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Improvement in DSS induced acute enteritis in mice with supplementation of bifidobacteria

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ABSTRACT

Bifidobacteria can maintain the ecological balance of intestinal microorganisms and are closely linked to the onset and progression of acute enteritis. Present research aimed to investigate the alleviation of DSS-induced acute enteritis by bifidobacteria. *In vivo* colonoscopy was performed in mice to observe the colorectal mucosa and the pathological damage of colon tissue and the colonic expression of tight junction proteins (Occludin, Claudin-1, ZO-1) and inflammatory factors (TNF-α, IL-1b, IL-6). The colon mucosa tissue samples were collected for bacterial 16S DNA sequencing and transcriptome sequencing. The intervention of bifidobacteria could effectively alleviate the trend of weight loss and colonic trauma in mice with DSS-induced acute enteritis. The bifidobacteria effectively restored expression of tight junction proteins (Occludin, Claudin-1, and ZO-1) and decreased expression of pro-inflammatory factors (TNF-α, IL-1b, IL-6). *Bifidobacterium longum* proved to be the most effective ($P < 0.05$). The altered composition of

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gut microbiota was reflected in the increase of the relative abundances of *Dubosiella* spp. in the *B. longum* treated group. The results suggested that bifidobacteria could repair intestinal barrier function, relieve the colon inflammation, and improve intestinal microbiota disorder; and *B. longum* demonstrated the best efficacy in mice with DSS-induced acute enteritis.

KEYWORDS

acute enteritis, bifidobacteria, intestinal microbes, tight junction protein, transcriptomics analysis

1. INTRODUCTION

Acute enteritis is a clinically common digestive system disease and usually associated with pathogen microorganisms invading the human digestive tract (Kitamoto et al., 2020). In acute enteritis, impairing intestinal mucosal barrier hampers the transportation and utilisation of nutrients and drugs, which in turn aggravates the deterioration of the disease and leads to poor prognosis (Shao et al., 2014; Li et al., 2021). The pathogenesis of acute enteritis may be related to factors such as genetics, environment, immunity, and intestinal dominant microbiota (Kim et al., 2021; Lee et al., 2022; Meng et al., 2022).

Researches have shown that there is a close relationship between intestinal microbiota and intestinal diseases (Zhang et al., 2018; Juge, 2022). Sustaining the dynamic equilibrium of dominant intestinal microbiota makes a contribution to preserve the functionality of the organism's immune system. Once chronic inflammation occurs in the intestine, it will promote the proliferation of bacteria, stimulate the intestinal mucosal immunity, and destruct the intestinal immune barrier, so that the progression of disease is accelerated. Therefore, regulating the intestinal microbiota is currently one of the main ways to treat and prevent the occurrence and development of acute enteritis.

Probiotics refer to a type of active microorganisms that play a beneficial role in the host by improving the balance of the intestinal microbiota. Probiotics providing high food safety through their products mainly belong to the genera *Bifidobacterium* and *Lactobacillus*, and bifidobacteria can construct a biological barrier on the intestinal mucosa, improve the immune function of the intestine, prevent the invasion of pathogenic microorganisms, and inhibit the growth of pathogenic microorganisms (Thursby and Juge, 2017; Floch, 2018; Khalili et al., 2018).

Although progress has been made in the treatment and prevention of acute enteritis by bifidobacteria, the potential mechanism remains to be further elucidated. The present research explored the intervention effects and mechanism of bifidobacteria to improve health conditions of mice with DSS-induced acute enteritis.

2. MATERIALS AND METHODS

2.1. Materials

Healthy male C57BL/6J mice (6–8 weeks old) were purchased from Hunan Slack Jingda Experimental Animal Co., Ltd and fed in specific pathogen-free environment (SPF). The manipulation

of animals was approved by the Ethics Committee Board of Hunan Normal University (D2020009).

Bifidobacteria (*Bifidobacterium adolescentis* BH-20, *Bifidobacterium longum* BB536, *Bifidobacterium animalis* bb12, and *Bifidobacterium breve* B-3) were gifted by Changsha Tianan Biotechnology Co., Ltd.

