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Systematic Review

The Effect of Probiotics on Intestinal Tight Junction Protein Expression in Animal Models: A Meta-Analysis

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Abstract: This study investigates the effect of probiotics supplementation on tight junction protein (TJP) expression in animal models by meta-analysis. We estimated the effect of probiotics administration in an animal inflammatory bowel disease model based on 47 collected articles from the databases, including Sciencedirect, Pubmed, Scopus, and Google Scholar. The effect size was analyzed with the standardized mean difference, and the heterogeneity of the effect sizes was assessed using Cochran's Q test. To explain the heterogeneity, moderate analyses, such as meta-ANOVA and meta-regression, were performed using the mixed effects model. Finally, publication bias was assessed using Egger's linear regression test. Among the evaluated items, zonula occluden (ZO)-1 showed the highest Q statistics value, and the effect sizes of all items were positive with high significance ($p < 0.0001$). The I^2 value of all items reflected high heterogeneity (in excess of 80%). From the results of the meta-ANOVA, the factors of the heterogeneity found in the probiotics strains were investigated. *Lactobacillus reuteri* was identified as having the greatest effect on claudin and ZO-1 expression. The publication bias was detected by the Egger's linear regression test, though it revealed that the occludin and ZO-1 had larger sample sizes than the claudin. In sum, this meta-analysis reveals that probiotics are effective at improving TJP expression in a gut environment of inflammatory bowel disease (IBD)-induced animal model. Our findings will interest IBD patients, as they suggest an area warranting future study.

Keywords: meta-analysis; probiotics; inflammatory bowel disease; tight junction protein

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1. Introduction

Probiotics are live microorganisms that, when properly administered, provide a host with various health benefits [1]. Probiotics, including various lactic acid bacteria and *bifidobacterium*, are mainly colonized in the gut of a host [2]. Some probiotics or their commercial mixtures, such as *L. rhamnosus*, *L. plantarum*, *L. acidophilus*, *E. faecium*, and VSL#3 (mixture of *lactobacilli* and *bifidobacterium*), have been shown to improve intestinal permeability and clinical scores in inflammatory bowel disease (IBD) patients [3–6].

The intestine acts not only as a barrier, but also enables nutrient absorption, and prevents antigens and pathogens from entering mucosal tissue and potentially causing disease. There are 10^{14} microorganisms living in the intestine [7] which affect intestinal epithelial cells and intestinal barrier function. An essential component of the intestinal barrier is the intercellular junctional complex, and the tight junction is a multifunctional complex that seals between adjacent epithelial cells [8]. Intestinal mucosal epithelial cells consist of a single layer interconnected by tight junctions (TJ) [9,10]. The TJ is a multiprotein complex that connects two or more cells. The TJ regulates the transportation of substances,

joins intestinal epithelial cells, and affects the gut permeation of external substances within the cell complex [11]. The TJ is comprised of tight junction proteins (TJPs), such as occludin, claudin, and zonula occludens-1 (ZO-1) [12,13]. The TJPs are unique proteins that form the outer wall of the intestine [11]. The occludin was the first integral membrane TJ protein, and its function is not yet fully understood. However, numerous animal and cell cultures studies indicate a crucial role in the TJ structure and permeability in the intestinal epithelia [14]. The claudin does not have any sequence similarity to occludin. Many studies have verified that claudins are one of the critical elements and the backbone of the TJ [15]. In addition, the ZO were the first identified TJ-specific proteins, consisting of three types—ZO-1, -2, and -3 [16]—with an essential role in TJ assembly regulation [17].

The destruction of the TJP causes an increase in antigen permeation and bacterial influx [18]. Therefore, it can be assumed that there may be some correlation between the expression of TJP and intestinal health. In a previous study [3], we discovered that probiotics improve several indicators related to IBD by inhibiting the expression of proinflammatory cytokines, thereby preventing the deterioration of gut health. In addition, we identified probiotics that improve specific indicators in IBD. Moreover, according to Jeon et al. [19], reduced TJP expression and weakened tight junctions (TJ) in the gut increase antigen permeability and proinflammatory cytokine expression. Therefore, we investigated the relationship between probiotics and TJP expression in IBD-induced animal models by meta-analysis in this study.

2. Materials and Methods

2.1. Data Collection

Research articles were collected using keywords such as 'ZO-1,' 'claudin,' 'occludin,' 'probiotics,' and 'animal,' or combinations thereof from various online databases, including Google Scholar (https://scholar.google.com/ (accessed on 8 August 2021)), Pubmed (https://pubmed.ncbi.nlm.nih.gov/ (accessed on 8 August 2021)), Science Direct (https://www.sciencedirect.com/ (accessed on 8 August 2021)), and Scopus (https://www.scopus.com/ (accessed on 8 August 2021)), by 5 researchers (Ahn, Cho, Chae, Jeon, and Park). Articles written in English were used as the study subjects regardless of the publication year.

2.2. Inclusion and Exclusion Criteria

A study was judged eligible when the following criteria were met regardless of the type of animal: (1) TJP expression in the animal study, (2) the determination of TJP expression by the administration of isolated probiotics (single or multiple strain) or commercial probiotic formulations, (3) TJP expression compared with and without probiotics administration. On the other hand, the studies conducted with cell culture only, TJP expression not related with intestinal tracts, and human clinical studies were excluded. The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline 2020 [20] was used to review the research articles. The articles were screened by reading their titles, abstracts, and full texts by 2 researchers (Ahn and Park) independently. When disagreements occurred, the researchers solved the issues through discussion until they reached a consensus.

2.3. Quality Assessment Methodology

The bias risk of the collected studies was assessed by two reviewers (Ahn and Park) using QualSyst [21], consisting of the 14 questionnaires for quantitative assessment and 10 questionnaires for the qualitative evaluation. The question sets included the following criteria: (1) description of the research objective, (2) clear and adequate study design, (3) sufficient description of subject and intervention, (4) random subject allocation into group; (5) result measurement, (6) sufficiently detailed report of outcomes. To complete the assessment, the reviewers scored each question, relying based on their knowledge. The questionnaires were evaluated as "yes," "partial," "no," and "N/A," implying 2, 1, 0 points, and not applicable, respectively. To present the final score, the average normalized score

from each reviewer was used. In this study, we judged the studies with a final score of over 50% as high quality [22].

2.4. Data Analysis

Changes in TJP expression were calculated with standardized mean difference (SMD) analysis [3]. The effect size analysis, regarding fixed or random effects models, was employed to compute a summary effect, as there were many different factors, such as the experimental period, sample size, animal strain, and type or dose of probiotics, used in each study. Cochran's Q test was performed to assess the statistical heterogeneity of the effect size, and the heterogeneity was discerned by the I^2 value. Subsequently, meta-ANOVA and meta-regression tests were conducted to investigate the factors that influenced the heterogeneity of the effect size. Finally, publication bias was analyzed to confirm the validity of the study results and to assess the risk of bias of individual studies. The funnel plot was drawn to visualize the bias, and Egger's linear test was performed to more accurately evaluate the publication bias with numerical data. Statistical analysis was conducted using R software (version 4.1.0, R Development Core Team, 2021, http://www.r-project.org (accessed on 8 August 2021)) with the meta, tidyverse, and metafor packages, and all hypothesis verification was performed within the 5% significance level.

3. Results

3.1. Data Set

Figure 1 shows a PRISMA diagram [20] of the procedure of data collection for the meta-analysis. As a result of searching articles, 1487 articles were detected in the various online databases, and those articles were screened and excluded the duplicated and inappropriate studies. Finally, 47 research articles with data expressed as mean and standard deviation or –error were collected and considered in the meta-analysis. The review articles, articles not related to TJP expression in intestinal tracts, and book chapters were excluded. Table 1 shows the properties of the collected research articles. The 47 included articles were published between 2007 and 2021. The animals used in the studies were mice, rats, rabbits, chicks, and turbots. Among these, most of the collected research (32 articles) was performed using mice, specifically strains C57BL/6, Balb/c, Swiss Albino, and ICR. The dextran sodium sulfate (DSS) was the most commonly identified factor in intestinal epithelial cell loss in the research. Other factors were 2,4,6-trinitrobenzene sulfonic acid (TNBS), dinitrobenzene sulfonic acid (DNBS), acetic acid, ovalbumin, water avoidance stress (WAS), adenine, homocysteine, pepsin-trypsin-digested gliadin (PTG), sodium fluoride, alcohol, aging, and microbes, including *S. typhimurium*, *E. coli* and *A. hydrophila*.

