Effect of dietary probiotics on colon length in an inflammatory bowel disease–induced murine model: A meta-analysis

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ABSTRACT

We investigated the effect of probiotic supplementation on inflammatory bowel disease (IBD) by meta-analysis. We included 30 studies to assess the effect of probiotic administration. We estimated the effect size using standardized mean difference, and we evaluated the statistical heterogeneity of the effect size using Cochran's Q test, followed by meta-ANOVA and meta-regression analysis to explain the heterogeneity of the effect size using a mixed-effects model. We conducted Egger's linear regression test to evaluate publication bias. Among the factors evaluated, colon length and myeloperoxidase showed the greatest Q statistic and I^2 index, respectively. Colon length, transforming growth factor- β , IL-10, superoxide dismutase, and glutathione showed positive effect sizes in the fixed- and random-effects models. The others (spleen weight, tumor necrosis factor α , IL-1 β , IL-6, IL-12, IL-17, IFN- γ , disease activity index, thiobarbituric acid reactive substances, nitric oxide, myeloperoxidase, malondialdehyde, histological score, and macroscopic inflammatory score) showed negative effect sizes in the fixed- and random-effects models. Probiotics showed a significant effect on all investigated factors, except IL-10. In meta-ANOVA and meta-regression analysis, *Lactobacillus paracasei* was the most effective probiotic for colon length. *Lactobacillus paracasei*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, and a mixture of *Lactobacillus bulgaricus* and *Saccharomyces boulardii* (LC + SB) were effective for colon length, tumor necrosis factor α , IL-6, IL-10, IFN- γ , and disease activity index. *Lactobacillus rhamnosus* was most effective for IL-10 and IFN- γ . Dietary probiotics are effective in improving the symptoms of IBD. Although the results of this meta-analysis had some limitations due to a lack of animal experiments, they will be meaningful to people with IBD.

Key words: meta-analysis, probiotics, inflammatory bowel disease

INTRODUCTION

Inflammatory bowel disease (IBD) includes ulcerative colitis and Crohn's disease. These diseases present with various symptoms, including loss of BW, bloody stool, fever, and contraction of colon length; in some cases, they progress to colorectal cancer (Kim and Chang, 2014). However, the etiology of IBD is still unclear (Krawisz et al., 1984; Weitzman and Gordon, 1990; Fiocchi, 1998; Hendrickson et al., 2002). Although the underlying causes of IBD have not been clearly elucidated, they are thought to be caused by a distorted immune response of the intestinal mucosa because of various environmental factors (Sartor, 2008). Among these environmental factors, the representative factor is the gut microbiota. Approximately 500 to 1,000 species of bacteria inhabit the human intestine (Salzman and Bevins, 2008). They form a varied and complex ecology and maintain an anaerobic environment in the intestine. They simultaneously absorb nutrition and control the immune response. The gut microbiota is well balanced in healthy people, but an unbalanced status of the gut microbiota leading to the growth of a harmful microbiome in the intestine—dysbiosis—induces a proinflammatory immune response. Consequently, the inflammatory response associated with IBD increases (Tamboli et al., 2004). For example, the microbiome associated with normal bowel function decreases in people with IBD (Frank et al., 2007; Franke et al., 2008; Scanlan and Marchesi, 2008), fungal presence is increased (Kühbacher et al., 2006; Ott et al., 2008) or methanogen diversity is reduced (Scanlan and Marchesi, 2008). Recently, the gut microbiota has become a major determinant of intestinal and non-intestinal diseases, based on the theory that IBD is related to the intestinal microflora, a concept that is supported by the differences in intestinal microflora between healthy individuals and people with IBD (Tamboli et al., 2004; Guinane and Cotter, 2013).

Probiotics are live microorganisms that help in maintaining good health, including gut health and intestinal homeostasis (Fuller, 1989; Hill et al., 2014), and they are useful for improving gut health as well (Hemara-

Received July 30, 2019.

Accepted October 11, 2019.

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jata and Versalovic, 2013). Some studies have reported positive effects of probiotics in IBD. Rembacken et al. (1999) reported that well-defined nonpathogenic *Escherichia coli* Nissle 1917 was effective in preventing the recurrence of IBD compared with placebo. *Saccharomyces boulardii* relieved the symptoms of IBD and reduced the risk of relapse (Guslandi et al., 2000). Consequently, probiotics may be considered good alternatives for the prevention or management of IBD.

Generally, glucocorticoid and sulfasalazine have been used to treat IBD, but they come with serious side effects (Misiewicz et al., 1965; Boumpas et al., 1993). Many studies have been conducted to discover probiotics that have no side effects. Generally, probiotics are known to be effective in alleviating IBD, improving intestinal mucosa, regulating cytokines, preventing colon cancer, and improving the immune system (Guarner and Schaafsma, 1998).

In murine models, the symptoms of IBD can be improved with probiotic supplementation. However, only a few comprehensive studies have investigated the specific effects of probiotics in improving the symptoms of IBD. The objective of this study was to conduct a meta-analysis of the effect of probiotics on colon length and changes in other indicators in murine IBD models.

MATERIALS AND METHODS

Data Set

We performed a literature search using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA; Liberati et al., 2009; Moher et al., 2009). We searched the following online databases: ScienceDirect (Elsevier B. V., Amsterdam, the Netherlands) and PubMed (United States National Library of Medicine, Bethesda, MD). The key words we used in both databases were “probiotics,” “IBD,” “rat,” and “mice.” Our search initially located 857 and 157 articles from ScienceDirect and PubMed, respectively. We screened all articles by title, abstract, and full text. We excluded review articles and studies at the cell culture level or studies investigating the administration of micro- or nanoencapsulated probiotics. We included studies that investigated changes in colon length and the immune system after the feeding of probiotics. A total of 30 studies exploring 19 factors were extracted and used to evaluate the effect of probiotic supplementation in a murine IBD model. We included studies that had an IBD group as a control; that induced IBD in the model using chemicals such as dextran sodium sulfate (DSS), 2,4,6-trinitrobenzene sulfonic acid (TNBS), dinitrobenzene sulfonic acid (DNBS), or oxazolone;

and that provided measured data with standard deviation or standard error.

