty acids. Another predicted mechanism is that probiotics may have a positive effect by reducing pathogens by changing the balance of bacteria in the intestine and inhibiting structural changes in TJ proteins.[86]

The effect of probiotics on intestinal barrier function is complex, and the specific mechanism of action may vary depending on the strain. Furthermore, beneficial effects may result from several mechanisms related to enzymes or metabolites produced by specific microorganisms. Probiotics improve the intestinal barrier by increasing mucus thickness in a colitis model and increasing TJ protein expression and localization and mucin-related genes.[85]

In addition to the primary contributions of probiotics in the treatment of colitis through microbiota, they may also have secondary positive effects. Colitis is known to cause a pathology in the lungs, especially in susceptible individuals. The idea that this relationship may be related to the gut–lung axis has recently attracted interest in terms of both pathophysiology and treatment.[87] Probiotics have many positive effects on the host's immune system. In the gut–lung axis, they

can contribute to the development of the lung mucosal defense system with the improvement they provide in the intestinal barrier. In addition, it is thought that they may provide a positive effect secondary to colitis-related pathologies in the lungs by eliminating the negative effects of systemic inflammation and oxidative stress and providing lipid homeostasis. However, it is also known that the mechanisms are not yet clear.[88]

Limitations

This systematic review has several limitations. First, only studies from the past 3 years were included due to the extensive literature available, and there was a lack of human studies that met the inclusion criteria. The variability among studies in terms of probiotic strains and species, dosage and duration of use, and the parameters evaluated for intestinal barrier function posed significant challenges in correlating results across studies. Additionally, studies utilizing encapsulated or vectorized forms of probiotics with new technologies were excluded, which, while reducing heterogeneity, could also be seen as a limitation. Furthermore, a meta-analysis could not be performed due to the insufficient amount of data and the high degree of heterogeneity among the studies.

Despite these limitations, this review has notable strengths. First, this study rigorously adhered to the PRISMA guidelines and its systematic approach was based on the PICOS criteria, which ensures a comprehensive and systematic evaluation of the evidence. This methodological framework ensures transparency, reproducibility, and reliability of findings. It does so by systematically evaluating the strength of evidence, as recommended, either in the Results or the Methods sections. It was conducted systematically, which helps mitigate the risk of reporting bias. Special attention was given to distinctly separating human studies from animal and cell studies when discussing the outcomes and conclusions of the articles. Moreover, probiotic species were classified as thoroughly as possible, clarifying their effects.

CONCLUSION

The bidirectional relationship between vitamin mineral deficiency and disease in IBD makes it challenging to characterize the precise role of each micronutrient. Decreased food consumption, decreased absorption, avoidance of food intake, decreased appetite, decreased intestinal surface area after surgical treatment, and increased gastrointestinal tract losses affect nutritional status in patients with IBD.[89]

Each epithelial cell plays an active role in nutrient absorption in the intestine while preventing harmful materials from entering the cell. Tight junction proteins are the structures that close the intercellular space and avoid leakage.[90] Many symptoms of IBD can cause vitamin and mineral deficiency.[89] Tight junction proteins are essential in regulating the permeability of nutrients, especially some amino acids, calcium, and magnesium, and in absorption, barrier integrity, and immunity.[91] Considering these effects, decreased TJ protein expression in colitis negatively affects colitis symptoms and disease duration. In addition, decreased TJ proteins due to their other functions have been associated with many problems ranging from obesity to autoimmune diseases, psychological diseases to cancer, and intestinal inflammation.[92] Therefore, prevention and/or improvement of the damage caused by colitis in TJ proteins significantly improves the quality of life.

Probiotics, which aim to regulate intestinal microorganisms, attract significant interest in treating colitis because they do not cause side effects, unlike traditional drugs.[38] Given the efficacy of probiotics in treating this condition as documented in this study, it is posited that they could serve as a beneficial adjunctive therapy in the treatment of this disease.

However, further research, including extensive clinical studies, is required to provide recommendations for preventing colitis and its complications as the current literature primarily consists of animal and cell studies that meet the study criteria.

Author Contributions

Study concept and design: M.G.K., B.Ş., D.S., M.Ş.B.; data collection and analysis: B.Ş., D.S., M.Ş.B.; writing of the draft manuscript: B.Ş., D.S., M.Ş.B.; revision of the draft manuscript: M.G.K., B.Ş., D.S., M.Ş.B.. All authors read and approved the final manuscript.

Supplementary Material

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Conflicts of Interest

None declared.

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