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

Authors	Animal (Strain)	*n*	Induced Chemical [1]	Treated Time (d)	Probiotics [2]	Administration Form	Analytical Items [3]	TJP Evaluation [4]
Chen et al. [23]	Mouse (C57Bl/6)	10	DSS	12	Mixed culture	Gavage	Occludin, ZO-1	Western blot
Miyauchi et al. [24]	Mouse (Balb/c)	3	DSS	3	*L. rhamnosus* OLL2838	Gavage	ZO-1	Western blot
Hagihara et al. [25]	Mouse (ICR)	5	DSS	42	*C. butyricum* MIYAIRI588	Gavage	Claudin, Occludin, ZO-1	Western blot
Tian et al. [26]	Mouse (C57Bl/6)	10	DSS	42	*B. breve*	Gavage	Claudin, Occludin, ZO-1	Western blot
Jin et al. [27]	Rat (Sprague-Dawley)	8	DSS	21	*L. rhamnosus* GG, *L. plantarum* Zhang LL	Gavage	Claudin, Occludin, ZO-1	Western blot
Chen et al. [28]	Mouse (C57Bl/6)	6	Alcohol	10	*L. rhamnosus* GG	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Xin et al. [29]	Mouse (ICR)	36	Sodium fluoride	28	*L. johnsonii* BS15	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Bao et al. [30]	Mouse (C57BL/6J)	10	*E coli* O157:H7	14	*B. amyloliquefaciens* TL106	Gavage	Claudin, Occludin, ZO-1	Western blot

Table 1. *Cont.*

Authors	Animal (Strain)	*n*	Induced Chemical [1]	Treated Time (d)	Probiotics [2]	Administration Form	Analytical Items [3]	TJP Evaluation [4]
Orlando et al. [31]	Rat (Wistar)	10	PTG	10	*L. rhamnosus* GG	Gavage	Claudin, Occludin, ZO-1	Western blot
Jeong et al. [32]	Rat (Fisher 344)	6	Aging	56	Mixed culture (IRT5)	Gavage	Claudin, Occludin, ZO-1	ELISA
Sheng et al. [33]	Mouse (C57BL/6J)	6	DSS	21	*B. infantis* ATCC 15697	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Dong et al. [34]	Crucian carp (*Carassius carassius*)	80	*A. hydrophila* NJ-35	7	*L. lactis* 16-7	Diet	Occludin, ZO-1	qRT-PCR
Seo et al. [35]	Mouse (ICR)	8	DSS	12	*L. sakei* K040706	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Rokana et al. [36]	Mouse (Swiss Albino)	8	*S. Typhimurium* LT2	7	*L. plantarum* MTCC 5690, *S. thermophilus*,	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Liang et al. [37]	Rat (Sprague-Dawley)	10	Aadenine, Homocysteine	30	Mixed culture (VSL#3)	Gavage	Claudin, Occludin, ZO-1	Western blot
Mennigen et al. [38]	Mouse (Balb/c)	6	DSS	7	Mixed culture (VSL#3)	Gavage	Claudin, Occludin, ZO-1	Western blot
Wang et al. [39]	Mouse (C57BL/6J)	8	DSS	14	*L. plantarum* ZS2058, *L. plantarum* ST-III	Gavage	ZO-1	qRT-PCR
Zhang et al. [40]	Mouse (C57BL/6J)	5	DSS	21	*B. subtilis* JNFE0126	Gavage	ZO-1	Western blot
Feng et al. [41]	Mouse (C57BL/6)	8	DSS	9	*Synechococcus* 7002	Gavage	Occludin, ZO-1	Western blot
Oh et al. [42]	Mouse (C57BL/6)	10	DSS	70	*L. gasseri* 505	Gavage	Occludin, ZO-1	Western blot
Li et al. [43]	Mouse (Kunming)	9	*E. coli* QBQ009	7	*L. rhamnosus* SHA113	Gavage	Occludin, ZO-1	Western blot
Wang et al. [44]	Mouse (C57BL/6J)	10	DSS	7	*B. fragilis* NCTC9343, *B. fragilis* FSHCM14E1, *7B. fragilis* FJ10SWX11BF	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Dai et al. [45]	Rat (Wistar)	10	Acetic acid	7	Mixed culture (VSL#3)	Gavage	Occludin, ZO-1	Western blot
Martin et al. [46]	Mouse (C57BL/6)	16	DNBS	10	*L. lactis* MG1363	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Gao et al. [47]	Mouse (C57BL/6)	8	DSS	9	*L. rhamnosus* GG HM0539	Gavage	ZO-1	Western blot
Biagiolo et al. [48]	Mouse (Balb/c)	6	TNBS	7	Mixed culture (VSL#3)	Gavage	Occludin	qRT-PCR
Rodríguez-Nogales et al. [49]	Mouse (C57BL/6J)	10	DSS	26	*E. coli* Nissle 1917	Gavage	Occludin, ZO-1	qRT-PCR
Dai et al. [50]	Rat (Wistar)	10	DSS	7	Mixed culture (VSL#3)	Gavage	Occludin, ZO-1	Western blot
Esposito et al. [51]	Mouse (C57BL/6J)	10	DSS	5	*L. paracasei* F19 (pLP)	Gavage	Occludin, ZO-1	Western blot
Fábrega et al. [52]	Mouse (C57BL/6J)	9	DSS	15	*E. coli* Nissle 1917	Gavage	Occludin, ZO-1	Western blot
Jeong et al. [53]	Mouse (C57BL/6N)	9	DSS	7	*L. gasseri* 4M13	Gavage	Occludin, ZO-1	qRT-PCR
Tulyeu et al. [54]	Rat (Brown Norway SPF)	7	Ovalbumin	49	*C. butyricum* MIYAIRI 588, *L. reuteri* DSM 17938	Gavage	Occludin, ZO-1	qRT-PCR
Yeo et al. [55]	Mouse (C57BL/6J)	8	DSS	14	*L. rhamnosus* LDTM 7511 *L. rhamnosus* ATCC 53103	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Rodríguez-Nogales et al. [56]	Mouse (C57BL/6J)	10	DSS	26	*L. salivarius* CECT5713 *L. fermentum* CECT5716	Gavage	Occludin, ZO-1	qRT-PCR
Vanhaecke et al. [57]	Rat (Sprague-Dawley)	6	WAS	14	*L. fermentum* CECT 5716	Gavage	ZO-1	Western blot
Ukena et al. [58]	Mouse (Balb/c)	3	DSS	7	*E. coli* Nissle 1917	Gavage	ZO-1	Western blot
Wang et al. [59]	Chick (Nick)	6	*S. typhimurium* CVCC542	6	*L. plantarum* LTC-113	Gavage	Claudin, Occludin, ZO-1	qRT-PCR
Xu et al. [60]	Rat (Sprague-Dawley)	6	DSS	42	*L. acidophilus*	Gavage	ZO-1	Immunohistochemical analysis
Zhou et al. [61]	Rat (Wistar)	8	Bile duct ligation	10	*L. plantarum* CGMCC 1258	Gavage	Claudin, Occludin, ZO-1	Western blot
Zakostelska et al. [62]	Mouse (BALB/c)	5	DSS	21	*L. casei* DN-114 001 (HK)	Gavage	Occludin, ZO-1	qRT-PCR

Table 1. *Cont.*

Authors	Animal (Strain)	*n*	Induced Chemical [1]	Treated Time (d)	Probiotics [2]	Administration Form	Analytical Items [3]	TJP Evaluation [4]
Chen et al. [63]	Mouse (BALB/c)	6	TNBS	7	B. longum HB5502, Mixed culture (VSL#3)	Gavage	Claudin, Occludin	Western blot
Xu et al. [64]	Mouse (C57BL/6)	10	*E. coli* K88	14	*L. casei* ATCC 393	Gavage	Claudin, Occludin	Western blot
Kim et al. [65]	Mouse (C57BL/6N)	8	DSS	8	*L. paracasei* KBL382 *L. paracasei* KBL385	Gavage	Claudin, ZO-1	qRT-PCR
Zhang et al. [66]	Turbot (*Scophthalmus maximus* L.)	8	*E. coli* 055:B5	7	*Shewanella* sp. MR-7	Diet	Claudin, Occludin, ZO-1	qRT-PCR
Rodrigues et al. [67]	Rat (Wistar)	8	Acetic acid	17	*L. rhamnosus* EM1107	Gavage	ZO-1	Immunohistochemical analysis
Luo et al. [68]	Rabbit (New Zealand white)	4	TNBS	5	*B. subtilis* HH2	Gavage	Claudin, Occludin, ZO-1	Western blot
Zeng et al. [69]	Mouse (C57BL/6)	7	DSS	7	*L. lactis* NZ9000, *L. lactis* NZ9000SHD-5	Gavage	Occludin, ZO-1	qRT-PCR