2.2. Methods

2.2.1. Experimental design and procedure of DSS-induced enteritis. The experiment set up control group (Control), acute enteritis model group (DSS), and bifidobacteria intervention group. Based on different *Bifidobacterium* spp., the bifidobacteria intervention groups were further divided into *B. adolescentis* group (DSS_ado), *B. animalis* group (DSS_ani), *B. longum* group (DSS_lon), and *B. breve* group (DSS_bre).

The mice in the control were gavaged with sterilised water every day, and the 3% DSS solution was given to the mice in the other groups daily for 7 days to induce enteritis. The mice in the control group drank sterilised water *ad libitum* every day, the mice in the bifidobacteria intervention groups were given a *Bifidobacterium* sp. suspension (10^9 CFU kg^{-1} b.w.) every day.

2.2.2. Mouse colonoscopy observation. The mice were anesthetised by intraperitoneal injection with chloral hydrate of 0.03 mL/10 g b.w., and colonoscopy (Guangzhou Red Pine Medical Instrument Co., Ltd, China) was used to observe colon and inflate the colon with air (Liao et al., 2021).

2.2.3. Western blotting. The proteins of colon tissues were subjected to SDS-PAGE electrophoresis, and were then electro-transferred to a PVDF membrane (Ludvigsen et al., 2020). After blotting, the PVDF membranes were successively incubated with the primary antibody solution and the secondary antibody solution. The membrane was visualised with enhanced chemiluminescence (ECL) solution. The gray value of the corresponding protein band was analysed with ImageJ software.

2.2.4. Histological analysis. The colon tissue segments were embedded in paraffin for tissue section and counterstained to evaluate the colon impairment (Liao et al., 2021). The pathological score was assessed according to the degree of tissue damage and inflammatory cell infiltration, based on the criteria described by Wirtz et al. (2017).

2.2.5. Immunohistochemistry analysis. To the deparaffinised sections 0.01 mol L^{-1} sodium citrate was used for epitope restoration, and 3% H_2O_2 was used to block endogenous peroxidases. Then, the slices were incubated in a specific monoclonal antibody solution, and the colour was developed according to the DAKO kit operating instructions. The images were captured by a light microscope (Olympus CX41) and the optical densities were analysed by the IPP 6.0 software.

2.2.6. Microbial sequencing of mouse colonic mucosa and bioinformatics analysis. A 16S amplicon library was established for mouse colon mucosa samples, and then bioinformatics analysis was conducted. Diversity analyses of community structure distribution were performed.

Statistical algorithms were used to calculate the differing species among different groups, and draw the heat map based on them.

2.2.7. Transcriptome sequencing of mouse colon tissue and bioinformatics analysis. Total RNA was extracted from mouse colon tissue to perform PCR amplification and then bioinformatics analysis was conducted by OE Biotech Company (Shanghai, China). The clean reads were compared with the reference genome of the species, and the condition of the sample was evaluated based on the genome comparison rate. Through the screening of differential genes, GO and KEGG enrichment analysis were performed to determine the main pathways or biological functions affected by the differential genes.

2.2.8. Statistical analysis. All statistical analyses were performed by GraphPad Prism 8 (GraphPad Software, USA). Data are expressed as means ± standard errors of the means (SEM). Normally distributed continuous data were analysed using the parametric Student's *t* test. Differences in mean values among groups were subjected to analysis of variance (ANOVA). A value of $P < 0.05$ (two-tailed) was considered to indicate statistical significance.

3. RESULTS AND DISCUSSION

3.1. Supplementation with bifidobacteria alleviated acute enteritis induced by DSS in mice

The mice with DSS-induced acute enteritis experienced weight loss, intestinal ulcers, and colon shortening, increase of spleen coefficient, loss of goblet cells and intestinal epithelial cells, and inflammatory cells infiltration. The intervention of bifidobacteria could effectively alleviate the trend of weight loss and colonic trauma (Fig. 1). *B. longum* was the most effective in relieving weight loss and reducing spleen coefficient of mice with acute enteritis ($P < 0.05$). Thus, bifidobacteria has the function of restoring the intestinal barrier and relieving acute enteritis in mice.

