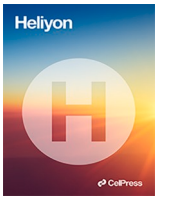
Heliyon 10 (2024) e30594

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Lycium barbarum polysaccharide remodels colon inflammatory microenvironment and improves gut health

Rong Li [a,1], Ping Yang [a,1], Bowen Liu [a], Ziru Ye [a], Puyue Zhang [a], Mingjian Li [a], Yanju Gong [b], Yong Huang [a,*], Lan Yang [b,**], Min Li [b,***]

[a] *School of Pharmacy, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, Sichuan, China*
[b] *School of Basic Medical Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu, 611137, Sichuan, China*

ARTICLE INFO

Keywords:
Polysaccharide
Colitis
Gut barrier
Intestinal microbiota
Bile acids
TGR5

ABSTRACT

Aim: Disturbed intestinal microbiota has been implicated in the inflammatory microenvironment of the colon, which usually results in ulcerative colitis (UC). Given the limitations of these drugs, it is important to explore alternative means of protecting the gut health from UC. This study aimed to investigate the potential of polysaccharides as beneficial nutrients in the regulation of the gut microbiota, which determines the inflammatory microenvironment of the colon.

Materials and methods: Mice were treated with dextran sulfate sodium (DSS) to evaluate the effects and mechanisms of *Lycium barbarum* polysaccharide (LBP) in remodeling the inflammatory microenvironment and improving gut health. Body weight and disease activity indices were monitored daily. Hematoxylin and eosin staining was used to analyze colon dynamics. The levels of inflammatory indicators and expression of MUC-2, claudin-1, ZO-1, and G-protein-coupled receptor 5 (TGR5) were determined using assay kits and immunohistochemistry, respectively. 16S rRNA high-throughput sequencing of the intestinal microbiota and liquid chromatography-tandem mass spectrometry for related bile acids were used.

Results: LBP significantly improved the colonic tissue structure by upregulating MUC-2, claudin-1, and ZO-1 protein expression. The bacterial genus *Dubosiella* was dominant in healthy mice, but significantly decreased in mice treated with DSS. LBP rehabilitated *Dubosiella* in the sick guts of DSS mice to a level close to that of healthy mice. The levels of other beneficial bacterial genera *Akkermansia* and *Bifidobacterium* were also increased, whereas those of the harmful bacterial genera *Turicibacter*, *Clostridium_sensu_stricto_1*, *Escherichia-Shigella*, and *Faecalibaculum* decreased. The activity of beneficial bacteria promoted the bile acids lithocholic and deoxycholic acids in mice with UC, which improved the gut barrier function through the upregulation of TGR5.

Conclusion: The inflammatory microenvironment in the gut is determined by the balance of the gut microbiota. LBP showed great potential as a beneficial nutrient for rehabilitating *Dubosiella* which is dominant in the gut of healthy mice. Nutrient-related LBP may play an important role in gut health management.

* Corresponding author.
** Corresponding author.
*** Corresponding author.
E-mail addresses: huangyong@cdutcm.edu.cn (Y. Huang), yanglan@cdutcm.edu.cn (L. Yang), 20152030@cdutcm.edu.cn (M. Li).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.heliyon.2024.e30594
Received 17 July 2023; Received in revised form 29 April 2024; Accepted 30 April 2024
Available online 9 May 2024

1. Introduction

Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is usually associated with chronic and spontaneous recurrent inflammation that begins in the rectum and progresses proximally to the colon, with ulceration and bloody diarrhea [1,2]. The etiology and pathogenesis of UC are not completely understood but most likely include genetic susceptibility, immune abnormalities, environmental factors, intestinal microbiota, and epithelial repair [3,4]. The side effects caused by long-term use of drugs to treat UC, including hypertension, diabetes, osteoporosis caused by steroids, and bone marrow suppression by mercaptopurine, have attracted widespread attention as safer and more convenient alternatives [5,6].

Lycium barbarum, a *L. barbarum* L. fruit, is a traditional herb in China that has served as a food medicine for more than 2500 years. *L. barbarum* has been used in traditional Chinese medicine for its ability to nurture the liver, improve blurred vision, relieve headaches, and alleviate abdominal pain [7]. Studies have demonstrated that *L ycium barbarum* polysaccharide (LBP) possesses multiple preventive and ameliorative effects, including antioxidant, anticancer, lipid-lowering, and lung lesion reduction [8–10]. Studies have shown that LBP has anti-inflammatory effects. For instance, LBP enhances the gut barrier function and suppresses gut inflammation by acting on the MLCK-MLC pathway [11]. Although LBP has been found to relieve intestinal inflammation, the pathogenesis of UC is complicated and the mechanism of LBP efficacy in UC has not been entirely elucidated. Further studies are required to investigate the mechanistic effects of LBP on the amelioration of UC.

Barrier function and gut microbiota have a profound impact on the initiation and development of UC [12]. The gut barrier protects the host against unfriendly intestinal microbiota and metabolic toxins present in the intestinal tract [13]. It is formed by a goblet cell-produced mucus layer and epithelial tight junctions that constitute a thick mucus barrier and maintain gut epithelial integrity, respectively [14,15]. Unbalanced intestinal microbiota induces inflammation, reduces gut mucosal barrier function, increases bacterial translocation, and destroys the structural barrier by altering intestinal tight junction proteins [16,17].

Furthermore, dysbiosis of the intestinal microbiota induces abnormal alterations in metabolic products, such as bile acids (BAs), which further worsen UC [18]. In terms of BAs, although a large proportion of primary BAs are absorbed through the terminal ileum into the liver, some BAs enter the colon and are transformed by the intestinal microbiota into secondary BAs [19]. Previous studies have found that BAs such as lithocholic acid (LCA) and deoxycholic acid (DCA) partly mitigate gut inflammation through G-protein-coupled receptor 5 (TGR5) [20]. LCA and DCA activate TGR5 to promote intestinal epithelial regeneration following injury, thereby improving the gut [21].

We hypothesized that the ameliorative effect of LBP on UC occurs through the regulation of the intestinal microbiota as well as BA metabolism, thereby enhancing the gut barrier. Thus, a UC model was created using dextran sulfate sodium (DSS) to explore the regulatory action of LBP on intestinal microbiota and BAs.

2. Materials and methods

2.1. Materials and reagents

DSS (36–50 kDa) was purchased from MP Biomedicals (Canada). Mesalazine was obtained from Sunflower Pharmaceutical Group Co. Ltd. (Heilongjiang, China). The crude extract of LBP was obtained from Yikangtang Pharmaceutical Co., Ltd. (Chengdu, China). Antibodies against MUC-2 (27675-1-AP) and claudin-1 (28674-1-AP) were purchased from Proteintech (Wuhan, China). Antibodies against ZO-1 (AF5145) and TGR5 (DF14067) were purchased from Affinity Biosciences (Jiangsu, China). Enzyme-linked immune sorbent assay (ELISA) kits based on IL-1β, IL-6, TNF-α, and lipopolysaccharides (LPS) were supplied by Meimian (Jiangsu, China). A myeloperoxidase (MPO) activity assay kit was obtained from Nanjing Jiancheng Bioengineering Institute (Nanjing, China). Chemicals and reagents were provided by Chron Chemicals (Chengdu, China).