[1] DSS, dextran sodium sulfate; TNBS, 2,4,6-trinitrobenzenesulphonic acid; DNBS, dinitrobenzene sulfonic acid; PTG, pepsin-trypsin-digested gliadin WAS, water avoidance stress. [2] IRT5, consisting of *L. casei, L. acidophilus, L. reuteri, B. bifidum,* and *S. thermophilus*; VSL#3, consisting of *S. thermophilus* DSM24731, *L. acidophilus* DSM24735, *L. delbrueckii* subsp. *bulgaricus* DSM24734, *L. paracasei* DSM24733, *L. plantarum* DSM24730, *B. longum* DSM24736, *B. infantis* DSM24737 and *B. breve* DSM24732. [3] ZO-1, zonula occludens-1. [4] qRT-PCR, quantitative real time-PCR.

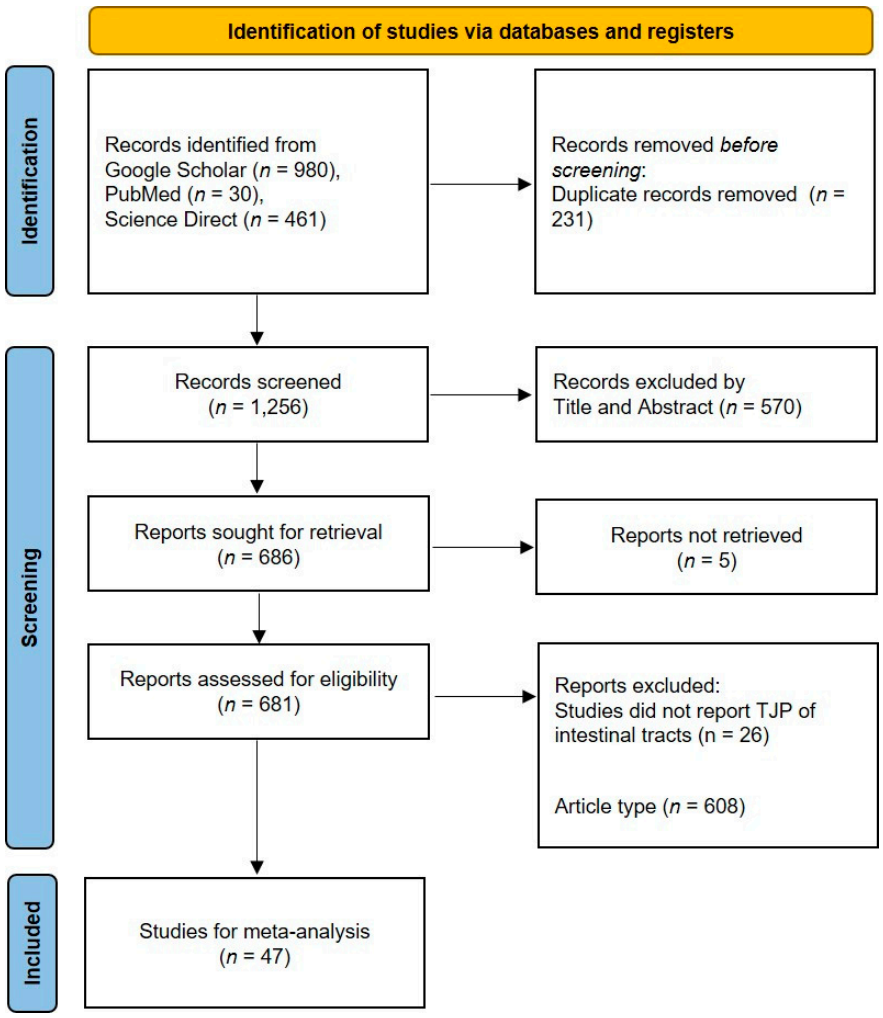

Figure 1. The PRISMA flow diagram of the procedure of data collection for the meta-analysis.

3.2. Evaluation of the Collected Studies

The QualSyst score of the included studies is listed in Table 2. The objective of the studies, experiment design, intervention, randomized housing, outcome measurement, and presentation of outcomes were generally well described. These studies showed high quality, with a mean 80.9% and a standard deviation of 0.16, and ranged between a maximum of 98.6 and a minimum of 64.0%. Therefore, the collected articles had enough quality to use in this meta-analysis.

Table 2. The assessed results by the QualSyst of the collected studies.

Authors	Average Summary Score (%)	Standard Deviation between Reviewer 1 and 2
Chen et al. [23]	95.9	0.009
Miyauchi et al. [24]	86.1	0.028
Hagihara et al. [25]	96.2	0.088
Tian et al. [26]	79.8	0.020
Jin et al. [27]	69.8	0.009
Chen et al. [28]	88.5	0.017
Xin et al. [29]	78.1	0.016
Bao et al. [30]	93.7	0.030
Orlando et al. [31]	94.4	0.009
Jeong et al. [32]	83.2	0.007
Sheng et al. [33]	91.0	0.041
Dong et al. [34]	81.8	0.043
Seo et al. [35]	87.5	0.009
Rokana et al. [36]	98.6	0.012
Liang et al. [37]	83.2	0.004
Mennigen et al. [38]	75.2	0.052
Wang et al. [39]	93.2	0.014
Zhang et al. [40]	82.3	0.027
Feng et al. [41]	64.0	0.033
Oh et al. [42]	89.1	0.014
Li et al. [43]	92.6	0.007
Wang et al. [44]	77.8	0.096
Dai et al. [45]	93.1	0.040
Martin et al. [46]	96.6	0.019
Gao et al. [47]	78.2	0.081
Biagiolo et al. [48]	87.9	0.005
Rodríguez-Nogales et al. [49]	94.6	0.029
Dai et al. [50]	88.8	0.011
Esposito et al. [51]	66.7	0.062
Fábrega et al. [52]	78.7	0.010
Jeong et al. [53]	72.4	0.044
Tulyeu et al. [54]	89.3	0.006
Yeo et al. [55]	92.7	0.011
Rodríguez-Nogales et al. [56]	76.4	0.027
Vanhaecke et al. [57]	93.0	0.009
Ukena et al. [58]	95.8	0.056
Wang et al. [59]	67.1	0.008
Xu et al. [60]	83.5	0.097
Zhou et al. [61]	94.2	0.023
Zakostelska et al. [62]	80.9	0.082
Chen et al. [63]	98.2	0.031
Xu et al. [64]	87.2	0.010
Kim et al. [65]	94.9	0.018
Zhang et al. [66]	65.8	0.085
Rodrigues et al. [67]	90.9	0.026
Luo et al. [68]	83.7	0.006
Zeng et al. [69]	74.8	0.081

3.3. Effect of Probiotics Administration on TJP Expression

The effect size on TJP expression is indicated in Figure 2. All analyzed items, including claudin, occludin, and ZO-1, showed a positive effect size in the random effects model by the administration of probiotics, and there was a significance (claudin, SMD: 4.45; 95% confidence interval (CI): 3.12–5.78; $p < 0.01$; $I^2 = 92\%$; occludin, SMD: 5.64; 95% CI: 4.44–6.83; $p < 0.01$; $I^2 = 90\%$; ZO-1, SMD: 4.20; 95% CI: 3.17–5.23; $p < 0.01$; $I^2 = 88\%$). This suggests that the administration of probiotics to animals positively affects TJP expression in damaged intestinal environments. In the case of claudin (Figure 2A), most studies indicated positive effect sizes. However, some studies, including those by Xu et al. [64], and Wang et al. [59], represented a negative effect size. Among the studies with positive effect sizes, Tian et al. [26], Martin et al. [46], Xu et al. [64], and Wang et al. [59] showed the most significant weight in the random effects model (4.9%). Figure 2B indicates occludin expression. Except for the studies by Wang et al. [59], and Zakostelska et al. [62], most studies indicated positive effect sizes. Among them, Li et al. [43] indicated the most significant effect size (SMD: 79.26; 95% CI: 49.95-108.57) in the random effect model. However, it showed the smallest weight in the random effect model (0.2%), and its influence was more minor than others. In ZO-1 expression (Figure 2C), only one study (Li et al. [43]) showed negative effect size. The studies of Dai et al. [45], Rodrigues et al. [67], Vanhaecke et al. [57] showed the highest weight (3.8%) among the studies that had positive effect size in the random effect model. In this study, the Q statistics of claudin was highest (340.94) and significant ($p < 0.0001$) (data not shown). Furthermore, all items, for instance, claudin, occludin, and ZO-1, showed a high level of I^2, especially claudin, which was highest at 92.4%. In other words, all items had significantly high heterogeneity.