3.2. Supplementation with bifidobacteria improved the impairment of intestinal barrier in acute enteritis mice

As illustrated in Fig. 2, in agreement with the results of Raj et al. (2023), the expression of tight junction proteins (Occludin, Claudin-1, and ZO-1) in the DSS group was significantly down-regulated, which could be restored through supplementation with bifidobacteria. *B. longum* was the most effective in recovering the expression of tight junction proteins ($P < 0.05$).

3.3. Supplementation with bifidobacteria alleviated the immune response in mice with DSS-induced acute enteritis

The transcriptome expression profile of the DSS group presented significant changes, and these differentially expressed genes mostly concentrated in the signal pathways related to immune modulation by KEGG enrichment analysis (Fig. 3). The key genes with up-regulated and down-regulated relative expression levels are presented in Table 1. The immune system in the mice with DSS-induced acute enteritis was activated, and the expression of pro-inflammatory factors

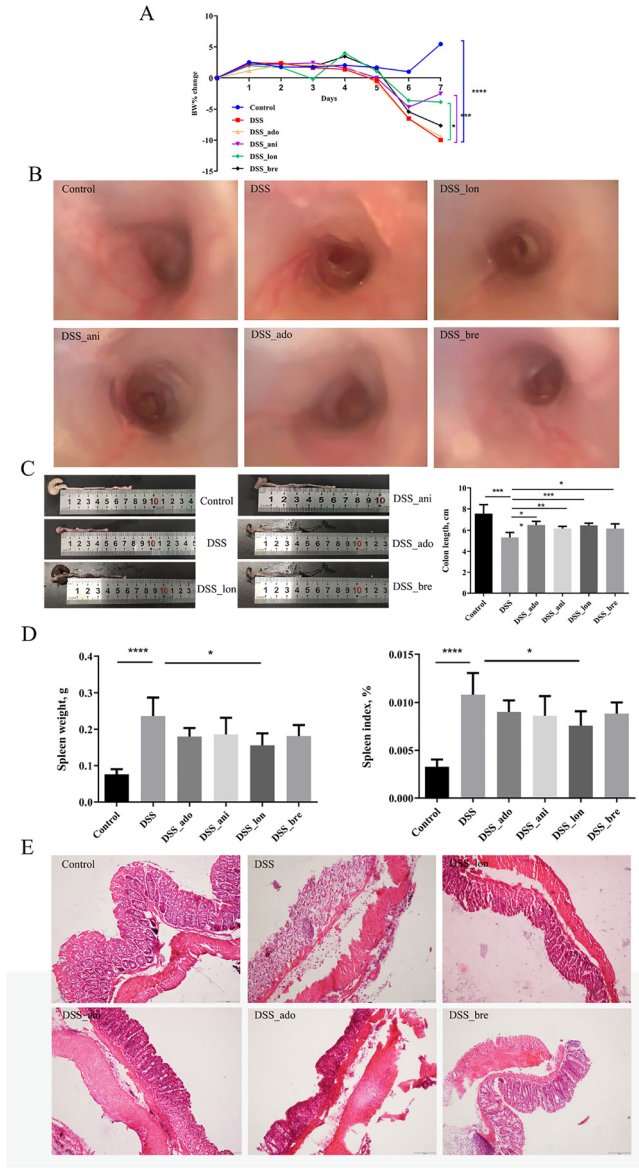

Fig. 1. Bifidobacteria supplementation attenuated disease activity in mice with acute enteritis
(A) body weight change; (B) colonoscopy; (C) colon length; (D) spleen weight and spleen index; (E) images of the colon morphology observed by microscopy after HE staining. *P* values were analysed by unpaired *t*-test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $^{****}P < 0.0001$, $n \geq 5$