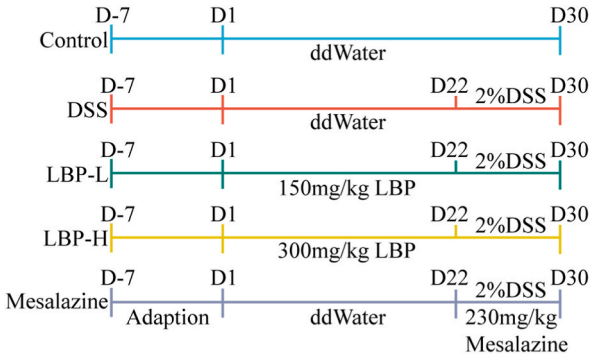


Fig. 1. Design of animal studies. Mice were given LBP preventively for 22 days after one week of adaptive feeding. UC model was induced with 2 % DSS starting on day 22 with concurrent LBP administration. LBP: *Lycium barbarum* polysaccharide; DSS: dextran sulfate sodium.

2.2. Animal experiment

A total of 30 C57BL/6 male mice (6–8 weeks old, 18–22 g) were obtained from Chengdu Dashuo Co., Ltd. (Sichuan, China). Mice were dieted in an animal laboratory at 20–25 °C with sufficient food and water. Mice were assigned to control, DSS, low-dose LBP (LBP-L), high-dose LBP (LBP-H), and mesalazine groups (n = 6 mice per group). According to the animal experimental plan referenced in the literature with appropriate adjustments [22,23], from days 1–30, mice in the control and DSS groups received water daily by gastric lavage, whereas mice in the LBP-L and LBP-H groups were administered 150 and 300 mg/kg LBP daily, respectively (Fig. 1). The mesalazine group received water daily from days 1–21 and 230 mg/kg mesalazine once daily from days 22–30. A 2 % (w/v) DSS solution was used to induce UC from days 22–30. Mesalazine was used as a positive control. The animals were euthanized on day 31 after stool and blood sample collection. Colon samples and colon contents were harvested and immediately frozen at −80 °C for future use.

2.3. Disease activity index

Individual mice from the five groups were weighed weekly during the first three weeks and every day for the following nine days when DSS was added. Rectal bleeding and stool consistency of these mice were monitored daily for the last nine days. The disease activity index (DAI) was assessed following previous literature [24].

2.4. Hematoxylin and eosin staining

Colon samples were immersed overnight in 4 % (v/v) paraformaldehyde. Immersed colons were subsequently dewatered, paraffin-embedded and cut into 5-μm thick slices. The sections were processed for hematoxylin and eosin (H&E) staining, covered with neutral gum, and examined under a microscope.

2.5. Measurement of pro-inflammatory cytokines and LPS and MPO content

Pro-inflammatory cytokines, including IL-1β, IL-6, and TNF-α in colon tissues as well as in the serum were detected among the five groups using ELISA kits, following the manufacturer's instructions. The concentration of LPS in the serum samples was examined using a mouse LPS assay kit, following the manufacturer's instructions. Colon tissues were homogenized in PBS buffer, and total protein was determined using a BCA kit. The serum was separated via 20 min centrifugation at 3000 rpm. MPO levels in colon samples were determined according to the manufacturer's protocol.

2.6. Immunohistochemical analysis

The mucosal layer protein, MUC-2, and proteins associated with tight junctions, including claudin-1 and ZO-1, were evaluated in the colon using immunohistochemistry. These proteins negatively correlated with UC [25,26]. In addition, the expression level of the BA receptor TGR5 in the colon was measured using immunohistochemical analysis. The antigens were repaired using buffered sodium citrate (pH 6.0). Peroxidase enzymes were blocked with 3 % hydroperoxide. The sections were then incubated with appropriate primary antibodies and secondary antibodies conjugated to HRP successively. Protein expression was visualized using DAB chromogenic solution. Images of sections were obtained using an optical microscope.

2.7. 16S rRNA sequencing of intestinal microbiota

The intestinal microbiota analysis of mouse colon content samples was performed at Majorbio Bio-Pham Technology Co., Ltd. (Shanghai, China). Total DNA was extracted from mouse colon samples using a DNA extraction kit. Following concentration and purity analyses, the DNA was frozen at −80 °C and used as the template for amplification via PCR. The 16S rRNA hypervariable region, V3–V4, was amplified by PCR using a set of 338F-806R primers. The PCR products were recovered, purified, quantified, and sequenced. Quality control, splicing, clustering, and classification of the original sequences were performed. Raw data were deposited in the Sequence Read Archive (SRA) database of NCBI (BioProject ID: PRJNA958471) and analyzed online on the Majorbio Cloud Platform (www.majorbio.com).

2.8. Fecal BA measurement

Briefly, fecal samples (20 mg) were homogenized with 200 μL methanol/acetonitrile (v/v = 2:8) and 10 μL internal standard mixed solution (1 μg/mL). The extracts were placed at −20 °C to precipitate protein for 10 min. The supernatant was collected by centrifugation (12,000 rpm, 4 °C) for 10 min, dried by evaporation, and redissolved with 100 μL 50 % methanol (v/v) for subsequent LC-MS detection. The temperature of the column was 40 °C and the ESI source temperature was 550 °C. BAs were analyzed using multiple reaction monitoring and quantitation was performed according to their respective standard curves.