Data Analysis

Corrected standardized mean difference (Hedge's g) and 95% confidence intervals were calculated for the control and treatment groups. The weight of the effect size was computed using inverse variance (Borenstein et al., 2009; Deek et al., 2011). Effect-size analysis of fixed- and random-effects models was used to calculate the summary effect due to differences in experimental period, sample size, animal strain, and dose of probiotics in each study. To assess the statistical heterogeneity of the effect size, we performed Cochran's Q test; we investigated the ratio of true heterogeneity to total variation in the observed effects with the I^2 index. We also conducted meta-ANOVA and meta-regression analyses to explain the heterogeneity of the effect size in mixed-effects models for factors with degrees of freedom >10 . We used means of control and treatment, number of replications, and standard deviations for within-study error as parameters in the effect-size calculations for both the fixed- and random-effects models. In the random-effects model, we added the tau square value (τ^2) to the variance calculation to consider within- and between-study variance together. Finally, we performed a publication bias analysis to verify the validity of the study results. Statistical analysis and visualization of the results were conducted using the packages meta, tidyverse, and metafor in the R statistical program (version 3.5.3; R Development Core Team, 2019, <http://www.r-project.org>).

RESULTS AND DISCUSSION

Data Set

The data sets and experimental conditions from the 30 published studies are summarized in Table 1. The included studies were published between 2004 and 2019. Most of the studies ($n = 23$) were conducted using mouse strains such as C57Bl/6, BALB/c, Swiss Albino, TLR4lps-/lps-, and ICR; the others used rat strains, including Wistar, Sprague-Dawley, and NC/Nga. The most common chemical used to induce IBD was DSS, and *Lactobacillus plantarum* and *Lactobacillus casei* were the most common probiotic strains used for supplementation.

Effect Size and Heterogeneity Analysis

Table 2 shows the effect of probiotics on IBD in mice and rats using fixed- and random-effects models. Fac-

Table 1. Studies used in the data set and information for meta-analysis

Author (year)	Animal (strain)	N	Induced chemical ¹	Probiotics ²	Factors for analysis ³
Chen et al. (2019)	Mouse (C57Bl/6)	10	DSS	LGG, LP	Colon length, spleen weight, TNF- α , IL-6, IL-10, IL-12, IL-17, IFN- γ , MDA
Luerce et al. (2014)	Mouse (C57Bl/6)	5	DSS	LL	Colon length, TNF- α , IL-6, IL-10, IL-12, IL-17, IFN- γ , macroscopic inflammatory score, histological score
Srutkova et al. (2015)	Mouse (BALB/c)	5	DSS	BL	DAI, colon length, TNF- α , IL-6, IL-10, IFN- γ
Santos Rocha et al. (2014)	Mouse (C57Bl/6)	7	DSS	LL	DAI, IL-6, IL-10, IL-12, IL-17, histological score
Feng et al. (2018)	Mouse (BALB/c)	10	Oxazolone	LB, LP1	Colon length, DAI, MDA, MPO
Li et al. (2018)	Mouse (C57Bl/6)	10	DSS	LP1	Colon length, MDA, MPO
Yoon et al. (2019)	Mouse (BALB/c)	6	DSS	LA + BL + ST + LB	Colon length, IL-6, IL-10, MPO
Chauhan et al. (2014)	Mouse (Swiss Albino)	8	DSS	LF	Colon length, DAI, MDA, histological score
Ghasemi-Niri et al. (2012)	Rat (Wistar)	6	TNBS	LC, LC + BB, LC + SB	TNF- α , MPO, microscopic inflammatory score, macroscopic inflammatory score
Kokesová et al. (2006)	Mouse (BALB/c)	10	DSS	EC O83, EC Nis, LC	Colon length
Qian et al. (2017)	Mouse (BALB/c)	10	Oxazolone	LB, LP	Colon length, DAI, MPO, MDA
Ghasemi-Niri et al. (2011)	Rat (Wistar)	6	TNBS	LC	TNF- α , MPO, microscopic inflammatory score, macroscopic inflammatory score
Hong et al. (2010)	Mouse (ICR)	5	DSS	LB + BL	Colon length, MPO, MDA
Santiago-López et al. (2018)	Mouse (C57Bl/6)	10	DSS	LF	Colon length, TNF- α , IL-6, IL-10, IL-17, IFN- γ
Liu et al. (2011)	Mouse (BALB/c)	8	DSS	LP1	Colon length, DAI, TNF- α , IL-1 β , IL-6, MPO, macroscopic inflammatory score, histological score
Lee et al. (2008)	Mouse (ICR)	10	DSS	LP1, LBr	colon length, IL-6, MPO
Moeinian et al. (2014)	Rat (Wistar)	7	TNBS	LC	TNF- α , IL-1 β , MPO, microscopic inflammatory score, macroscopic inflammatory score
Gholami et al. (2016)	Rat (Wistar)	7	TNBS	LC	MPO, microscopic inflammatory score, macroscopic inflammatory score
Chung et al. (2008)	Mouse (TLR4lps-/lps-)	8	DSS	LC	IL-6, IL-10, IL-12, MPO, histological score
	Mouse (BALB/c)	10			
		10			
		14			
		14			
Ogita et al. (2011)	Mouse (BALB/c)	4	DSS	ST	Colon length
Zhang et al. (2014)	Rat (Sprague-Dawley)	7	TNBS	FP, BL	Colon length
Choi et al. (2019)	Mouse (NC/Nga)	7	TNBS	EF	Colon length, DAI, histological score
Celiberto et al. (2017)	Rat (Wistar)	10	DSS	LH + EF	DAI, macroscopic inflammatory score
Nishitani et al. (2009)	Mouse (C57Bl/6)	3	DSS	LL	Colon length
		6			
		6			
Jang et al. (2013)	Mouse (ICR)	6	TNBS	LBr	Colon length, TNF- α , IL-1 β , IL-6, IL-10, MPO
Schreiber et al. (2009)	Rat (Sprague-Dawley)	6	DSS	LR	DAI
Sokol et al. (2008)	Mouse (BALB/c)	9	TNBS	FP	Colon length, TNF- α , IL-10, IL-12
Toumi et al. (2013)	Mouse (Swiss albino)	4	DSS	LA + LP1 + BL + BB	Colon length
Yoda et al. (2014)	Mouse (C57Bl/6)	5	DSS	LGG	Colon length
Ahl et al. (2016)	Mouse (C57Bl/6)	11	DSS	LR	DAI, TNF- α , IL-1 β , IL-6, histological score