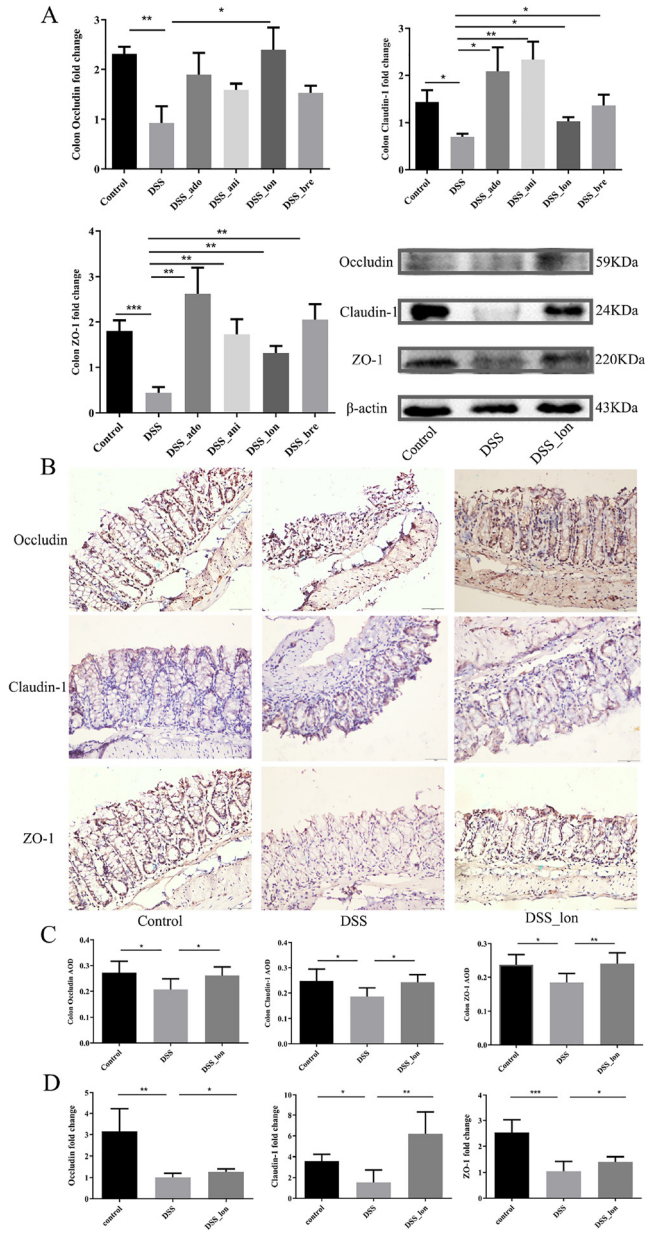

Fig. 2. Bifidobacteria supplementation prevented the loss of epithelium tight junction proteins in mice with acute enteritis

(A) the colonic expression of ZO-1, Occludin, and Claudin-1 examined by western blot; (B) expression levels of ZO-1, Occludin, and Claudin-1 by immunohistochemical evaluation; (C) AOD quantitative analysis of the expression levels of ZO-1, Occludin, and Claudin-1 in the colon by immunohistochemistry; (D) the colonic expression of ZO-1, Occludin, and Claudin-1 examined by RT-qPCR. *P* values were analysed by unpaired *t*-test. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, $n \geq 5$