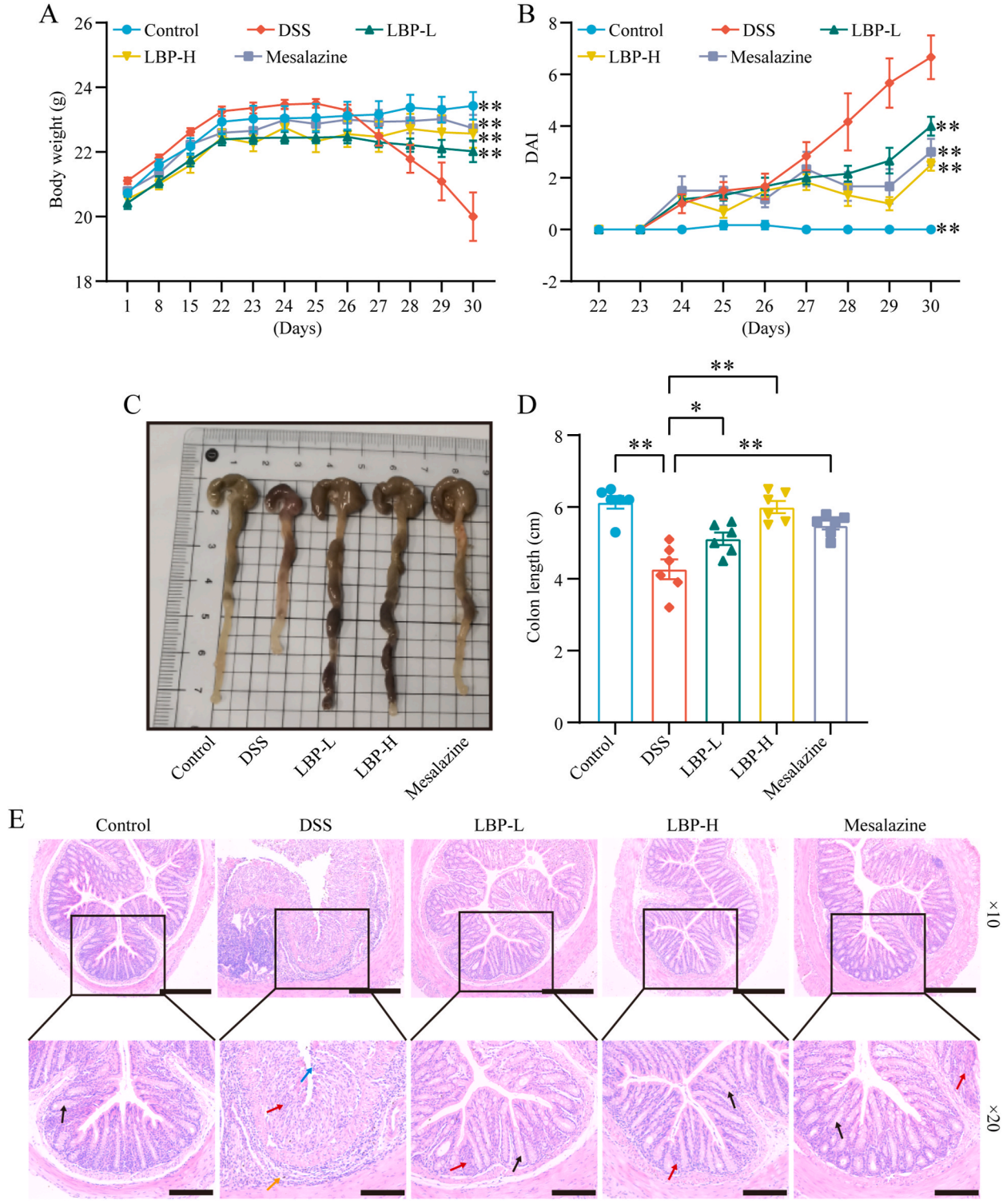
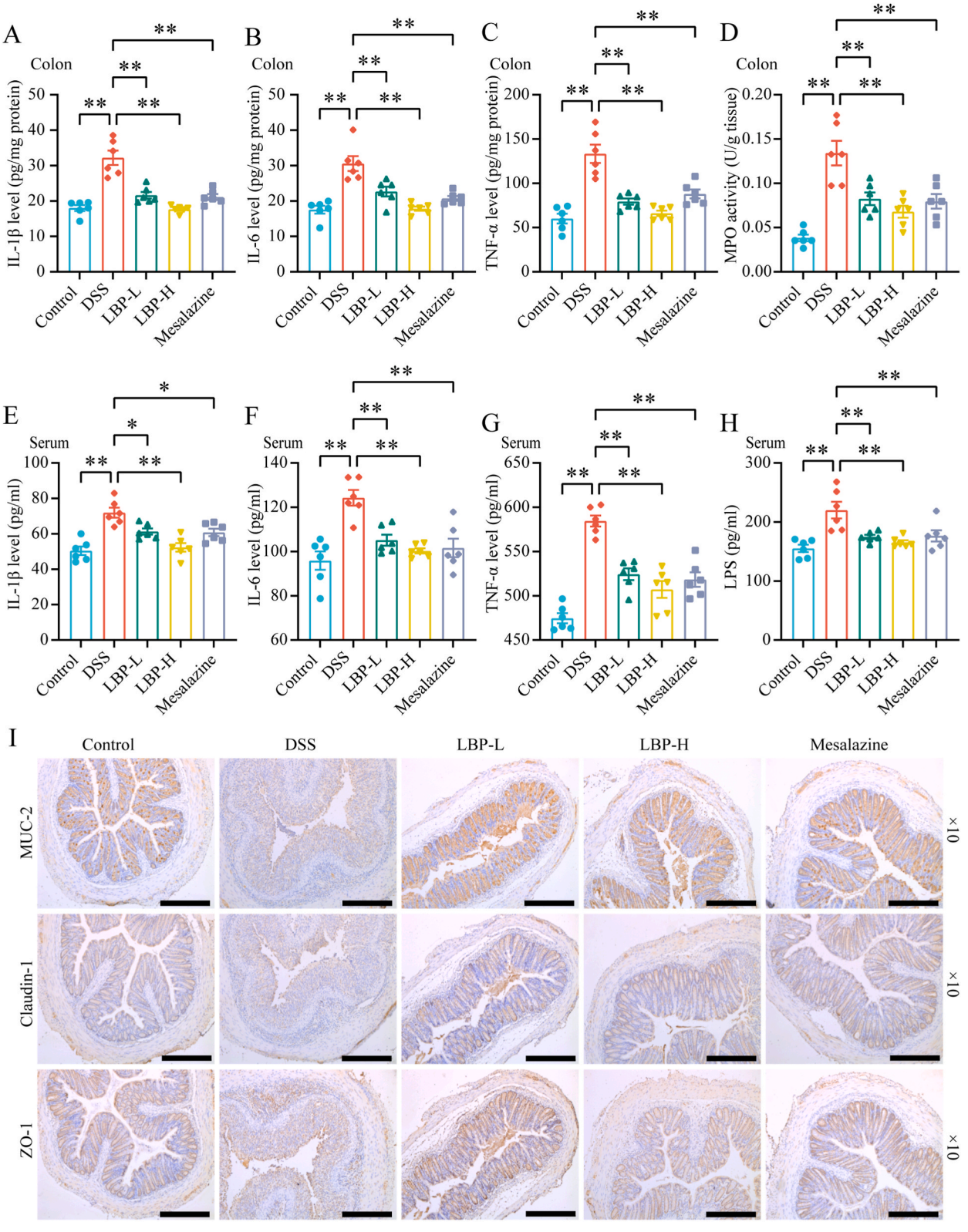


Fig. 2. LBP alleviated UC symptoms. (A) Body weight comparison. (B) DAI. (C) Macroscopic pictures of colons. (D) Colon length comparison. (E) H&E stains of colon sections with scale bars of 50 μm (× 10) and 20 μm (× 20). Blue arrow denotes surface epithelial erosion, black arrows denote crypt structure, red arrows denote inflammatory cell infiltration, and yellow arrow denotes submucosal edema. Data are shown as mean ± SEM (n = 6). One-way and two-way ANOVA was performed to assess statistically significant differences. Body weight and DAI analysis were performed with two-way ANOVA and others with one-way ANOVA. *p ≤ 0.05 and **p ≤ 0.01 compared to DSS group. LBP: *Lycium barbarum* polysaccharide; DAI: disease activity index; UC: ulcerative colitis; DSS: dextran sulfate sodium



(caption on next page)

Fig. 3. LBP inhibited production of inflammation-related indicators and improved gut barrier function. (A–C) IL-1β, IL-6, and TNF-α levels among colon tissues. (D) MPO levels in colon tissues. (E–G) IL-1β, IL-6, and TNF-α levels in serum. (H) LPS levels in serum. (I) Immunohistochemical analysis of gut barrier-associated proteins MUC-2, claudin-1, and ZO-1 with scale bar of 50 μm (× 10). Data are shown as mean ± SEM (n = 6). One-way ANOVA was performed to assess statistically significant differences. *p ≤ 0.05 and **p ≤ 0.01. LBP: *Lycium barbarum* polysaccharide; MPO: myeloperoxidase.