¹DNBS = dinitrobenzene sulfonic acid; DSS = dextran sodium sulfate; TNBS = 2,4,6-trinitrobenzenesulphonic acid.

²BB = *Bifidobacterium bifidum*; BL = *Bifidobacterium longum*; EF = *Enterococcus faecalis*; FP = *Faecalibacterium prausnitzii*; LA = *Lactobacillus acidophilus*; LB = *Lactobacillus bulgaricus*; LBr = *Lactobacillus brevis*; LC = *Lactobacillus casei*; LF = *Lactobacillus fermentum*; LGG = *Lactobacillus rhamnosus* GG; LH = *Lactobacillus helveticus*; LL = *Lactobacillus lactis*; LP = *Lactobacillus paracasei*; LP1 = *Lactobacillus plantarum*; LR = *Lactobacillus reuteri*; SB = *Streptococcus bouardii*; ST = *Streptococcus thermophilus*; EC O83 = *Escherichia coli* O83; EC Nis = *Escherichia coli* Nissle.

³DAI = disease activity index; MDA = malondialdehyde; MPO = myeloperoxidase; TNF- α = tumor necrosis factor α .

tors such as colon length, transforming growth factor (TGF- β), IL-10, superoxide dismutase, and glutathione showed positive effect sizes in both the fixed- and random-effects models, and all effects were significant ($P < 0.0001$) except for TGF- β . However, other factors showed significant negative effect sizes in fixed- and random-effects models ($P < 0.05$). According to Kim et al. (2013), the administration of *Aucklandia lappa* in a murine IBD model was effective in improving the symptoms of IBD by decreasing IFN- γ , tumor necrosis factor α (TNF- α), and IL-6, and increasing TGF- β and IL-10. Similarly, Jeon et al. (2016) found a significant decrease of TNF- α , IL-1 β , IL-6, and IFN- γ after administration of *Zostera marina* extract in a murine IBD model and the decreased colon length induced by administration of DSS was recovered.

These results showed that probiotic supplementation was effective in improving the symptoms of IBD, including contraction of colon length, increase in spleen weight, and scores related to inflammation. Colon length was significantly increased ($P < 0.0001$), and spleen weight, histological score, and inflammatory score were significantly decreased (i.e., improved; $P < 0.0001$). Usually, destruction of the gut structure by widespread permeation of inflammatory cells, edema of the large intestine, and ulcers is found in people with IBD, leading to contraction of colon length (Wu et al., 2011). Thus, reduction in colon length can be a marker for the diagnosis of IBD (Yoda et al., 2014). The spleen is the largest organ in the lymphatic system, and it plays a major role in antibody formation, so it tends to enlarge as a result of infection (King and Shumacker, 1952).

Cytokines are secreted by activated lymphocytes and macrophages, and regulate the function of cells associated with the cell-mediated immune response. They also play an important role in the inflammatory response (Zhang and An, 2007). Recently, cytokines have been recognized as key players in the pathophysiology of IBD (Kim et al., 2003). One of the proinflammatory cytokines is TNF- α , which plays an important role in immune response expression and regulation. An increase in TNF- α has been observed in the mucosa of people with IBD (Dionne et al., 1997). Interferon- γ is a protein with antiviral activity, and 3 IFN types, α , β , and γ , activate immunocytes. Among these, IFN- γ is secreted by T cells and natural killer cells and acts as a macrophage-activating factor (Tau and Rothman, 1999). The cytokine IL-1 β is an intermediary of inflammatory response, and inflammation-inducing factor in acute or chronic IBD (Tau and Rothman, 1999). Cytokine IL-6 is generated in activated T cells and is known to be induced in the stage at which B cells differentiate into antibody-producing cells (Barnes

Table 2. Effect size of probiotics on inflammatory bowel disease in a murine model