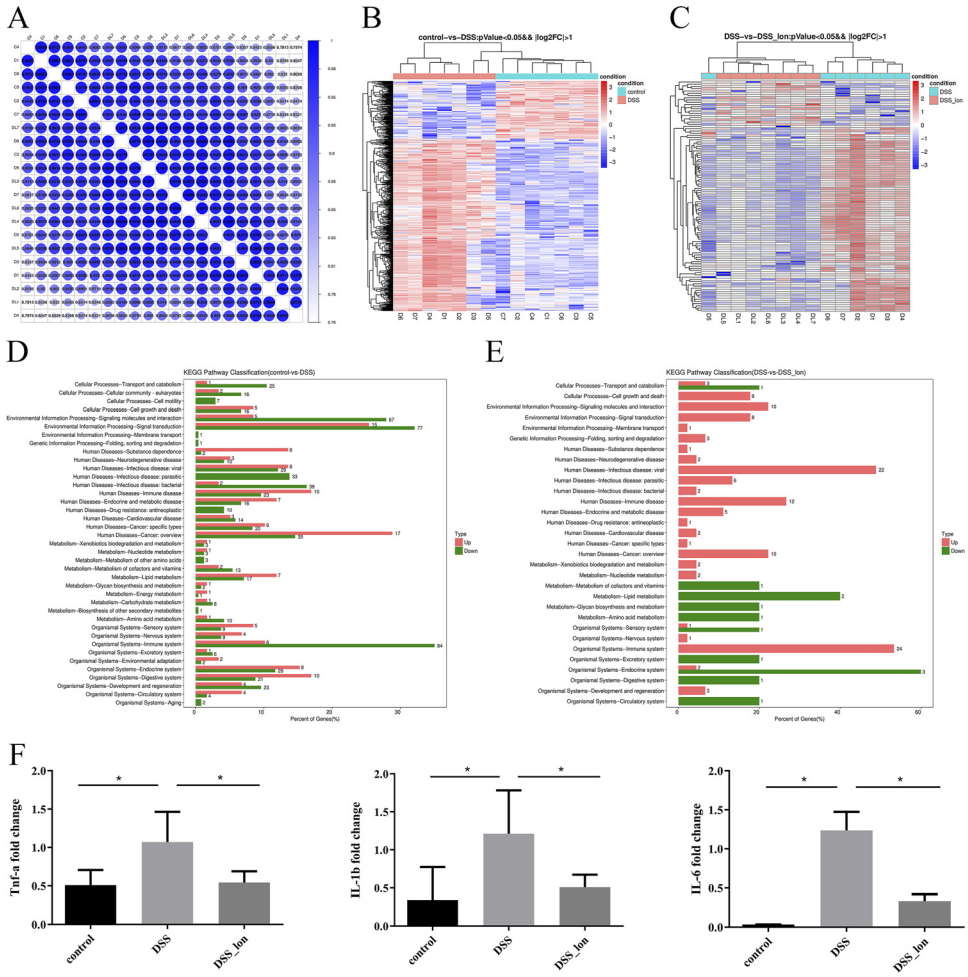

Fig. 3. Bifidobacterium longum supplementation altered the gene expression profile in mice with acute enteritis

(A) heatmap of correlation coefficient between samples. The colours represent the magnitude of the correlation coefficient; (B–C) cluster diagram of differential gene groupings, the red and blue, respectively, represent the protein encoding genes with relatively high expression and low expression; (D–E) KEGG Level2 distribution map of differently expressed genes. The numbers to the right of the column represent the number of differently expressed genes, and the red and blue, respectively, represent the genes with relatively high expression low expression; (F) the mRNA expression of TNF-α, IL-6, and IL-1b were examined by RT-qPCR. *P* values were analysed by unpaired *t*-test. $^{*}P < 0.05$, $n \geq 5$

such as TNF-α, IL-1b, and IL-6 significantly increased. The intervention of *B. longum* could effectively reduce the expression of corresponding factors and alleviate intestinal inflammation ($P < 0.05$).

Table 1. Relative expression of related genes in mouse colon tissue

Experimental comparison group	Group-DSS upregulation		Group-DSS downregulation	
	Gene	Relative value	Gene	Relative value
DSS vs Control	IL 17ra	0.023	IL 2	1.206
	IL 17re	0.041	IL4	0.416
	IL 13ra2	1.055	IL 5	2.025
	IL 18	1.126	IL 9r	0.710
	IL 6	3.177	IL 25	2.069
	IL 1a	2.982	IL4i1	0.499
	IL 1b	2.796	IL12a	0.448
	Tnf	1.287	IL 17rb	0.582
	Tnfaip2	1.278	IL18r1	0.484
	Tnfrsf9	1.695	IL 22ra2	0.644
			Tnfrsf13c	1.176
	Tnfsf9	1.124	Tnfrsf17	0.994
			Tnfrsf19	0.775
DSS vs DSS_lon	Tnf	0.866	IL 11	−0.095
	Tnfsf4	0.099	IL 10rb	−0.003
	Tnfrsf14	0.103		
	IL 1f8	0.460		
	IL 1b	0.403	Ifnar1	−0.021
	IL 1a	0.387		
	IL 1f9	0.370		
	IL 17b	0.271	IL 12a	−0.120
	IL 17d	0.104		
	IL 17f	0.091		
	IL 17ra	0.102	IL 2ra	0.360
	IL 17re	0.102		
	IL 18bp	0.896		
	Tnfaip8l1	0.160	IL 34	−0.082
	Tnfaip8l2	0.065		
	Tnfaip8l3	0.259		