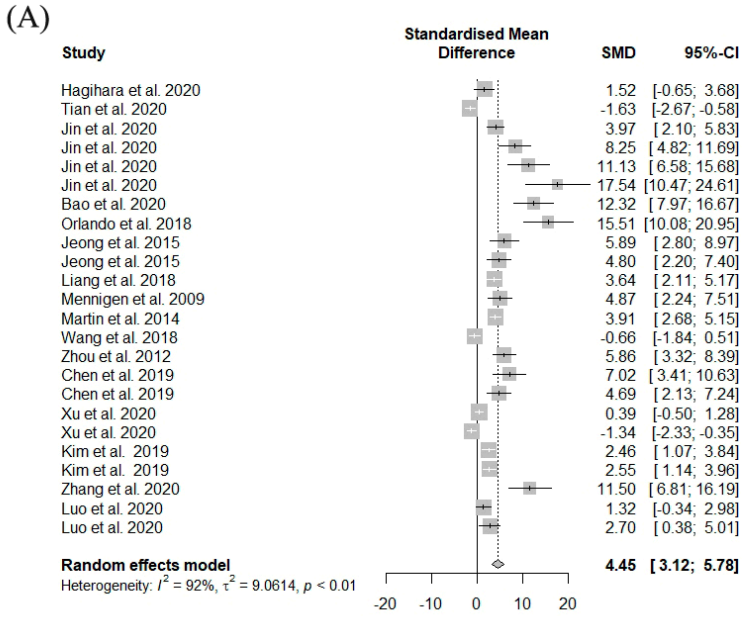

Figure 2. *Cont.*

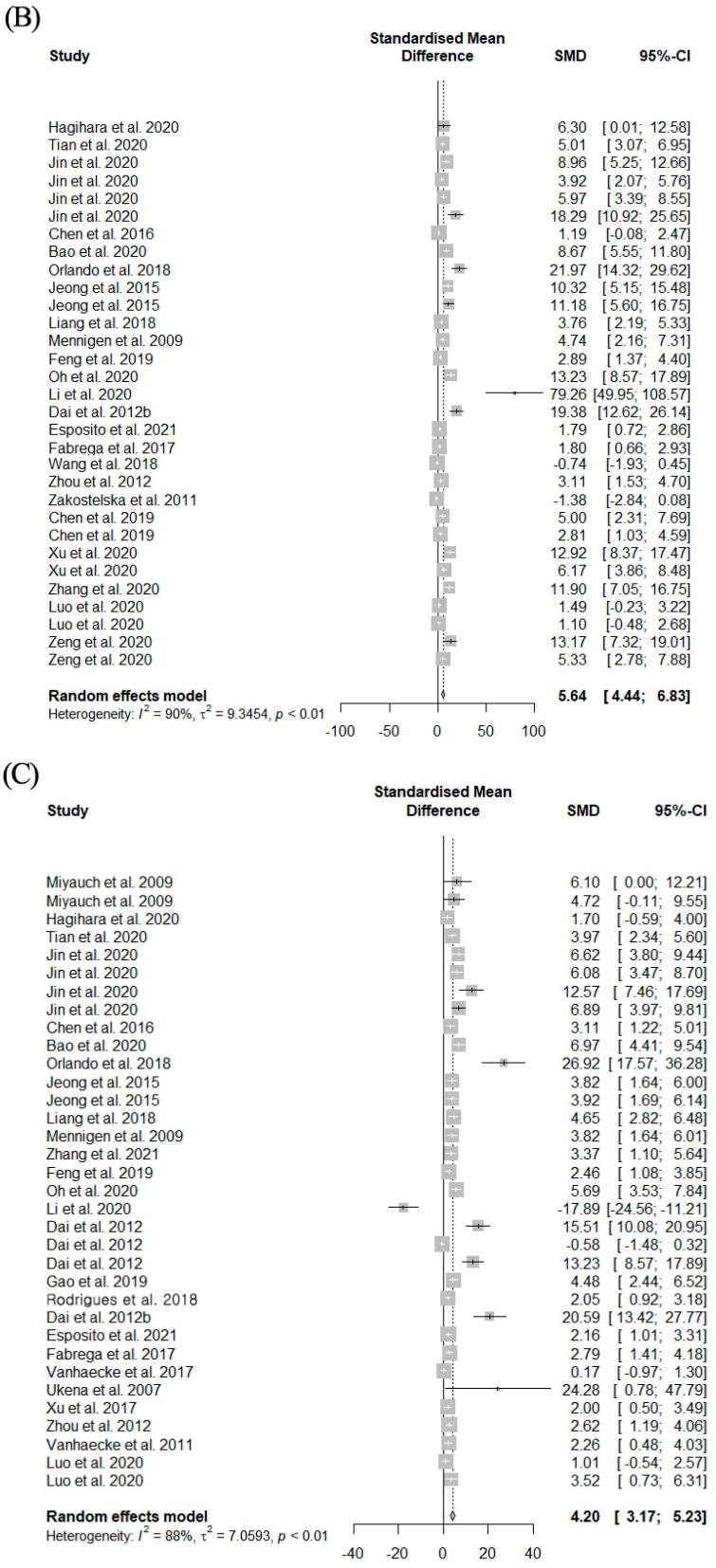

Figure 2. Forest plot for effect size of probiotics administration on tight junction protein expression by random effect model. (**A**) claudin; (**B**) occludin; (**C**) ZO−1, [24–28,30,32,37,38,40–43,45–47,50,51,57,59,61–69].

Figure 3 denotes the effect size on mRNA expression of TJP. All analyzed items, including claudin, occludin, and ZO-1, showed a positive effect model. There were significance in

all analyzed items (claudin, SMD: 2.08; 95% CI: 0.61–3.55; $p < 0.01$; $I^2 = 94\%$; occludin, SMD: 3.37; 95% CI: 2.35–4.38; $p < 0.01$; $I^2 = 94\%$; ZO-1, SMD: 3.94; 95% CI: 3.20–4.68; $p < 0.01$; $I^2 = 90\%$). It means that probiotics administration is effective for mRNA expression of TJP in an animal model. In the case of claudin (Figure 3A), some studies, such as Seo et al. [35] and Yeo et al. [55], showed a negative effect size. However, except for two studies, all other studies showed a positive effect size. Figure 3B shows the mRNA expression of occludin. Most studies indicated a positive effect size except for Biagiolo et al. [48] and Rodriguez-Nogales et al. [49]. In particular, Sheng et al. [33] denoted the largest effect size (SMD: 29.45; 95% CI: 15.03–43.86). Similarly, most studies showed a positive effect size in Figure 3C except for Yeo et al. [55]. Tulyeu et al. [54] showed the largest SMD (SMD: 20.43; 95% CI: 11.44–29.41). However, its weight in the random effect model was 0.6%. On the other hand, the study of Xin et al. [29] showed the highest weight (3.5%) in the random effect model. Among the analyzed items, occludin showed the highest Q statistics (499.12) with significance ($p < 0.0001$) in the random effect model of TJP mRNA expression.