Item	Fixed-effects model		Random-effects model		Heterogeneity ¹			
	Effect size	P-value	Effect size	P-value	df	Q (P-value)	I ² (%)	τ^2
Colon length	1.8169	<0.0001	2.5244	<0.0001	39	201.07 (<0.0001)	80.6	2.0096
Spleen weight	-0.9594	<0.0001	-1.7804	0.0019	8	68.85 (<0.0001)	88.4	2.5204
Tumor necrosis factor α	-2.3634	<0.0001	-3.4922	<0.0001	15	14.58 (<0.0001)	89.4	7.3365
Transforming growth factor- β	0.5372	0.0678	0.1534	0.8939	3	39.80 (<0.0001)	92.5	4.8372
IL-1 β	-3.2779	<0.0001	-3.2779	<0.0001	5	2.78 (0.7333)	0.0	0.0000
IL-6	-1.6249	<0.0001	-2.0466	<0.0001	15	91.43 (<0.0001)	83.6	2.0280
IL-10	1.4366	<0.0001	1.8182	0.0009	12	94.75 (<0.0001)	87.3	3.3265
IL-12	-1.7521	<0.0001	-3.0381	0.0003	7	76.88 (<0.0001)	90.9	5.0336
IL-17	-0.8219	0.0016	-2.0878	0.0343	5	65.05 (<0.0001)	92.3	5.2198
IFN- γ	-0.7817	<0.0001	-1.2988	0.0049	10	67.88 (<0.0001)	85.3	1.9368
Disease activity index	-3.6288	<0.0001	-4.9837	<0.0001	14	106.41 (<0.0001)	86.8	5.8988
Superoxide dismutase	1.6365	<0.0001	2.9510	0.0002	5	42.72 (<0.0001)	88.3	2.9706
Thiobarbituric acid reactive substances	-6.5117	<0.0001	-8.1340	<0.0001	7	20.16 (0.0052)	65.3	7.1392
Nitric oxide	-2.7775	<0.0001	-3.2055	<0.0001	5	18.44 (0.0024)	72.9	1.3691
Glutathione	4.8807	<0.0001	6.1199	<0.0001	7	34.29 (<0.0001)	79.6	4.4883
Myeloperoxidase	-2.8387	<0.0001	-6.7254	<0.0001	8	121.61 (<0.0001)	93.4	16.3405
Malondialdehyde	-2.9429	<0.0001	-3.1444	<0.0001	7	15.36 (0.0316)	54.4	0.6094
Histological score	-3.4330	<0.0001	-4.0125	<0.0001	9	26.83 (0.0015)	67.1	1.6243
Macroscopic inflammatory score	-2.7388	<0.0001	-4.6280	<0.0001	8	51.89 (<0.0001)	84.6	6.1381

¹Q = χ^2 statistic; I² = Higgins statistic; τ^2 = true heterogeneity.

and Karin, 1997). Finally, IL-10 is known as a cytokine inhibitor; it regulates inflammatory responses by inhibiting the secretion of IFN- γ and IL-2. Levels of IL-10 are decreased in people with IBD, and clinical manifestations and endoscopic improvements have been observed with IL-10 supplementation in people with IBD (Tau and Rothman, 1999; Fedorak et al., 2000; Schreiber et al., 2000).

As the secretion of IL-10 and TGF- β increases, the symptoms of IBD decrease. In contrast, the secretion of IFN- γ , TNF- α , IL-17, and IL-6 induces symptoms of IBD (Jeon et al., 2016). According to the results of the current meta-analysis, IL-10 and TGF- β showed a positive effect size, and IFN- γ , TNF- α , IL-17, and IL-6 showed negative effect sizes, with significant differences ($P < 0.0001$). However, the effect size of TGF- β was not significant ($P > 0.05$). These results suggest that the proinflammatory cytokines may be inhibited by probiotic supplementation. As well, these results were consistent with the findings of Lee et al. (2008), who reported that probiotic supplementation could improve IBD by suppressing the biosynthesis of proinflammatory cytokines.

Pawar et al. (2011) and Nieto et al. (2000) showed that reactive oxygen species (ROS) also mediate inflammation along with proinflammatory cytokines, and ROS can contribute to the inflammatory chain reaction regulating the immune system that is associated with IBD. Injury mediated by oxidants plays a leading part in the pathophysiology of IBD (Byrne and Viney, 2006; Neuman, 2007; Oz and Ebersole, 2008). Reduced glutathione and antioxidant activity leads to disease progression. Moreover, ROS mediators enhance the production of proinflammatory biomolecules such as IL-1 β , IL-6, and TNF- α . These inflammatory markers are increased in people with IBD and in IBD animal models (Zhong et al., 2006). An increase in proinflammatory biomolecules correlates with the downregulation of antioxidant activity; thus, activating ROS results in intestinal inflammation. An increase in antioxidants attenuates the level of TNF- α and reduces inflammation in IBD (Oz et al., 2005, 2007). Consequently, oxidative and nitrosative stresses are strongly associated with IBD progression and healing of gut injury (Koppikar et al., 2014).

Nitric oxide is vigorously reactive, and its molecules are always present in the biological system (Petersson et al., 2007). It is related to inflammation and other pathological states. In addition, malondialdehyde, a volatile compound involved in lipid peroxidation, is assayed for thiobarbituric acid using the thiobarbituric acid reactive substances (TBARS) test (Koppikar et al., 2014). In the present study, TBARS, nitric oxide,

and malondialdehyde showed negative effect sizes ($P < 0.0001$), indicating that supplementation with probiotics effectively protected the gut mucosa from oxidative stress. Furthermore, antioxidants such as superoxide dismutase and reduced glutathione were significantly increased after probiotic supplementation ($P < 0.0001$). This may be due to antioxidants derived from yogurt fermented with probiotics. Kudoh et al. (2001) isolated a DPPH (2,2-diphenyl-1-picrylhydrazyl) radical-scavenging peptide derived from κ -casein in yogurt fermented with *Lactobacillus bulgaricus*. Sah et al. (2014) observed antioxidant activity in yogurt fermented with various strains of probiotics.

In the present study, we calculated Q statistics and I^2 values to evaluate the heterogeneity of the effect sizes. High Q statistics and significantly low P-values denote statistically high heterogeneity among studies. Moreover, when the Q statistic is greater than the degrees of freedom, the likelihood of study heterogeneity is statistically significant, but it depends on the number of studies (Fleiss, 1986). In the current study, the highest Q statistics were detected for colon length, which was significant ($P < 0.0001$) and greater than the degrees of freedom. To resolve the disadvantage of the Q statistics, we used I^2 values to analyze heterogeneity (Higgins et al., 2003). For most factors, I^2 values were above 70% in the included studies, indicating that most factors had significant levels of heterogeneity. In particular, the I^2 and τ^2 values for myeloperoxidase were the highest, at 93.4% and 16.3405, respectively, and those for IL-1 β were the lowest, at 0% and 0, respectively.