2.9. Statistical analysis

One-way and two-way analysis of variance (ANOVA) were performed using GraphPad Prism software (version 9.0). Data were displayed as mean ± standard error of the mean (SEM). Statistical significance was set at $p < 0.05$.

3. Results

3.1. LBP significantly reduced inflammatory symptoms in mice with UC

The efficacy of LBP in mice with UC was investigated. DSS induces obvious clinical characteristics of UC in humans, including decreased body weight, diarrhea, and bloody stools. In the DSS group, the body weight of the mice was remarkably lower than that in

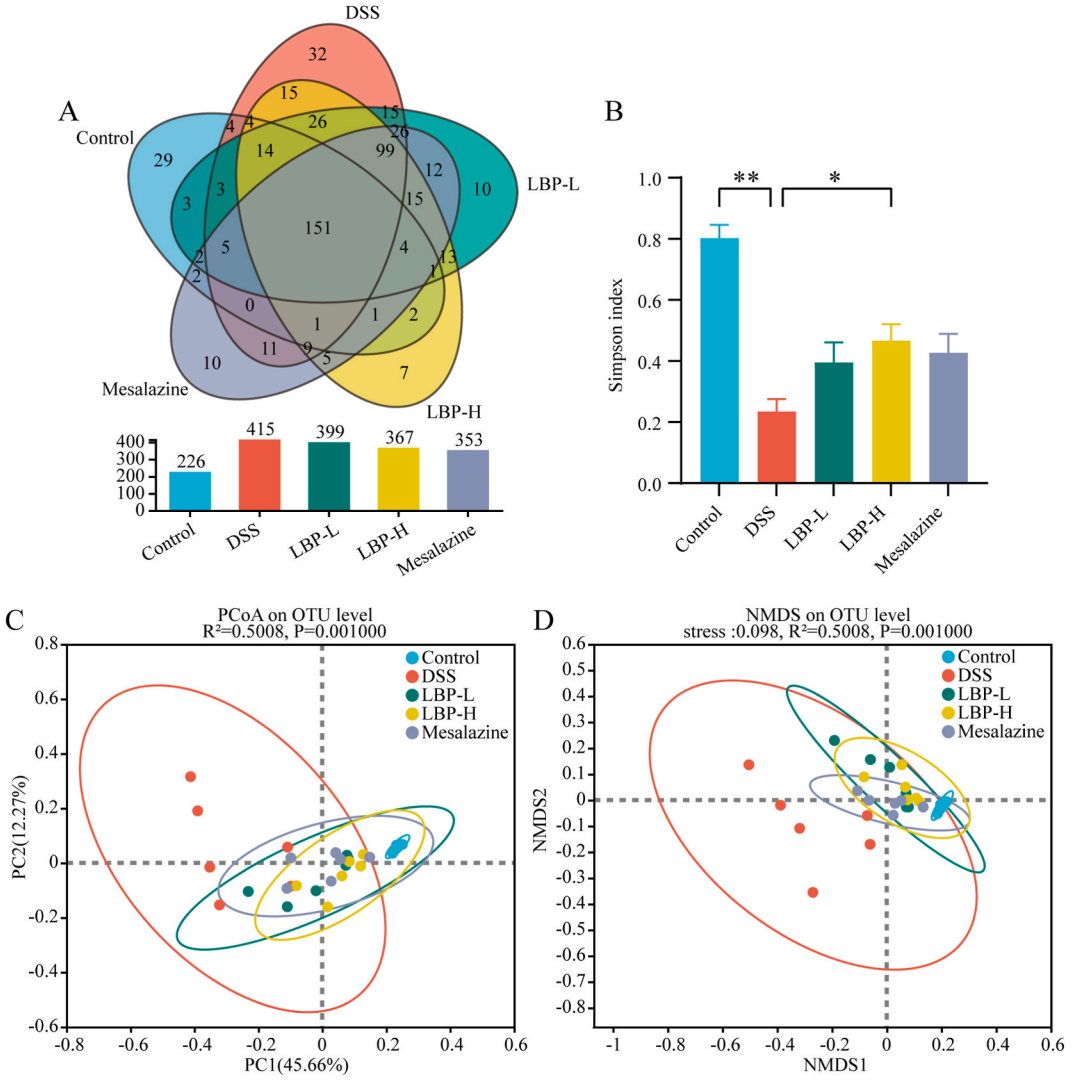


Fig. 4. Analysis of 16S rRNA of microbiota in colon contents on OTU level and alpha and beta diversities. (A) Analysis of Venn diagram among the five groups. (B) Simpson index analysis of alpha diversity. (C) PCoA analysis. (D) NMDS analysis. Data are shown as mean ± SEM (n = 6). One-way ANOVA was performed to assess statistically significant differences. *p ≤ 0.05 and **p ≤ 0.01. OTU: operational taxonomic unit.