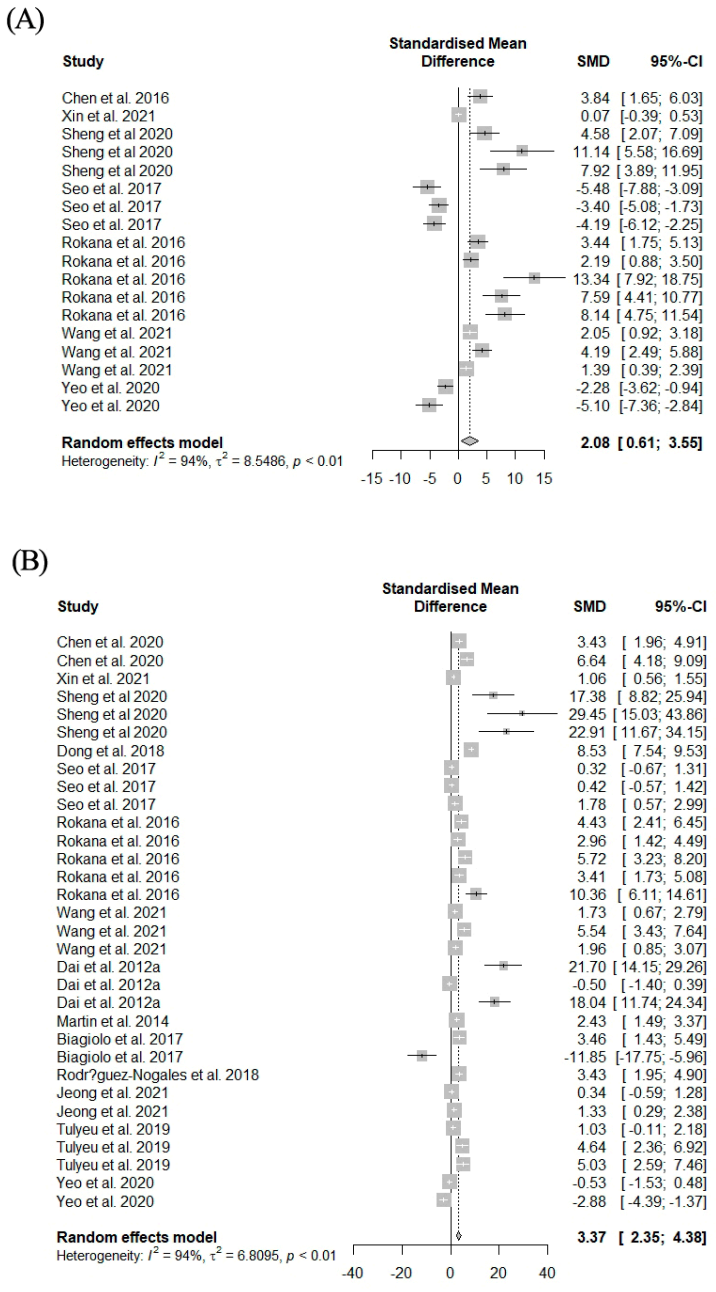

Figure 3. *Cont.*

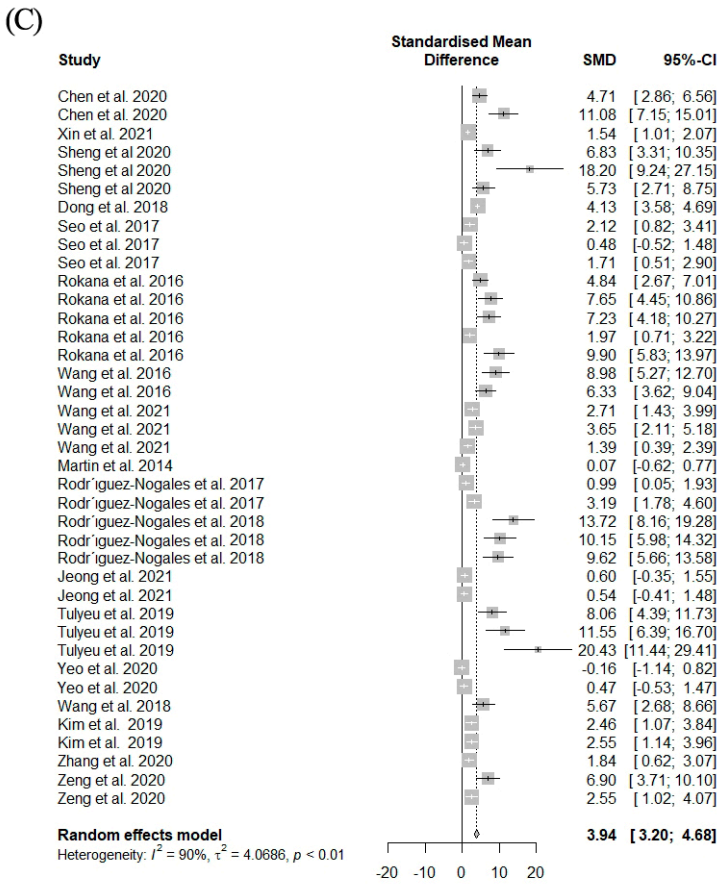

Figure 3. Forest plot for the effect size of probiotics administration on the mRNA expression of the tight junction protein by the random effects model. (**A**) claudin, (**B**) occludin, (**C**) ZO−1, [23,29,33–36,44,46,48–50,53,56,59,65,66,69].

3.4. Moderator Analysis

As high heterogeneity was observed, an additional moderator analysis had to be performed. Table 3 shows the results of a meta-ANOVA analysis of the probiotic administration effect by strain on TJP expression in the animal models. It revealed that *L. reuteri* was the most effective probiotic in claudin and ZO-1 expression, and that prebiotics were most effective in occludin expression. After unification of τ^2 for the variance between subgroups, the Q statistics between groups (Q_b) of the claudin, occludin, and ZO-1were 346.83 (df = 20, $p < 0.0001$), 369.17 (df = 25, $p < 0.0001$), and 236.59 (df = 26, $p < 0.0001$), respectively. In addition, the SMD of the medicine was lower than that of the probiotics, except for some probiotics in all TJPs. In the meta-regression test (Table 4), some items showed significance ($p < 0.05$), such as *B. breve, B. fragilis, L. casei, L. johnsonii, L. rhamnosus,* and *L. sakei* in claudin, and prebiotics in occludin expression. On the other hand, there was no significance in the administration time and dosage ($p > 0.05$). As a result, a significant regression model could not be obtained ($R^2 = 0.00$), which means that there is no explanatory power in the regression model.

Table 3. Meta-ANOVA to analyze the effect of probiotics strain on the tight junction protein expression of intestinal tracts in the animal model.