Moderator Analysis

The results of the analysis revealed significant heterogeneity among the analyzed studies, so we performed an additional moderator analysis. We conducted meta-ANOVA on factors with sufficient sample sizes, including colon length, TNF- α , IL-6, IL-10, IFN- γ , and disease activity index. As shown in Table 3, supplementation with *Lactobacillus paracasei* showed the greatest effect size in terms of colon length. After unification of the variance between subgroups (τ^2), we tested subgroup differences. The Q statistic between groups (Q_b) was 37.66 (df = 12; $P = 0.0002$), and the effect size between groups was assumed to be significantly different. We then used meta-regression to analyze the effect size between probiotics groups (Table 4) and found that the effects of *L. paracasei* ($P < 0.0001$), *L. plantarum* ($P = 0.0046$), and *Lactobacillus rhamnosus* ($P = 0.009$) were significant. Among them, *L. paracasei* was the most effective probiotic in preventing the shrinkage of colon length caused by IBD. For TNF- α , a mixture of

Table 3. Meta-ANOVA of the effect of probiotic strains on inflammatory bowel disease¹

Variable and probiotic ²	k	Fixed-effects model			Random-effects model			Q	τ^2	Q _b	df	P-value
		SMD	95% CI		SMD	95% CI						
			Lower	Upper		Lower	Upper					
Colon length												
<i>Bifidobacterium longum</i>	3	0.7626	-0.0110	1.5361	1.1033	-0.4499	2.6565	6.64	1.2891	37.64	12	0.0002
<i>Escherichia coli</i>	2	0.3892	-0.2379	1.0162	0.3892	-1.3047	2.0831	0.00	1.2891	0.0		
<i>Enterococcus faecalis</i>	2	2.5713	1.4846	3.6579	2.5740	0.6614	4.4867	0.03	1.2891	0.0		
<i>Faecalibacterium prausnitzii</i>	2	1.6486	0.7789	2.5182	1.7937	-0.0112	3.5986	4.23	1.2891	76.3		
<i>Lactobacillus brevis</i>	3	2.1812	1.3535	3.0089	2.5549	0.9587	4.1511	3.81	1.2891	47.6		
<i>Lactobacillus bulgaricus</i>	2	2.5863	1.7005	3.4720	2.5888	0.7829	4.3947	0.04	1.2891	0.0		
<i>Lactobacillus fermentum</i>	5	1.5641	1.0805	2.0477	1.7769	0.6534	2.9004	7.36	1.2891	45.6		
<i>Lactobacillus lactis</i>	2	2.6525	1.2452	4.0597	3.1437	0.9396	5.3477	4.96	1.2891	79.8		
<i>Lactobacillus paracasei</i>	3	6.0072	4.6921	7.3224	6.0072	4.6921	7.3224	1.95	1.2891	0.0		
<i>Lactobacillus plantarum</i>	8	2.9067	2.3744	3.4389	3.7682	2.7654	4.7709	48.19	1.2891	85.5		
<i>Lactobacillus rhamnosus</i>	2	3.1021	1.8639	4.3403	3.2989	1.2871	5.3107	6.40	1.2891	84.4		
Mixed culture	3	1.9759	0.9566	2.9952	2.3171	0.5759	4.0582	3.10	1.2891	35.4		
<i>Streptococcus thermophilus</i>	2	0.3348	-0.7378	1.4074	0.4250	-1.4846	2.3346	2.31	1.2891	56.7		
Tumor necrosis factor α												
<i>Lactobacillus rhamnosus</i>	1	-5.1538	-7.1399	-3.1676	-5.1538	-8.6395	-1.6680	0.00	—	46.40	9	<0.0001
<i>Lactobacillus paracasei</i>	3	-4.0718	-5.0502	-3.0934	-4.3361	-6.2816	-2.3907	4.05	2.1361	50.6		
<i>Lactobacillus lactis</i>	1	-4.3579	-6.7675	-1.9483	-4.3579	-8.1012	-0.6147	0.00	—	—		
<i>Bifidobacterium longum</i>	2	-1.3252	2.4963	-0.1542	-2.0868	-4.5530	0.3794	5.74	2.1361	82.6		
<i>Lactobacillus casei</i>	2	-1.9033	-3.0276	-0.7791	-3.0062	-5.5367	-0.4757	7.89	2.1361	87.3		
LC + BB	1	-17.2740	-25.7821	-8.7659	-17.2740	-26.2514	-8.2966	0.00	—	—		
LC + SB	1	-25.1630	-37.4987	-12.8273	-25.1630	-37.8269	-12.4991	0.00	—	—		
<i>Lactobacillus plantarum</i>	1	-3.6713	-5.4339	-1.9086	-3.6713	-7.0347	-0.3078	0.00	—	—		
<i>Lactobacillus brevis</i>	2	2.1483	1.0289	3.2677	2.3275	-0.0087	4.6637	1.62	2.1361	38.2		
<i>Lactobacillus reuteri</i>	2	-3.7549	-4.8750	-2.6348	-3.8205	-6.1386	-1.5024	1.33	2.1361	24.9		
IL-6												
<i>Lactobacillus rhamnosus</i>	1	-2.7116	-3.9952	-1.4280	-2.7116	-5.5456	0.1225	0.00	—	9.75	7	0.2033
<i>Lactobacillus paracasei</i>	3	-2.6961	-3.4577	-1.9344	-2.9541	-4.6168	-1.2914	5.68	1.6620	64.8		
<i>Lactobacillus lactis</i>	2	-0.1858	-1.4670	1.0953	-0.3576	-2.5579	1.8426	23.18	1.6620	95.7		
Mixed culture	1	-2.2430	-3.5703	-0.9158	-2.2430	-5.0972	0.6111	0.00	—	—		
<i>Lactobacillus plantarum</i>	2	-1.7056	-2.5461	-0.8652	-2.2123	-4.2407	-0.1839	5.98	1.6620	83.3		
<i>Lactobacillus brevis</i>	3	-1.6126	-2.3372	-0.8881	-1.7908	-3.4481	-0.1336	1.80	1.6620	0.0		
<i>Lactobacillus casei</i>	2	-0.3106	-0.8850	0.2638	-0.3697	-2.2498	1.5104	1.17	1.6620	14.8		
<i>Lactobacillus reuteri</i>	2	-3.8036	-4.8709	-2.7362	-3.8703	-5.9554	-1.7852	1.44	1.6620	30.3		
IL-10												
<i>Lactobacillus rhamnosus</i>	1	3.3350	1.8864	4.7837	3.3350	0.5544	6.1157	0.00	—	22.85	6	0.0008
<i>Lactobacillus paracasei</i>	3	3.7770	2.8353	4.7188	4.1574	2.4523	5.8625	6.75	1.4664	70.4		
<i>Lactobacillus lactis</i>	2	-0.6199	-1.4631	0.2233	-0.8237	-2.7160	1.0687	3.82	1.4664	73.8		
<i>Bifidobacterium longum</i>	2	-0.5552	-1.5357	0.4253	-0.7298	-2.6848	1.2251	3.64	1.4664	72.5		
Mixed culture	1	2.4115	0.7786	4.0444	2.4115	-0.4694	5.2924	0.00	—	—		
<i>Lactobacillus casei</i>	2	1.6801	0.9732	2.3870	2.1328	0.2709	3.9946	6.52	1.4664	84.7		
<i>Lactobacillus brevis</i>	2	2.1483	1.0289	3.2677	2.3089	0.2690	4.3488	1.62	1.4664	38.2		
IFN- γ												
<i>Lactobacillus rhamnosus</i>	1	-3.3191	-4.7634	-1.8749	-3.3191	-4.8254	-1.8128	0.00	—	59.98	4	<0.0001
<i>Lactobacillus paracasei</i>	3	-2.5757	-3.3055	-1.8459	-2.5885	-3.3606	-1.8163	2.18	0.0476	8.4		
<i>Lactobacillus lactis</i>	1	-3.2693	-5.2257	-1.3129	-3.2693	-5.2720	-1.2667	0.00	—	—		
<i>Bifidobacterium longum</i>	2	-0.6435	-1.6221	0.3352	-0.6619	-1.6887	0.3649	3.13	0.0476	68.1		
<i>Lactobacillus fermentum</i>	4	0.2163	-0.2265	0.6591	0.2168	-0.2749	0.7086	1.70	0.0476	0.0		