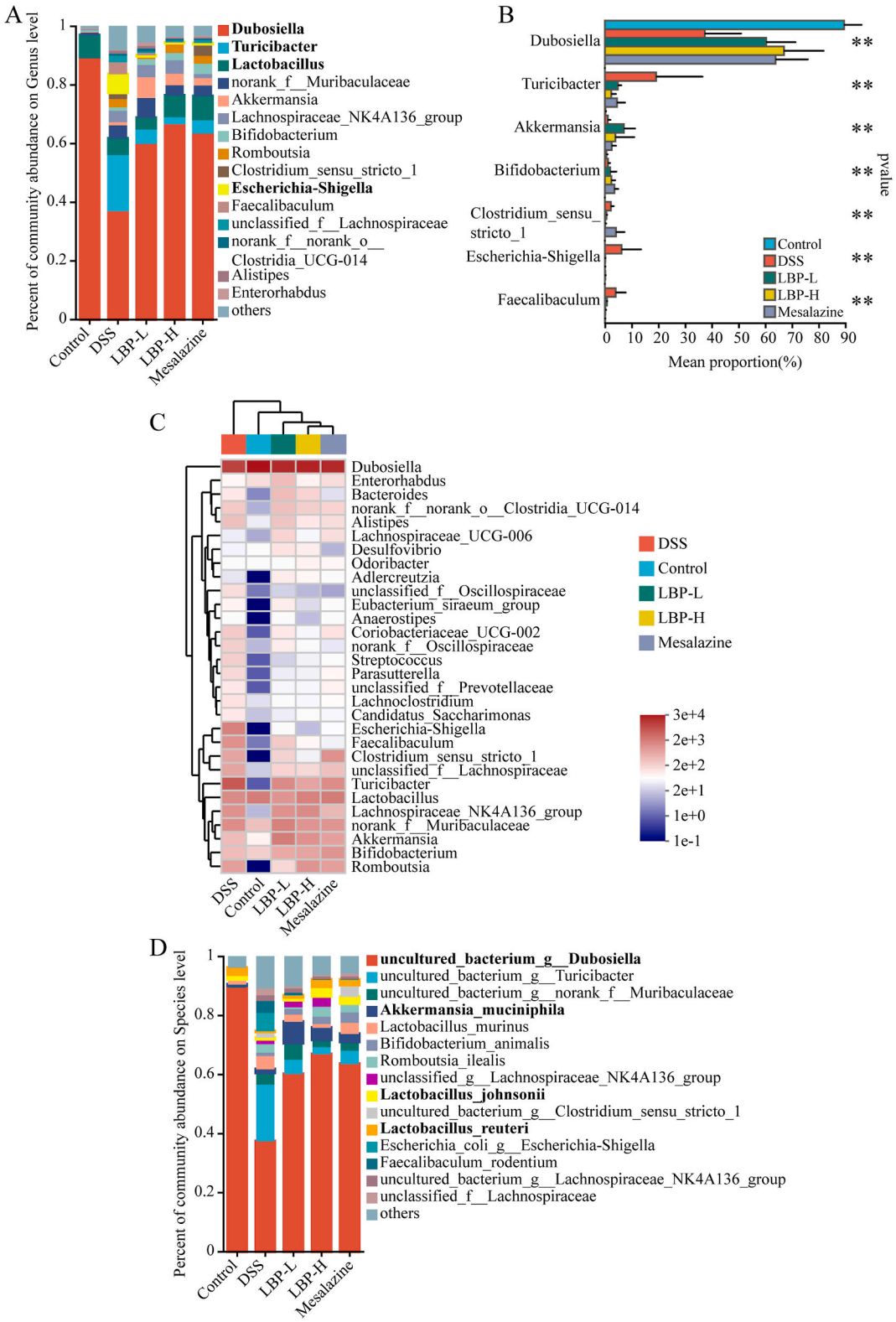


Fig. 5. Analysis of intestinal microbial community compositions. (A) Alteration of microbial composition at genus level. (B) Significantly altered bacteria at genus level. (C) Heatmap of top 30 genera in community. (D) Alteration in microbial composition at species level. Kruskal-Wallis H test was performed to assess statistically significant differences. **$p \leq 0.01$.

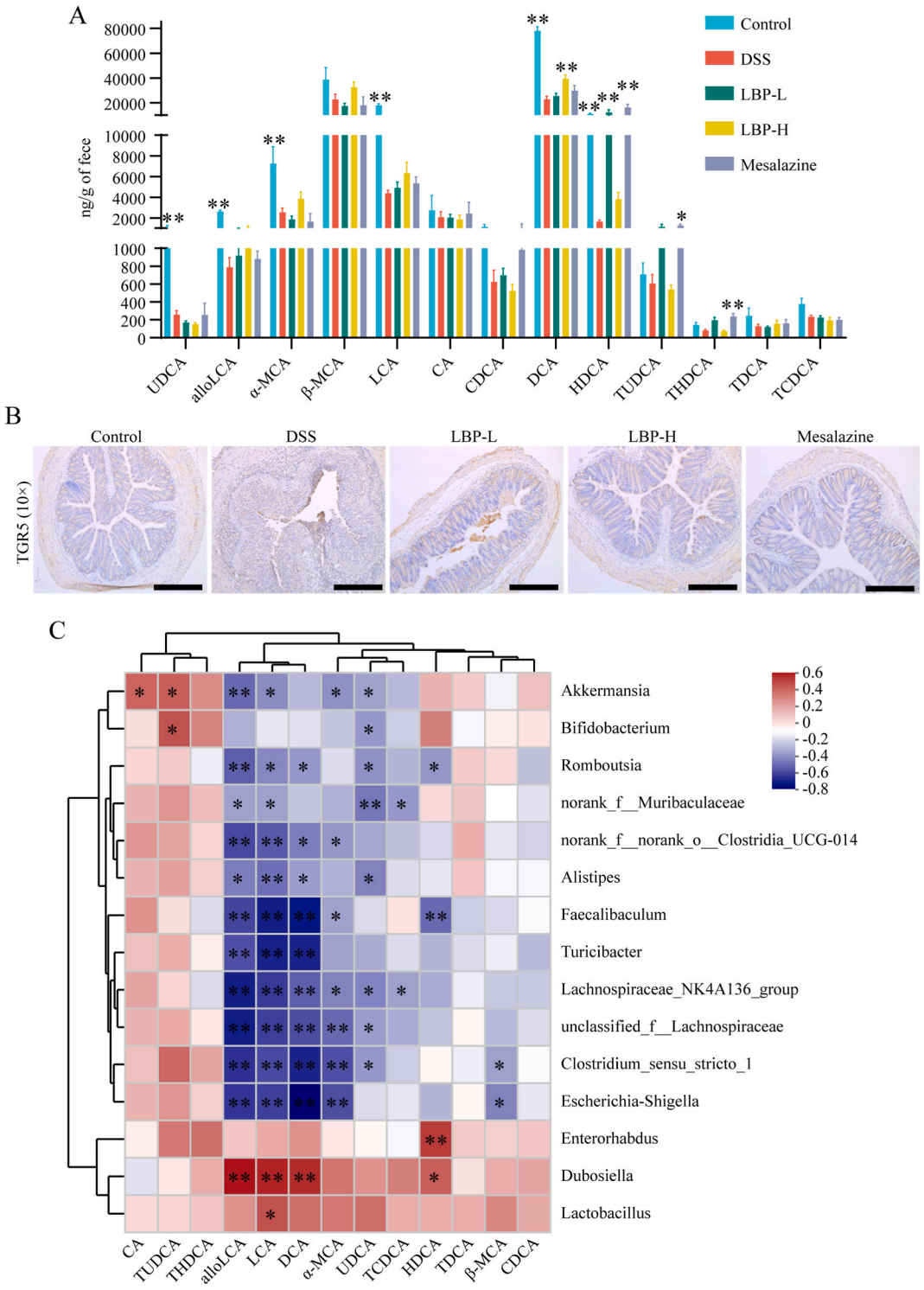


Fig. 6. LBP improved BA dysmetabolism in mice with UC. (A) Content of BAs in the five groups. Data are shown as mean ± SEM (n = 6). One-way ANOVA was performed to assess statistically significant differences. *p ≤ 0.05 and **p ≤ 0.01 compared to DSS group. (B) Expression of BAs related to TGR5 in colon tissue with scale bar of 50 μm (× 10). (C) Correlation of spearman between fecal BAs and intestinal microbiota. Red indicates positive correlation and blue indicates negative correlation. Color intensity is proportionally related to spearman correlation strength. *p ≤ 0.05 and **p ≤ 0.01. LBP: *Lycium barbarum* polysaccharide; BA: bile acid; DSS: dextran sulfate sodium; TGR5: G-protein-coupled receptor 5