Item [1]	Subgroup		Estimate	SE [3]	*p*-Value [4]	CI. lb [5]	CI. ub [6]	R^2 (%)
Claudin	Probiotics strain	Intercept [2]	12.3197	3.9377	0.0018 **	4.6020	20.0374	0.00
		B. breve	−13.3197	5.1349	0.0066 **	−24.0091	−3.8806	
		B. fragilis	−9.8015	4.3794	0.0252 *	−18.3850	−1.2181	
		B. infantis	−4.3984	5.5055	0.4243	−15.1891	6.3923	
		B. longum	−5.2956	5.4295	0.3294	−15.9372	5.3459	
		B. subtilis	−11.0005	5.1768	0.0336 *	−21.1469	−0.8541	
		C. butyricum	−6.1354	4.8116	0.2023	−15.5660	3.2952	
		L. casei	−12.7922	4.5728	0.0052 **	−21.7547	−3.8297	
		L. johnsonii	−12.2498	5.1128	0.0166 *	−22.2707	−2.2289	
		L. lactis	−8.4080	5.1461	0.1023	−18.4943	1.6783	
		L. paracasei	−9.8159	4.5881	0.0324 *	−18.8093	−0.8235	
		L. platarum	−5.8372	4.1768	0.1623	−14.0236	2.3492	
		L. reuteri	14.9535	7.9587	0.0603	−0.6452	30.5522	
		L. rhamnosus	−10.1128	4.2426	0.0171 *	−18.4282	−1.7974	
		L. sakei	−16.1100	4.6066	0.0005 ***	−25.1389	−7.0812	
		Medicine	−14.0232	4.3397	0.0012 **	−22.5288	−5.5176	
		Mixed culture	−6.3576	4.2563	0.1353	−14.6998	1.9845	
		Prebiotics	−7.7392	5.2650	0.1416	−18.0584	2.5800	
		S. thermophiles	−10.1320	5.1511	0.0492 *	−20.2279	−0.0361	
		Shewanella sp.	−0.8224	5.6405	0.8841	−11.8776	10.2329	
		Synbiotics	−2.9140	4.8327	0.5465	−12.3860	6.5579	
	Administration time	Intercept	4.8498	2.0891	0.0203	0.7552	8.9445	0.00
		Day	0.0207	0.0731	0.7775	0.1226	0.1640	
	Dosage	Intercept	−2.0531	13.1000	0.8755	−27.7285	23.6223	0.00
		Dosage	0.7001	1.4574	0.6310	−2.1564	3.5567	
Occludin	Probiotics strain	Intercept	8.6724	3.3722	0.0101 *	2.0631	15.2817	0.00
		B. breve	−3.6635	4.6024	0.4260	−12.6841	5.3571	
		B. fragilis	−5.6702	3.8086	0.1365	−13.1349	1.7945	
		B. infantis	8.7071	6.2667	0.1647	−3.5755	20.9896	
		B. longum	−3.6720	4.6995	0.4346	−12.8829	5.5389	
		B. subtilis	−7.1787	4.5800	0.1170	−16.1552	1.7979	
		C. butyricum	−3.4568	4.2446	0.4154	−11.7760	4.8624	
		E. Coli Nissle	−6.0720	4.0014	0.1291	−13.9146	1.7706	
		L. casei	−3.7033	3.8745	0.3392	−11.2972	3.8905	
		L. fermentum	−3.9842	4.5919	0.3856	−12.9841	5.0158	
		L. gasseri	−4.8758	3.8509	0.2055	−12.4234	2.6719	
		L. johnsonii	−7.6132	4.5017	0.0908	−12.4234	2.6719	
		L. lactis	−2.0662	3.7498	0.5816	−9.4157	5.2833	
		L. paracasei	−6.8846	4.5278	0.1284	−15.7589	1.9897	
		L. platarum	−4.4105	3.5894	0.2192	−11.4457	2.6247	
		L. reuteri	−3.6473	4.6628	0.4341	−12.7863	5.4916	
		L. rhamnosus	−4.8075	3.6865	0.1922	−12.0329	2.4179	
		L. sakei	−7.5784	3.6865	0.1922	−12.0329	2.4179	
		L. salivarius	−5.5702	4.5498	0.2208	−15.4050	0.2481	
		Medicine	−6.9143	3.6598	0.0589	−14.0873	0.2587	
		Mixed culture	−2.6412	3.5224	0.4534	−9.5450	4.2625	
		Prebiotics	20.7735	8.6211	0.0160 *	3.8766	37.6705	
		S. thermophiles	−5.7126	4.5623	0.2105	−14.6545	3.2293	
		Shewanella sp.	3.2302	5.1308	0.5290	−6.8260	13.2863	
		Synbiotics	4.7622	4.6464	0.2105	−14.6545	3.2293	
		Synechococcus	−5.7857	4.5603	0.2045	−14.7238	3.1524	
	Administration time	Intercept	6.6502	2.0584	0.0012	2.6159	10.6846	0.00
		Day	−0.0111	0.0771	−0.1444	0.8852	−0.1623	
	Dosage	Intercept	30.9506	13.2133	0.0192	5.0530	56.8463	0.00
		Dosage	−2.5663	1.3829	0.0635	−5.2768	0.1441	

Table 3. *Cont.*

Item [1]	Subgroup		Estimate	SE [3]	*p*-Value [4]	CI. lb [5]	CI. ub [6]	R^2 (%)
ZO−1	Probiotics strain	Intercept	6.9744	2.8378	0.0140 *	1.4124	12.5364	0.00
		B. breve	−3.0068	3.8836	0.4388	−10.6185	4.6049	
		B. fragilis	−4.4113	3.2109	0.1695	−10.7046	1.8819	
		B. infantis	−0.1449	4.1975	0.9725	−8.3718	8.0820	
		B. subtilis	−4.8395	3.4213	0.1572	−11.5450	1.8661	
		C. butyricum	−1.6496	3.5955	0.6464	−8.6966	5.3975	
		E. Coli Nissle	−4.0765	3.3698	0.2264	−10.6812	2.5281	
		L. aciophilus	−4.9774	3.8695	0.1983	−12.5614	2.6067	
		L. casei	−4.7159	3.9004	0.2266	−12.3605	2.9287	
		L. fermentum	−5.3177	3.3815	0.1158	−11.9454	1.3101	
		L. gasseri	−4.8525	3.2160	0.1313	−11.1557	1.4507	
		L. johnsonii	−5.4356	3.8033	0.1530	−12.8899	2.0188	
		L. lactis	−3.8105	3.1339	0.2240	−9.9528	2.3318	
		L. paracasei	−4.5868	3.2121	0.1533	−10.8824	1.7088	
		L. platarum	−1.2755	2.9966	0.6704	−7.1488	4.5978	
		L. reuteri	13.4512	5.9509	0.0238	1.7876	25.1149	
		L. rhamnosus	−2.8947	2.9952	0.3338	−8.7653	2.9758	
		L. sakei	−5.8836	3.3734	0.0811	−12.4954	0.7282	
		L. salivarius	−5.9818	3.8240	0.1177	−13.4766	1.5130	
		Medicine	−3.1009	3.0642	0.3116	−9.1066	2.9048	
		Mixed culture	0.2984	3.0611	0.9223	−5.7012	6.2980	
		Mixed culture + medicine	6.2538	4.4766	0.1624	−2.5201	15.0278	
		Prebiotics	11.2244	5.9390	0.0588	−0.4157	22.8646	
		S. thermophilus	0.6803	4.1318	0.8692	−7.4177	8.7784	
		Shewanella sp.	−5.1300	3.8449	0.1821	−12.6658	2.4058	
		Synbiotics	0.4962	3.3391	0.8819	−6.0483	7.0407	
		Synechococcus	−4.5101	3.5893	0.2426	−12.0741	3.0539	
	Administration time	Intercept	4.7298	1.4227	0.0009	1.9414	7.5183	0.00
		Day	−0.0541	0.0727	0.4572	−0.1966	0.0884	
	Dosage	Intercept	0.1495	32.3965	0.9963	−63.3465	63.6454	0.00
		Day	0.2520	3.9322	0.9489	−7.4550	7.7591	

[1] ZO−1, zonula occludens−1. [2] SMD, standardized mean difference. [3] SE, standard error. [4] * $p<0.05$, ** $p<0.01$, *** $p<0.001$. [5] CI. lb, lower limit of 95% confidence interval. [6] CI. ub, upper limit of 95% confidence interval.

Table 4. Meta-regression to analyze the effect of probiotics strain, administration time, and dosage on the expression of the tight junction protein.

Item [1]	Subgroup		Estimate	SE [3]	*p*−Value [4]	CI. lb [5]	CI. ub [6]	R^2 (%)
Claudin	Probiotics strain	Intercept [2]	12.3197	3.9377	0.0018 **	4.6020	20.0374	0.00
		B. breve	−13.3197	5.1349	0.0066 **	−24.0091	−3.8806	
		B. fragilis	−9.8015	4.3794	0.0252 *	−18.3850	−1.2181	
		B. infantis	−4.3984	5.5055	0.4243	−15.1891	6.3923	
		B. longum	−5.2956	5.4295	0.3294	−15.9372	5.3459	
		B. subtilis	−11.0005	5.1768	0.0336 *	−21.1469	−0.8541	
		C. butyricum	−6.1354	4.8116	0.2023	−15.5660	3.2952	
		L. casei	−12.7922	4.5728	0.0052 **	−21.7547	−3.8297	
		L. johnsonii	−12.2498	5.1128	0.0166 *	−22.2707	−2.2289	
		L. lactis	−8.4080	5.1461	0.1023	−18.4943	1.6783	
		L. paracasei	−9.8159	4.5881	0.0324 *	−18.8093	−0.8235	
		L. platarum	−5.8372	4.1768	0.1623	−14.0236	2.3492	
		L. reuteri	14.9535	7.9587	0.0603	−0.6452	30.5522	
		L. rhamnosus	−10.1128	4.2426	0.0171 *	−18.4282	−1.7974	
		L. sakei	−16.1100	4.6066	0.0005 ***	−25.1389	−7.0812	
		Medicine	−14.0232	4.3397	0.0012 **	−22.5288	−5.5176	
		Mixed culture	−6.3576	4.2563	0.1353	−14.6998	1.9845	
		Prebiotics	−7.7392	5.2650	0.1416	−18.0584	2.5800	
		S. thermophiles	−10.1320	5.1511	0.0492 *	−20.2279	−0.0361	
		Shewanella sp.	−0.8224	5.6405	0.8841	−11.8776	10.2329	
		Synbiotics	−2.9140	4.8327	0.5465	−12.3860	6.5579	
	Administration time	Intercept	4.8498	2.0891	0.0203	0.7552	8.9445	0.00
		Day	0.0207	0.0731	0.7775	0.1226	0.1640	
	Dosage	Intercept	−2.0531	13.1000	0.8755	−27.7285	23.6223	0.00
		Dosage	0.7001	1.4574	0.6310	−2.1564	3.5567	