3.4. Supplementation with bifidobacteria modulated the intestinal microbiota in mice with DSS-induced acute enteritis

No significant differences could be found in alpha diversity, but a significant separation of colonic microbes could be seen between the control group and DSS model group. The alpha diversity in the DSS_lon group significantly decreased and the microbial diversity between the DSS group and DSS_lon group showed a trend of separation without significant difference (Fig. 4 ABCD).

Further analysis was conducted to assess the differences at the taxonomic level of the intestinal microbiota among these groups (Fig. 4 EFGH). At the genus level, the relative abundance of *Dubosiella* spp. in the DSS-induced mice significantly increased after the intervention of *B. longum*. The results indicated that the intervention of *B. longum* was able to improve the intestinal microbiota disorder in mice with DSS-induced acute enteritis.

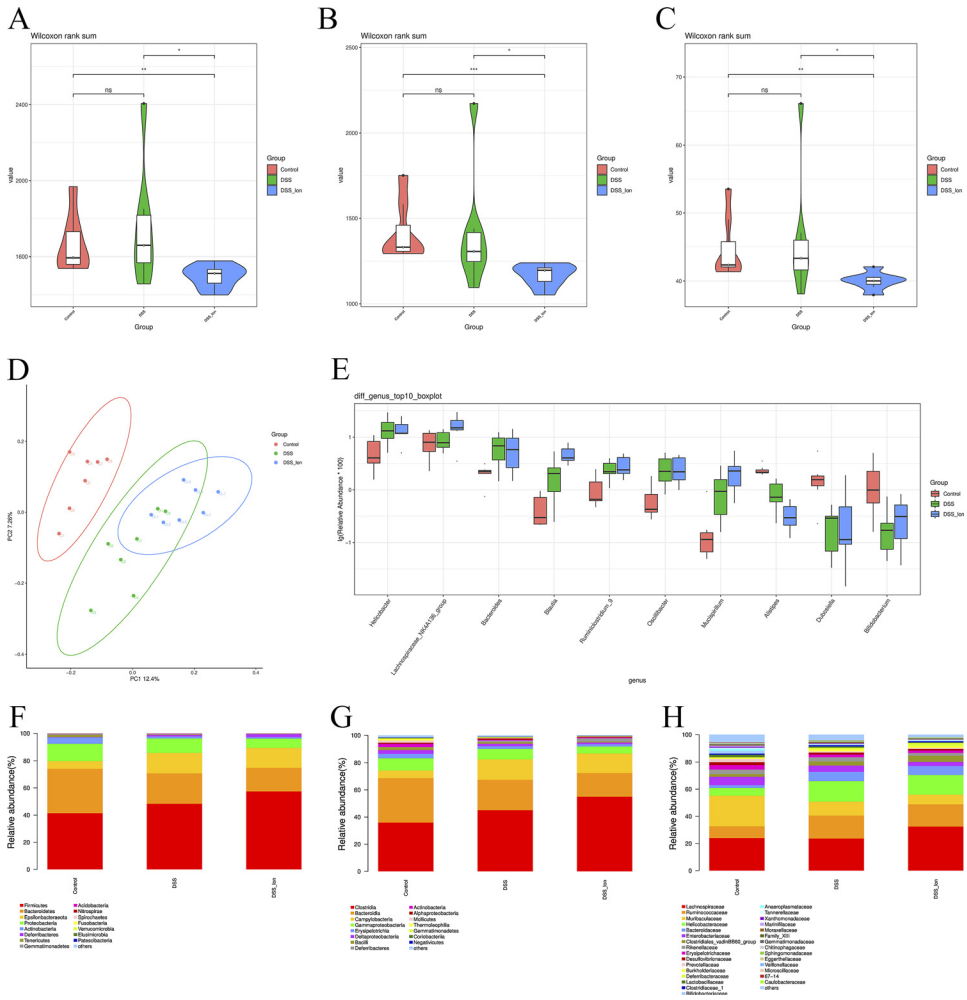

Fig. 4. Bifidobacterium longum supplementation modulated the gut microbiota in mice with acute enteritis
The microbial composition of colon mucosa was analysed by 16s rDNA sequencing in each group of mice (A–C) α-diversity analysis using the violin plot of OTU diversity index comparison between groups; (D) β-diversity analysis of PCoA; (E–G) bar charts of sample community structure at (E) phylum taxa of top-15, (F) class taxa of top-15, (G) family taxa of top-30; (H) Top-10 boxplot of the abundance of different genera

3.5. Discussion

As a classic inducer of acute enteritis, DSS is widely used in animal modelling (Eichele and Kharbanda, 2017). In this study, the mice with DSS-induced acute enteritis presented epithelial damage, the disruption of barrier function of the intestine, and alterations in the microbial balance.

As probiotics that often colonise the intestinal tract, species of *Bifidobacterium* and *Lactobacillus* account for about half of the intestinal microbiota (Benito et al., 2021). Bifidobacteria play a crucial role in maintaining intestinal health and immunological homeostasis (Shang et al., 2022). This study explored the efficacy of bifidobacteria (including *B. adolescentis*, *B. animalis*, *B. longum*, and *B. breve*) in alleviating DSS-induced acute enteritis in mice.