the control group; however, both LBP-L and LBP-H significantly attenuated body weight loss (Fig. 2A). The DAI was considerably higher in the DSS group compared to the control group (Fig. 2B). LBP-L and LBP-H had a significant effect on UC with mild diarrhea and bloody stools compared to the DSS group. The colon was cut short due to UC, and LBP-L and LBP-H reversed the adverse effects on colon length in mice with UC (Fig. 2C and D). LBP-H showed better efficacy than LBP-L in alleviating the symptoms of weight loss, increasing the DAI, and shortening the colon caused by UC. The colon structure in the DSS group was severely disrupted with surface epithelial erosion, crypt destruction, inflammatory cell infiltration, and submucosal edema (Fig. 2E). LBP-L and LBP-H alleviate structural disruption in mice with UC.

3.2. LBP attenuated colon damage by suppressing production of inflammatory indicators and upregulating mucin and tight junction proteins

Inflammation-related indicators were examined in colon tissue and serum samples. The pro-inflammatory cytokines IL-1β, IL-6, and TNF-α were remarkably raised in the DSS group compared to the control group (Fig. 3A–C). However, treatment with LBP-L and LBP-H significantly reversed this effect. MPO marks tissue damage and neutrophilic inflammation, and indicates the degree of intestinal inflammation [27]. MPO content in the DSS group was substantially elevated compared to that in the control group, while LBP-L and LBP-H reduced its expression (Fig. 3D). Pro-inflammatory cytokines levels were determined together with LPS levels in the serum (Fig. 3E–H). In addition, the levels of these indicators were considerably higher in the DSS group compared to the control group. In contrast to those in the DSS group, the levels of LBP-L and LBP-H were significantly reduced. The results of inflammation-related indicators showed that LBP-H reduced the levels of these indicators to a greater extent than LBP-L and showed a superior anti-inflammatory effect (Fig. 3A–H). LBP was further evaluated on the barrier function of intestinal epithelial cells, as indicated by the mucosal layer protein MUC-2 and tight junction proteins claudin-1 and ZO-1 (Fig. 3I). The levels of MUC-2, claudin-1, and ZO-1 in the colonic epithelial tissues were lower in the DSS group than those in the control group. However, these proteins showed higher expression levels in the LBP group than in the DSS group. These findings suggest that LBP can inhibit inflammatory indicators to reduce UC and reverse the reduction in gut barrier function in mice with UC.

3.3. LBP regulated intestinal microbiota composition

3.3.1. LBP changed microbiota at operational taxonomic unit level and diversity

We identified the intestinal microbiota structures of all groups based on the variable regions V3–V4 by sequencing the 16S rRNA genes. The Venn diagram revealed that 151 unique operational taxonomic units (OTUs) were shared among the five groups (Fig. 4A). In the control group, 226 OTUs were identified: 415 in the DSS group, 399 in the LBP-L group, 367 in the LBP-H group, and 353 in the mesalazine group. The microbial diversity in the DSS group differed from that in the control and LBP-H groups (Fig. 4B). The overall microbial community structure similarity was analyzed using beta diversity. The results of PCoA and NMDS based on the Bray-Curtis analysis demonstrated that the microbial community structure of the DSS group was different from that of the control group (Fig. 4C and D). Compared to the DSS group, the structure of the microbial community in the LBP-L and LBP-H groups was more similar to that of the control group.

3.3.2. LBP influenced microbial community compositions of the gut

The relative abundance of the intestinal microbiota was investigated. The abundance of the top 15 species among all experimental groups is shown (Fig. 5A). *Turicibacter* and *Escherichia-Shigella* were undetectable in the control group. *Dubosiella* levels decreased but those for *Turicibacter* and *Escherichia-Shigella* increased in the DSS group. The microbiota in mice with UC that were treated with LBP-L and LBP-H were brought towards that presented in the control group. LBP-H also elevated *Lactobacillus* levels in mice with UC. *Dubosiella* levels were high in the control group and recovered after the administration of LBP, and LBP-H recovered its abundance to a greater extent than LBP-L. The bacteria that were significantly altered at the genus level in the five groups are shown (Fig. 5B). In addition to the genera that varied significantly among the five groups, the enrichment of *Clostridium_sensu_stricto_1* and *Faecalibaculum* was elevated in the DSS group compared to the control group. Both LBP-L and LBP-H increased *Akkermansia* and *Bifidobacterium* richness and reduced *Clostridium_sensu_stricto_1* and *Faecalibaculum* abundance compared to the DSS group. The heatmap shows the gut bacterial composition of the top 30 genera in terms of total abundance on genus level (Fig. 5C). The dominant bacterial genera in the DSS group differed from those in the control group. The dominant bacteria in the LBP-L and LBP-H groups were similar to those in the control group, indicating that LBP may affect the intestinal microbiota richness of mice with UC to restore UC-induced intestinal microbiota imbalance. The community compositions of the five groups at the species level are shown (Fig. 5D). The *uncultured_bacterium_g_Dubosiella*, belonging to the genus *Dubosiella* and showing the highest variation in abundance among the five groups, was not annotated because it could not be cultured. Some specific bacterial strains in the DSS group were found to be less abundant than those in the control group, including *Lactobacillus_johnsonii* and *Lactobacillus_reuteri* but were increased in the LBP-H group. Administration of LBP increased the abundance of the *Akkermansia_muciniphila*.

3.4. Effect of LBP on BA metabolism

Since dysbiosis of BAs promotes intestinal inflammation [20], we further analyzed the effect of LBP on BA metabolism and its association with the intestinal microbiota. In the present study, 13 BAs were identified in the fecal samples from the five groups (Fig. 6A). The levels of most BA metabolites were higher in the LBP-L and/or LBP-H groups than in the DSS group. Notably, the contents of LCA and DCA, the natural ligands of TGR5, were diminished in the DSS group compared to the control group, whereas

LBP-H slightly elevated the LCA content and significantly increased DCA. TGR5 expression in the DSS group was lower than that in the control group (Fig. 6B). However, it was upregulated after LBP treatment. Spearman's correlation analysis was performed on fecal BA and intestinal microbiota genera to explore the relationship between unbalanced fecal BA metabolism and intestinal microbiota dysbiosis during UC (Fig. 6C). We found that LCA and DCA positively correlated with *Dubosiella* and *Lactobacillus*, and negatively correlated with *Faecalibaculum*, *Turicibacter*, *Clostridium_sensu_stricto_1*, and *Escherichia-Shigella*. These results suggest that LBP ameliorates UC-induced BA imbalance and upregulates TGR5 expression.