Continued

Table 3 (Continued). Meta-ANOVA of the effect of probiotic strains on inflammatory bowel disease¹

Variable and probiotic ²	k	Fixed-effects model			Random-effects model					P-value			
		SMD	95% CI		SMD	95% CI		Q	τ^2		I^2	Q _b	df
			Lower	Upper		Lower	Upper						
Disease activity index													
<i>Bifidobacterium longum</i>	2	-2.3496	-3.7993	-0.9000	-3.4870	-6.8232	-0.1507	5.29	3.9186	81.1	21.87	6	0.0013
<i>Lactobacillus lactis</i>	1	-6.9601	-10.1767	-3.7435	-6.9601	-11.9999	-1.9202	0.00	—	—	—	—	—
<i>Lactobacillus bulgaricus</i>	2	-3.6435	-4.7307	-2.5562	-3.6656	-6.6183	-0.7129	0.22	3.9186	0.0	—	—	—
<i>Lactobacillus plantarum</i>	5	-2.6136	-3.2782	-1.9490	-3.6745	-5.5672	-1.7818	38.87	3.9186	89.7	—	—	—
<i>Lactobacillus fermentum</i>	1	-32.8623	-46.0135	-19.7110	-32.8623	-46.5739	-19.1507	0.00	—	—	—	—	—
LH + EF	1	-6.3820	-8.7567	-4.0072	-6.3820	-10.9303	-1.8330	0.00	—	—	—	—	—
<i>Lactobacillus reuteri</i>	3	-6.3428	-7.5332	-5.1525	-6.7956	-9.4988	-4.0923	1.84	3.9186	0.0	—	—	—

¹ I^2 = Higgins statistic; k = number of treatments; Q = χ^2 statistic; Q_b = χ^2 statistic between groups; SMD = standardized mean difference; τ^2 = true heterogeneity.

² LC + BB = mixed culture of *Lactobacillus casei* and *Bifidobacterium bifidum*; LC + SB = mixed culture of *Lactobacillus casei* and *Streptococcus boulardii*; LH + EF = mixed culture of *Lactobacillus helveticus* and *Enterococcus faecalis*; mixed culture = mixed culture of *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus*.

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L. bulgaricus and *S. boulardii* showed the greatest effect size, and after the unification of τ^2 , Q_b was 46.40. In meta-regression tests, the mixture of *L. bulgaricus* and *S. boulardii* and a mixture of *L. casei* and *Bifidobacterium bifidum* showed significant differences ($P = 0.0005$ and 0.0014 , respectively). For IFN- γ , *L. paracasei* and *L. rhamnosus* showed the highest effect size, and the Q_b was 53.61 ($df = 4$; $P < 0.0001$), indicating that the effect size between the groups had a significant difference. Meta-regression testing also indicated significant differences ($P = 0.0033$ and 0.0043 , respectively). Also according to the meta-regression tests, the R^2 values were 70.88 and 97.54, respectively, suggesting that the regression models had high explanatory power.