Table 4. *Cont.*

Item [1]	Subgroup		Estimate	SE [3]	$p-$Value [4]	CI. lb [5]	CI. ub [6]	R^2 (%)
Occludin	Probiotics strain	Intercept	8.6724	3.3722	0.0101 *	2.0631	15.2817	0.00
		B. breve	−3.6635	4.6024	0.4260	−12.6841	5.3571	
		B. fragilis	−5.6702	3.8086	0.1365	−13.1349	1.7945	
		B. infantis	8.7071	6.2667	0.1647	−3.5755	20.9896	
		B. longum	−3.6720	4.6995	0.4346	−12.8829	5.5389	
		B. subtilis	−7.1787	4.5800	0.1170	−16.1552	1.7979	
		C. butyricum	−3.4568	4.2446	0.4154	−11.7760	4.8624	
		E. Coli Nissle	−6.0720	4.0014	0.1291	−13.9146	1.7706	
		L. casei	−3.7033	3.8745	0.3392	−11.2972	3.8905	
		L. fermentum	−3.9842	4.5919	0.3856	−12.9841	5.0158	
		L. gasseri	−4.8758	3.8509	0.2055	−12.4234	2.6719	
		L. johnsonii	−7.6132	4.5017	0.0908	−12.4234	2.6719	
		L. lactis	−2.0662	3.7498	0.5816	−9.4157	5.2833	
		L. paracasei	−6.8846	4.5278	0.1284	−15.7589	1.9897	
		L. platarum	−4.4105	3.5894	0.2192	−11.4457	2.6247	
		L. reuteri	−3.6473	4.6628	0.4341	−12.7863	5.4916	
		L. rhamnosus	−4.8075	3.6865	0.1922	−12.0329	2.4179	
		L. sakei	−7.5784	3.6865	0.1922	−12.0329	2.4179	
		L. salivarius	−5.5702	4.5498	0.2208	−15.4050	0.2481	
		Medicine	−6.9143	3.6598	0.0589	−14.0873	0.2587	
		Mixed culture	−2.6412	3.5224	0.4534	−9.5450	4.2625	
		Prebiotics	20.7735	8.6211	0.0160 *	3.8766	37.6705	
		S. thermophiles	−5.7126	4.5623	0.2105	−14.6545	3.2293	
		Shewanella sp.	3.2302	5.1308	0.5290	−6.8260	13.2863	
		Synbiotics	4.7622	4.6464	0.2105	−14.6545	3.2293	
		Synechococcus	−5.7857	4.5603	0.2045	−14.7238	3.1524	
	Administration time	Intercept	6.6502	2.0584	0.0012	2.6159	10.6846	0.00
		Day	−0.0111	0.0771	−0.1444	0.8852	−0.1623	
	Dosage	Intercept	30.9506	13.2133	0.0192	5.0530	56.8463	0.00
		Dosage	−2.5663	1.3829	0.0635	−5.2768	0.1441	
ZO−1	Probiotics strain	Intercept	6.9744	2.8378	0.0140 *	1.4124	12.5364	0.00
		B. breve	−3.0068	3.8836	0.4388	−10.6185	4.6049	
		B. fragilis	−4.4113	3.2109	0.1695	−10.7046	1.8819	
		B. infantis	−0.1449	4.1975	0.9725	−8.3718	8.0820	
		B. subtilis	−4.8395	3.4213	0.1572	−11.5450	1.8661	
		C. butyricum	−1.6496	3.5955	0.6464	−8.6966	5.3975	
		E. Coli Nissle	−4.0765	3.3698	0.2264	−10.6812	2.5281	
		L. aciophilus	−4.9774	3.8695	0.1983	−12.5614	2.6067	
		L. casei	−4.7159	3.9004	0.2266	−12.3605	2.9287	
		L. fermentum	−5.3177	3.3815	0.1158	−11.9454	1.3101	
		L. gasseri	−4.8525	3.2160	0.1313	−11.1557	1.4507	
		L. johnsonii	−5.4356	3.8033	0.1530	−12.8899	2.0188	
		L. lactis	−3.8105	3.1339	0.2240	−9.9528	2.3318	
		L. paracasei	−4.5868	3.2121	0.1533	−10.8824	1.7088	
		L. platarum	−1.2755	2.9966	0.6704	−7.1488	4.5978	
		L. reuteri	13.4512	5.9509	0.0238	1.7876	25.1149	
		L. rhamnosus	−2.8947	2.9952	0.3338	−8.7653	2.9758	
		L. sakei	−5.8836	3.3734	0.0811	−12.4954	0.7282	
		L. salivarius	−5.9818	3.8240	0.1177	−13.4766	1.5130	
		Medicine	−3.1009	3.0642	0.3116	−9.1066	2.9048	
		Mixed culture	0.2984	3.0611	0.9223	−5.7012	6.2980	
		Mixed culture + medicine	6.2538	4.4766	0.1624	−2.5201	15.0278	
		Prebiotics	11.2244	5.9390	0.0588	−0.4157	22.8646	
		S. thermophilus	0.6803	4.1318	0.8692	−7.4177	8.7784	
		Shewanella sp.	−5.1300	3.8449	0.1821	−12.6658	2.4058	
		Synbiotics	0.4962	3.3391	0.8819	−6.0483	7.0407	
		Synechococcus	−4.5101	3.5893	0.2426	−12.0741	3.0539	
	Administration time	Intercept	4.7298	1.4227	0.0009	1.9414	7.5183	0.00
		Day	−0.0541	0.0727	0.4572	−0.1966	0.0884	
	Dosage	Intercept	0.1495	32.3965	0.9963	−63.3465	63.6454	0.00
		Day	0.2520	3.9322	0.9489	−7.4550	7.7591	

[1] ZO-1, zonula occludens-1. [2] mixed culture, IRT5 consisting of *L. casei*, *L. acidophilus*, *L. reuteri*, *B. bifidum*, and *S. thermophilus*; VSL#3 consisting of *S. thermophilus* DSM24731, *L. acidophilus* DSM24735, *L. delbrueckii* subsp. *bulgaricus* DSM24734, *L. paracasei* DSM24733, *L. plantarum* DSM24730, *B. longum* DSM24736, *B. infantis* DSM24737 and *B. breve* DSM24732. [3] SE: standard error. [4] * $p<0.05$, ** $p<0.01$, *** $p<0.001$. [5] CI. lb, lower limit of 95% confidence interval. [6] CI. ub, upper limit of 95% confidence interval.

3.5. Publication Bias

A publication bias analysis was performed to investigate the presence or absence of errors in this meta-analysis regarding the analyzed factors: claudin, occludin, and ZO-1. As shown in Figure 4, publication bias was present in the funnel plots (the black data points). Egger's linear regression tests were conducted to confirm the publication bias with more acute statistical values, and the results are listed in Table 5. The significance was detected in all items ($p < 0.0001$), indicating a statistical significance between the effect size and standard error [70]. The analysis implies that there is a publication bias in these results. The trim-and-fill procedure arranged the publication bias that was detected in the funnel plots, and the amended effect sizes are listed in Table 6. The effect sizes and Q statistics of all items increased and were significant ($p < 0.0001$).