4. Discussion

UC is an IBD with clinical manifestations such as recurrent bellyache, abdominal diarrhea, and blood in the stool. Over the past few years, the global prevalence of UC has increased rapidly [28,29]. Because UC is characterized by prolonged progression and easy recurrence, it often affects the lives of patients and increases the risk of colorectal cancer [30]. Only a few specific drugs are available for UC treatment. The approaches include innovative drugs to break the inflammatory cycle, promote epithelial barrier repair, and restore gut microbial homeostasis, such as FMT [31,32]. Mesalazine is a conventional drug recognized for its therapeutic effects on UC so was used as a positive control in the current study.

Natural compounds have received considerable attention for their ability to alleviate inflammatory diseases because of their low toxicity and efficacy. LBP was found to ameliorate inflammatory diseases. LBP extract significantly reduced the expression of inflammatory mediators and matrix metalloproteinases in type II collagen-induced arthritis, maintained bone integrity, and attenuated arthritis in mice [33]. LBP inhibits liver inflammation by modulating intestinal bacterial homeostasis, reducing intestinal permeability, and decreasing LPS [34]. Additionally, LBP regulates immunity and improves overall health. Because of the remarkable potency of LBP with few side effects, its function as an alternative for UC amelioration is worth investigating.

In the present study, we assessed the effects of LBP on UC. We estimated the efficacy of LBP in the remission of UC, improvement of gut barrier integrity, and modulation of the intestinal microbiota and BAs metabolic products. LBP showed a remarkable effect in recovering disruptions in mice with UC. LBP reversed body weight loss in mice with UC. The decrease in DAI, increase in colon length, and protection of the colon structure resulting from LBP were similar to those observed with mesalazine. The pro-inflammatory cytokines IL-1β, IL-6, and TNF-α have been frequently detected and related to inflammation severity in UC [35]. In the current study, their concentrations increased dramatically in the DSS group. LBP significantly reduced the MPO and LPS levels. These results indicate that LBP-H was more effective than LBP-L. This suggests that LBP ameliorates UC by mitigating inflammatory symptoms and inhibiting proinflammatory cytokines.

Intestinal microbiota is vital for the well-being of the host and is involved in UC progression [36–38]. UC is associated with intestinal microbiota [39]. The Simpson index results showed that LBP reversed changes in intestinal microbiota diversity among mice with UC, making them more similar to healthy mice. PCoA and NMDS analyses revealed that LBP restored the intestinal bacterial community disturbed by UC to healthy communities, as in the control group. Both LBP and mesalazine ameliorated intestinal microbiota dysbiosis in mice with UC. Notably, PCoA and intestinal microbiota composition analyses showed similarities in the intestinal microbiota composition and structure between the LBP and mesalazine groups. We speculate that LBP and mesalazine have similar alleviative effects on the intestinal microbiota in mice with UC.

The present study showed that *Turicibacter*, *Clostridium_sensu_stricto_1*, *Escherichia-Shigella*, and *Faecalibaculum* were significantly elevated in the DSS group versus the control group. *Turicibacter*, *Clostridium_sensu_stricto_1*, and *Escherichia-Shigella* are usually linked to UC and belong to opportunistic pathogens that increase in the intestine of mice with colitis [40–43]. *Faecalibaculum*, which are considered harmful bacteria, is negatively correlated with the production of beneficial metabolites in the intestine [44]. Both LBP-L and LBP-H considerably lowered the abundance of these genera, which became closer to that of the control group. Meanwhile, the genera *Akkermansia* and *Bifidobacterium* were increased in the LBP-L and LBP-H groups and have been reported to be beneficial for intestinal health [45,46]. *Akkermansia_muciniphila*, *Lactobacillus_johnsonii*, and *Lactobacillus_reuteri* have been isolated and shown to have good anti-inflammatory effects in the treatment of UC [47–50]. *Akkermansia_muciniphila* stimulates mucin production and improves the gut barrier function to alleviate inflammation [51]. These bacteria were abundant after LBP administration in mice with UC, which may explain the significant effects of LBP on UC remission.

In particular, *Dubosiella* was dominant in the guts of healthy mice, with the most prominent alterations in abundance among all groups. *Dubosiella* has been reported to dramatically decrease in abundance in a mouse model of UC, and may play a role in reducing colitis [52]. As a beneficial bacterial genus, it is negatively correlated with the level of inflammation in UC and protects against UC [53,54]. Few studies have reported the biological properties and effects of *Dubosiella* [55]. The exact mechanism underlying *Dubosiella* in UC is even less clear, partly because this genus cannot be cultured and isolated; therefore, further *in vivo* experiments have not been performed to verify this. The effect of *Dubosiella* on UC requires further exploration. In this study, both LBP-L and LBP-H significantly restored the abundance of *Dubosiella* in mice with UC, and LBP-H was more potent, suggesting that the role of changes in the abundance of *Dubosiella* in improving UC via LBP is attractive.

Celery soluble dietary fiber antagonizing flavonoids could alleviate DSS-induced colitis in mice by reducing the abundance of the harmful bacterial genera *Escherichia-Shigella* and *Clostridium_sensu_stricto_1* while promoting the colonization of the beneficial bacterial genus *Akkermansia* in the gut [56]. In addition, *Atractylodes macrocephala* Koidz. volatile oil ameliorates UC by increasing *Akkermansia* and decreasing the pathogenic bacterial genus *Turicibacter* [57]. In our study, LBP could also alleviate UC by modulating intestinal bacteria, reducing the colonization of the *Escherichia-Shigella*, *Clostridium_sensu_stricto_1*, and *Turicibacter* while promoting the colonization of *Akkermansia*, which is consistent with the literature. Notably, the modulation of *Dubosiella*, a potentially beneficial intestinal bacterial genus, by LBP was the most obvious and unique finding in this study, and further mechanisms regarding the

improvement of UC by LBP through such modulation deserve to be investigated more thoroughly. The significant modulation of *Dubosiella* by LBP was similar to that of mesalazine, which is recognized as an effective drug for the treatment of UC, suggesting that LBP has a remarkable ameliorative effect against UC. Other polysaccharides, such as Crataegus pinnatifida polysaccharide [58] and Astragalus polysaccharide [59], could improve UC by modulating gut bacteria. However, LBP had a unique advantage in significantly modulating *Dubosiella* similar to mesalazine.

Intestinal microbiota can influence the production of intestinal metabolites, which mediate the interaction between intestinal bacteria and the host [18]. BAs, which act as beneficial intestinal metabolites, significantly affect the regulation of metabolic homeostasis and local immunomodulation by binding to TGR5 [60]. Previous studies have found that LCA and DCA can reduce intestinal inflammation in part, depending on TGR5, which promotes intestinal epithelial regeneration [20,21]. The present study indicates that LBP promotes the production of LCA and DCA and the expression of TGR5 in mice with UC. Intestinal inflammation destroys the gut barrier and increases intestinal permeability, thereby exacerbating inflammation [61,62]. An intact gut barrier prevents damage to the intestinal microbiota and harmful metabolites from invading the host [13]. The intestinal mucosal protein MUC-2 and tight junction proteins claudin-1 and ZO-1 are major constituents of the gut barrier. In this study, LBP maintained the integrity of the intestinal epithelium and crypt structure, upregulated MUC-2, claudin-1, and ZO-1 protein expression, and improved gut barrier function. These results suggest that LBP influences intestinal BA metabolism by regulating intestinal bacteria, and the promotion of LCA and DCA production by LBP improves gut barrier function to alleviate colonic inflammation by upregulating TGR5 expression.