Traditionally, sulfasalazine, 5-aminosalicylic acid, corticosteroids, and anti-TNF drugs have been used to treat IBD (Choi et al., 2017). These treatments improve IBD symptoms resulting from the reduction of prostaglandin; the attenuation of T-lymphocytes; the synthesis of IL-1, IL-2, IL-8, and NF- κ B; and the inhibition of protein secretion related to inflammation, such as collagenase, elastase, and plasminogen activators (Shanahan et al., 1990; Cominelli et al., 1992; Bantel et al., 2000; Choi and Choi, 2005). However, these treatments have been associated with side effects such as headache, nausea, fever, interstitial nephritis, anemia, and reversible male sterility (Levi et al., 1979; Kornbluth and Sachar, 2010).

The administration of probiotics is related to the expression of anti-inflammatory cytokines, which induce TGF- β expression and attenuate the symptoms of IBD (Torii et al., 2007). Treatment of IBD with probiotics has been reported to demonstrate positive effects. Schultz et al. (2002) reported that onset of IBD could be prevented and established colitis reduced in IL-10-deficient mice by treatment with *L. plantarum* 299v. Mao et al. (1996) reported that the administration of *L. plantarum* 299v could delay the onset and reduce the severity of colitis. *Lactobacillus reuteri* (R2LC) abated colitis in mice with IL-10 deficiency (Madsen et al., 1999). Gupta et al. (2000) showed that the administration of *L. rhamnosus* GG to people with IBD for 6 mo led to a decrease in clinical disease activity. Kruis et al. (1997) reported that the probiotics-treated group in their study showed a similar relapse rate to the mesalazine group. Guslandi et al. (2000) found that combined treatment with *S. boulardii* and 5-aminosalicylic acid reduced the relapse rate from 38 to 6% after 6 mo of treatment. Malchow (1997) reported that the relapse rate was reduced by combination treatment with prednisolone and probiotics. The administration of probiotics could be effective in improving the symptoms of IBD and could be a promising alternative for IBD treatment.

Publication Bias

We examined publication bias with respect to the factors we investigated, including colon length, TNF- α , IL-6, IL-10, IFN- γ , and disease activity index, using funnel plots (Figure 1) and Egger's linear regression

test (Table 5). As shown in Figure 1, we found publication bias for all factors. Although we found some asymmetry in the funnel plot for IL-10 (Figure 1F), we did not detect significance in the Egger's linear regression test. However, we found significant differences in the other groups ($P < 0.05$), indicating that the

Table 4. Meta-regression analysis of the effect of probiotic strains on inflammatory bowel disease¹

Variable and probiotic ¹	Estimate	SE	P-value	95% CI		R ² (%)
				Lower	Upper	
Intercept	1.1033	0.7925	0.1638	-0.4499	2.6565	35.71
Colon length						
<i>Escherichia coli</i>	-0.7142	1.1726	0.5425	-3.0123	1.5840	
<i>Enterococcus faecalis</i>	1.4707	1.2571	0.2420	-0.9932	3.9346	
<i>Faecalibacterium prausnitzii</i>	0.6904	1.2149	0.5699	-1.6908	3.0715	
<i>Lactobacillus brevis</i>	1.4515	1.1347	0.2007	-0.7721	3.6758	
<i>Lactobacillus bulgaricus</i>	1.4855	1.2153	0.2216	-0.8965	3.8674	
<i>Lactobacillus fermentum</i>	0.6736	0.9781	0.4910	-1.2434	2.5905	
<i>Lactobacillus lactis</i>	2.0403	1.3757	0.1380	-0.6560	4.7367	
<i>Lactobacillus paracasei</i>	5.0258	1.2342	<0.0001	2.6068	7.4448	
<i>Lactobacillus plantarum</i>	2.6648	0.9433	0.0047	0.8161	4.5136	
<i>Lactobacillus rhamnosus</i>	2.1956	1.2968	0.0904	-0.3460	4.7372	
Mixed culture	1.2137	1.1905	0.3079	-1.1195	3.5470	
<i>Streptococcus thermophilus</i>	-0.6784	1.2559	0.5891	-3.1399	1.7831	
Tumor necrosis factor α	-2.0868	1.2583	0.0972	-4.5530	0.3794	70.88
<i>Lactobacillus brevis</i>	4.4143	1.7332	0.0109	1.0172	7.8113	
<i>Lactobacillus casei</i>	-0.9194	1.8028	0.6101	-4.4529	2.6140	
<i>Lactobacillus lactis</i>	-2.2711	2.2871	0.3207	-6.7538	2.2115	
<i>Lactobacillus paracasei</i>	-2.2493	1.6027	0.1605	-5.3905	0.8918	
<i>Lactobacillus plantarum</i>	-1.5845	2.1279	0.4565	-5.7552	2.5862	
<i>Lactobacillus reuteri</i>	-1.7337	1.7269	0.3154	-5.1183	1.6509	
<i>Lactobacillus rhamnosus</i>	-3.0670	2.1786	0.1592	-7.3369	1.2030	
LC + BB	-15.1872	4.7501	0.0014	-24.4972	-5.8772	
LC + SB	-23.0762	6.5827	0.0005	-35.9780	-10.1744	
IL-6	-1.7908	0.8455	0.0342	-3.4481	-0.1336	18.05
<i>Lactobacillus casei</i>	1.4212	1.2787	0.2664	-1.0851	3.9274	
<i>Lactobacillus lactis</i>	1.4332	1.4054	0.3078	-1.3213	4.1877	
<i>Lactobacillus paracasei</i>	-1.1632	1.1977	0.3314	-3.5108	1.1843	
<i>Lactobacillus plantarum</i>	-0.4214	1.3364	0.7525	-3.0407	2.1979	
<i>Lactobacillus reuteri</i>	-2.0794	1.3589	0.1260	-4.7429	0.5840	
<i>Lactobacillus rhamnosus</i>	-0.9207	1.6751	0.5825	-4.2038	2.3623	
Mixed culture	-0.4522	1.6839	0.7883	-3.7526	2.8482	
IL-10	-0.7298	0.9975	0.4644	-2.6848	1.2251	55.92
<i>Lactobacillus brevis</i>	3.0388	1.4416	0.0350	0.2133	5.8642	
<i>Lactobacillus casei</i>	2.8626	1.3774	0.0377	0.1629	5.5623	
<i>Lactobacillus lactis</i>	-0.0939	1.3882	0.9461	-2.8147	2.6270	
<i>Lactobacillus paracasei</i>	4.8872	1.3235	0.0002	2.2931	7.4813	
<i>Lactobacillus rhamnosus</i>	4.0649	1.7343	0.0191	0.6658	7.4640	
Mixed culture	3.1414	1.7765	0.0770	-0.3406	6.6233	
IFN- γ	-0.6619	0.5239	0.2064	-1.6887	0.3649	97.54
<i>Lactobacillus fermentum</i>	0.8788	0.5809	0.1303	-0.2597	2.0172	
<i>Lactobacillus lactis</i>	-2.6074	1.1483	0.0232	-4.8579	-0.3568	
<i>Lactobacillus paracasei</i>	-1.9265	0.6555	0.0033	-3.2112	-0.6418	
<i>Lactobacillus rhamnosus</i>	-2.6572	0.9301	0.0043	-4.4801	-0.8342	
Disease activity index	-3.4870	1.7022	0.0405	-6.8232	-0.1507	33.57
<i>Lactobacillus bulgaricus</i>	-0.1787	2.2731	0.9374	-4.6338	4.2765	
<i>Lactobacillus fermentum</i>	-29.3753	7.1999	<0.0001	-43.4870	-15.2637	
<i>Lactobacillus lactis</i>	-3.4731	3.0837	0.2601	-9.5171	2.5709	
<i>Lactobacillus plantarum</i>	-0.1875	1.9570	0.9237	-4.0232	3.6482	
<i>Lactobacillus reuteri</i>	-3.3086	2.1908	0.1310	-7.6025	0.9853	
LH + EF	-2.8950	2.8782	0.3145	-8.5362	2.2762	