The treatment with bifidobacteria effectively improved the pathological features and alleviated colon inflammation in mice with acute enteritis (Chen et al., 2022; Cui et al., 2022; Wang et al., 2022). Moreover, bifidobacterial intervention significantly enhanced the expression of tight junction proteins (Occludin, Claudin-1 and ZO-1). *B. longum* proved to be the most efficacious in improving the integrity of the intestinal barrier (Kaur et al., 2021). The integrity of the intestinal barrier is vitally important for maintaining gut health and the characteristics of the barrier destruction are alterations in tight junction proteins (Oshitani et al., 2005).

In addition, bifidobacteria alleviated acute enteritis in mice by regulating the intestinal microbiota and attenuating the expression of inflammation factors. The relative abundance of *Dubosiella* spp. in the mice with DSS-induced acute enteritis significantly increased with the intervention of *Bifidobacterium longum*. *Dubosiella* spp. can also reduce the levels of IL-4, IL-5, IL-13, and IgG1, increase the proportion of Treg cells, and alleviate inflammation in the body (Hu et al., 2021). Thus, the results suggested that *Bifidobacterium longum* might alleviate the acute enteritis *via* modulating the abundance of *Dubosiella* spp., which needs to be further verified with metabolomics.

This study provided better understanding of bifidobacteria and their potentials in improving health conditions of mice with DSS-induced acute enteritis, and combining *B. longum* with other therapeutic approaches may be the focus of future researches.

4. CONCLUSIONS

This study demonstrated that bifidobacteria exerted a positive effect on preventing DSS-induced acute enteritis in mice, repairing parts of intestinal barrier function, relieving colon inflammation, and improving intestinal microbiota disorder. *B. longum* demonstrated superior efficacy in ameliorating DSS-induced acute enteritis in mice compared to *B. adolescentis*, *B. animalis* and *B. breve*. *B. longum* proved to be more efficient in recovering the expression of tight junction proteins than other *Bifidobacterium* species. The expression of pro-inflammatory factors was effectively reduced and intestinal inflammation was relieved with the intervention of *B. longum*. Additionally, *B. longum* could increase the relative abundance of intestinal microbiota and improve the intestinal microbiota disorder in mice with acute enteritis.

Conflict of interest: The authors declare that there is no conflict of interests.

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