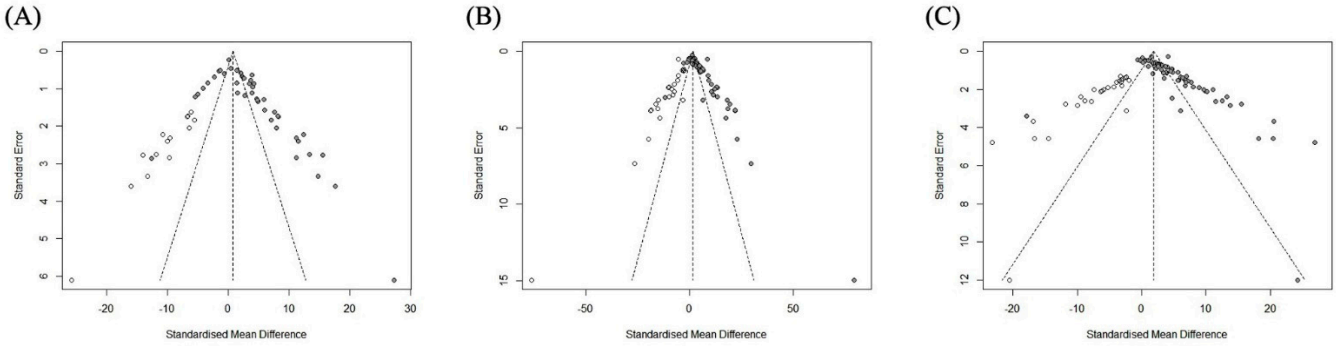

Figure 4. Funnel plot to evaluate publication bias. (**A**) claudin, (**B**) occludin, (**C**) ZO-1.

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

Items [1]	Bias	Se. Bias [2]	Intercept	*t*	df [3]	*p*-Value
Claudin	3.8205	0.8085	−1.4250	4.73	43	<0.0001
Occludin	4.4028	0.6205	−0.7640	7.10	63	<0.0001
ZO-1	3.6468	0.4838	−0.0727	7.54	71	<0.0001

[1] ZO-1, zonula occludens-1. [2] Se. bias, standard error of bias. [3] df, degree of freedom.

Table 6. Trimmed effect size of probiotics on the tight junction protein expression of intestinal tracts in the animal model.

Items [1]	df [2]	Fixed Effect Model		Random Effect Model		Heterogeneity		
		Effect Size	*p*-Value	Effect Size	*p*-Value	Q [3] (*p*-Value)	I^2 (%)	τ^2
Claudin	53	0.7299	<0.0001	1.0118	0.0512	901.22 (<0.0001)	93.6	12.6892
Occludin	13	1.5067	<0.0001	1.8429	<0.0001	1481.58 (<0.0001)	94.1	12.5371
ZO-1	99	1.8644	<0.0001	2.0862	<0.0001	1062.17 (<0.0001)	90.7	7.4204

[1] ZO-1, zonula occludens-1. [2] df, degree of freedom. [3] Q, Q statistics.

4. Discussion

There is a specific correlation between protein expression and its related mRNA expression, and although many studies have been conducted on the relationship, they are not entirely consistent [71]. Therefore, in this study, the effect of probiotics administration was investigated by separately dividing TJP expression and mRNA expression for TJP. Administration of probiotics was shown to act positively on mRNA expression for TJP. In particular, administration appeared to work more thoroughly on mRNA expression

for ZO-1 expression. The ZO-1 binds to transmembrane proteins, such as claudin and occludin, and plays a role in linking with cytoskeletal actin [25]. Thus, it is considered that the increase of mRNA expression for ZO-1 and ZO-1 expression by probiotics is evidence that probiotics play a significant role in improving intestinal health. In this study, the administration of the probiotics was found to positively affect TJP expression in the intestinal tract. In this regard, Din et al. [72] reported that the feeding of *B. bifidum* ATCC 29,521 promoted ZO-1 expression in DSS-colitis-induced mice. Hsieh et al. [73] mentioned that the role of probiotics in maintaining epithelial cell and restoring TJP is clear. According to Arrieta et al. [74], as well as Groschwitz and Hogan [75], an intestinal TJ barrier with a defect could be an etiological factor for various gastrointestinal diseases, including allergies, celiac disease, Crohn's disease, and IBD. The administration of probiotics that can be colonized in the gut can induce long-term beneficial effects on intestinal health, and relieves gut barrier damage by inhibiting structural changes in TJP caused by stress, inflammation, and inflammatory cytokines [76]. In contrast, orally administered medicines or dietary ingredients have shown only temporary results [73]. Ahn et al. [3] reported that the administration of probiotics decreased the amount of inflammatory cytokine expression. The result from the present study is related to some prior studies, such as those by Caffarelli et al. [77], Laudat et al. [78], Groschwit and Hogan [75], and Cho and Hwang [79], in which the increase in inflammatory cytokines decreased TJP expression and deteriorated intestinal health. The results from the present study are based on the results from animal studies. However, the results of this study can be applied to the human body. According to Gupta et al. [80], the probiotics treatment reduced intestinal permeability in Crohn's disease patients. Karczewski et al. [81] studied the *in vitro* effect of *L. plantarum* on epithelial TJ. According to them, the ZO-1 and occludin expression were increased in the intestinal epithelial cell line, Caco-2 cells, by administering *L. plantarum*. In addition, the researchers found that the administration of the *L. plantarum* was effective in regulating human epithelial TJ proteins in vivo and conferred protective effects against chemically induced epithelial barrier disruption. Similarly, Hsieh et al. [73] found that the *Bifidobacterium* species strengthened the TJ barrier in Caco-2 cell monolayers, and reported that the *Bifidobacterium* species promoted wound repair in Caco-2 cell monolayers treated with TNF-a for 48 h.

Usually, medicines such as sulfasalazine, mesalazine, budesonide, prednisone, and azathioprine are utilized as representative treatments to relieve IBD symptoms [82]. In this review, the SMD of the medicine was lower than that of the probiotics, suggesting that supplementation with probiotics has a greater effect on TJP expression than medicine. In contrast, a previous study [3] determined that the SMD of medicine was higher than that of probiotics in the alleviation of the diverse indices of IBD, suggesting that medicine was more helpful for the relief of various IBD-related indices. Similarly, White et al. [83] reported that parallel therapy with probiotics and prednisone was more effective in enhancing TJP expression in IBD-induced dogs.

In a heterogeneity analysis, a large Q and low p-value with significance means that there is high heterogeneity among the gathered articles. Although Q statistics are used to verify homogeneity or heterogeneity, the analysis may be influenced by the number of studies, k [84]. The I^2 value was used to compensate the shortcomings of the Q statistics, with 25, 50, and 75% showing low heterogeneity, moderate heterogeneity, and high heterogeneity, respectively [85].

Publication bias refers to an error in which research results are not published or published depending on the properties or directions of the study. In other words, publication bias occurs when the published results do not represent all performed studies [86], thereby potentially influencing the results of any meta-analysis. Generally, publication bias makes a funnel plot asymmetric [87]. Figure 3B, and C, in particular, reflect black dots at the top of the plots, indicating that the research with a large sample size tended to be located at the top and center of the funnel plot [86]. In this study, Egger's linear test was used to statistically verify the funnel plot with digitization by linear regression [87]. Generally,

when the *p*-value has significance, there is a meaningful relationship between the effect size and standard error in Egger's linear regression test, meaning that there is publication bias. If the publication status depends on the statistical significance of study results, publication bias could occur [88]. Since the publication bias could affect the results of the meta-analysis, various techniques were applied to check the data to prevent a potential publication bias problem [88,89]. Publication bias is a systematic error generated when synthesizing evidence that cannot represent the fundamental fact. Publication bias is one of reasons why scientific studies with favorable results overstate synthesized evidence in meta-analyses, as they are more likely to be published. A trim-and-fill method is a popular tool for detecting and adjusting publication bias. The trim-and-fill method involves cleaning the studies that lead to the asymmetrical funnel plot so that the overall effect estimates generated in the rest of the studies can be considered to be minimally affected by publication bias. Then, it involves filling the imputed missing studies in the funnel plot based on bias-adjusted overall estimates [90]. In Table 6, the trimmed effect sizes of all items decreased in the fixed and random effects models. Significantly, the *p*-value of claudin was not significant in the random effect model ($p > 0.05$). Therefore, it can be concluded that the administration of probiotics is effective in occludin and ZO-1 expression in the murine intestine with significance ($p < 0.05$).

5. Conclusions

We describe the results of our meta-analysis of the effects of probiotic administration on TJP expression in intestinal epithelial cell-injured animal models. Probiotics were shown to be helpful in improving TJP expression in the animal models. This may be closely related to the improvement of various symptoms caused by IBD due to the probiotics administration. This study is a meta-analysis performed based on the results of animal experiments. Thus, it is considered to have the advantage of obtaining various data that are difficult to obtain in human experiments. Since the research result was obtained based on data from an animal study, it can help identify trends. However, there is a disadvantage, as it is difficult to apply this result directly to the human body. Although this work is based on animal studies, further clinical studies on probiotics would therefore be worthwhile.

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