¹LC + BB = mixed culture of *Lactobacillus casei* and *Bifidobacterium bifidum*; LC + SB = mixed culture of *Lactobacillus casei* and *Streptococcus boulardii*; LH + EF = mixed culture of *Lactobacillus helveticus* and *Enterococcus faecalis*; mixed culture = mixed culture of *Lactobacillus acidophilus*, *Bifidobacterium lactis*, *Streptococcus thermophilus*, and *Lactobacillus bulgaricus*.

Table 5. Egger's linear regression test for publication bias

Item	Bias	SE	Slope	T-value	df	P-value
Colon length	5.756694	0.6122046	-1.947667	9.4032	38	<0.0001
Tumor necrosis factor α	-4.757640	1.6531910	1.680228	-2.8779	14	0.0122
IL-6	-5.198753	1.8272670	1.485141	-2.8451	14	0.1297
IL-10	4.395828	2.8241380	-1.467641	1.5565	11	0.1479
IFN- γ	-8.328726	1.8856970	3.832194	-4.4168	9	0.0017
Disease activity index	-5.528796	1.0101130	1.049389	-5.4734	13	<0.0001

Table 6. Trimmed effect size of probiotics on inflammatory bowel disease in a murine model

Item	df	Fixed-effects model		Random-effects model		Heterogeneity ¹		
		Effect size	P-value	Effect size	P-value	Q (P-value)	I ² (%)	τ^2
Colon length	53	1.3283	<0.0001	1.4327	<0.0001	387.83 (<0.0001)	86.3	3.6251
Tumor necrosis factor α	20	-1.8701	<0.0001	-2.0869	0.0058	202.32 (<0.0001)	90.1	9.3193
IL-6	20	-1.1730	<0.0001	-1.2636	0.0018	150.11 (<0.0001)	86.8	2.8866
IL-10	14	1.1641	<0.0001	1.2697	0.0248	126.64 (<0.0001)	89.0	4.1485
IFN- γ	13	-0.3717	0.0211	-0.5586	0.2514	112.92 (<0.0001)	88.5	2.8561
Disease activity index	21	-2.7516	<0.0001	-3.0575	<0.0001	196.17 (<0.0001)	89.4	8.8171

¹Q = χ^2 statistic; I² = Higgins statistic; τ^2 = true heterogeneity.

Figure 1. Funnel plots to evaluate publication bias: (A) colon length; (B) tumor necrosis factor α ; (C) IL-6; (D) IL-10; (E) IFN- γ ; and (F) disease activity index.

relationship between effect size and standard error is statistically significant, and it can statistically prove the asymmetry of the funnel plots (Egger et al., 1997). Thus, we used the trim-and-fill procedure to arrange asymmetry for all factors, and the resulting trimmed effect sizes are listed in Table 6. Most of the effects were significant ($P < 0.05$), except for IFN- γ . Colon length and IL-10 showed a positive effect size, and the other factors showed negative effect sizes.

CONCLUSIONS

This study showed the effect of probiotic supplementation on IBD, synthesizing the results by meta-analysis. We found that probiotics can help improve the symptoms of IBD. The present study had some limitations, one being the lack of meta-analysis results from animal experiments. However, this meta-analysis will be useful for future studies on probiotics for people with IBD.

ACKNOWLEDGMENTS

This study was supported by the Cooperation Research Program for Agriculture Science and Technology Development (PJ01197802), Rural Development Administration, Republic of Korea.

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