Furthermore, the association analysis of intestinal microbiota and BAs revealed that *Dubosiella* and *Lactobacillus* were positively associated with the production of most BAs, whereas *Faecalibaculum*, *Turicibacter*, *Clostridium_sensu_stricto_1*, and *Escherichia-Shigella* were negatively related to the production of some BAs. *Dubosiella* significantly promotes LCA and DCA production. In mice with colitis, the abundance of *Dubosiella* decreased sharply; however, LBP significantly increased the abundance of *Dubosiella* towards that in normal mice, suggesting that *Dubosiella* may play an important role in ameliorating colitis by regulating BA metabolism. Nonetheless, the relationship between *Dubosiella* and UC and the mechanisms of regulation still need to be further explored.

5. Conclusion

Our study showed that LBP ameliorated the symptoms of UC. To the best of our knowledge, this is the first instance revealing the possible mechanism that LBP can boost the abundance of *Dubosiella* in intestinal microbiota, resulting in an increase in LCA and DCA, thereby increasing the expression of TGR5 and ultimately strengthening the intestinal barrier (Fig. 7). In this process, the change in the abundance of *Dubosiella* was the most significant triggering factor. Our study showed that LBP could alleviate UC symptoms and

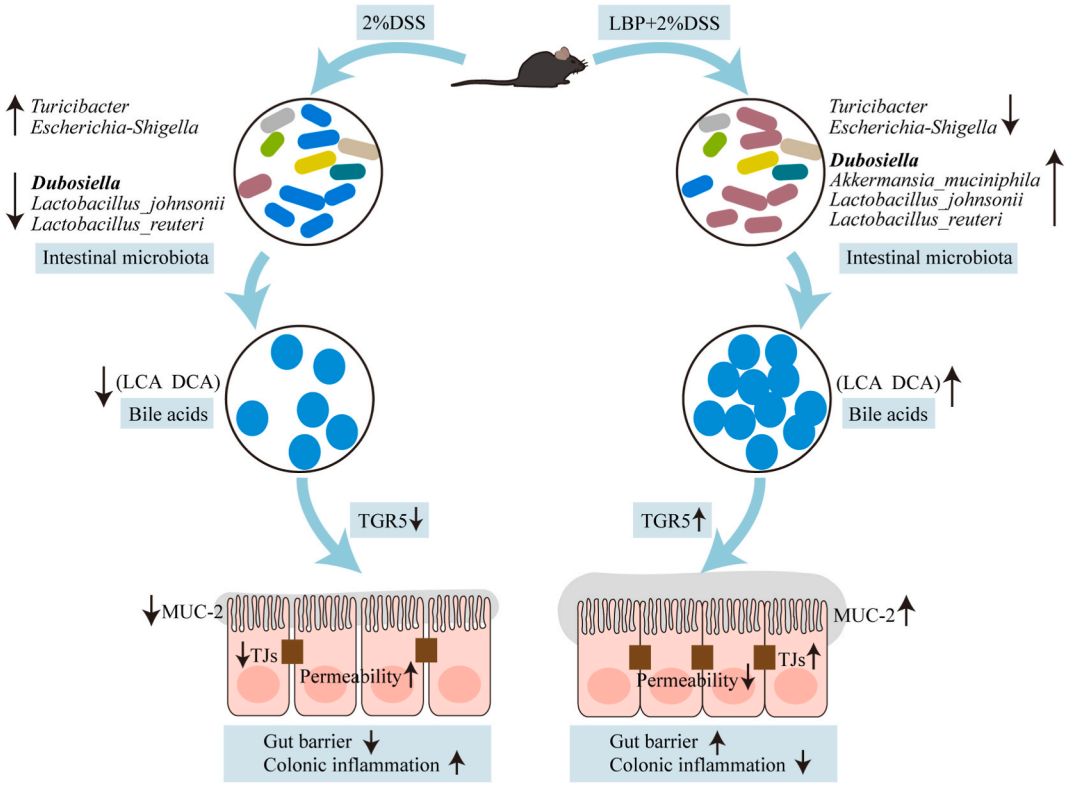


Fig. 7. Schematic diagram representing influence of LBP on intestinal microbiota, bile acid metabolites, and gut barrier in mice with UC. LBP: *Lycium barbarum* polysaccharide; UC: ulcerative colitis.

achieve an effect similar to that of mesalazine. We propose that certain ingredients derived from foods could be used as a new alternative strategy for the amelioration of UC. Moreover, owing to their high efficiency and low toxicity, they can be safely used. The mechanism of action of *Dubosiella* in LBP remodeling of the colonic inflammatory microenvironment and improvement of intestinal health needs to be further investigated.

Ethics statement

This study was reviewed and approved by the Experimental Animal Ethics Committee of Chengdu University of Traditional Chinese Medicine, with the approval number: 2019-04.

Data availability statement

The data relevant to this study have not been deposited in publicly available repositories. The data will be made available upon request.

Funding statement

This study was financially supported by the Sichuan Provincial Science and Technology Program Foundation (grant no. 2019YFS0160) and financial support by Chengdu University of Traditional Chinese Medicine, China.

CRediT authorship contribution statement

Rong Li: Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Ping Yang:** Writing – original draft, Visualization, Software, Methodology, Formal analysis, Data curation, Conceptualization. **Bowen Liu:** Visualization, Software, Methodology, Formal analysis. **Ziru Ye:** Visualization, Software, Methodology. **Puyue Zhang:** Software, Methodology, Formal analysis. **Mingjian Li:** Software, Methodology, Investigation. **Yanju Gong:** Validation, Formal analysis, Data curation. **Yong Huang:** Writing – review & editing, Resources, Project administration, Funding acquisition. **Lan Yang:** Writing – review & editing, Supervision, Project administration. **Min Li:** Writing – review & editing, Validation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] F. Algieri, A. Rodriguez-Nogales, N. Garrido-Mesa, P. Zorrilla, N. Burkard, I. Pischel, H. Sievers, B. Benedek, B. Feistel, B. Walbroel, M.E. Rodriguez-Cabezas, J. Galvez, Intestinal anti-inflammatory activity of the Serpylli herba extract in experimental models of rodent colitis, J. CROHNS COLITIS. 8 (2014) 775–788, https://doi.org/10.1016/j.crohns.2013.12.012.

[2] T. Kobayashi, B. Siegmund, C. Le Berre, S.C. Wei, M. Ferrante, B. Shen, C.N. Bernstein, S. Danese, L. Peyrin-Biroulet, T. Hibi, Ulcerative colitis, Nat. Rev. Dis. Prim. 6 (2020) 74, https://doi.org/10.1038/s41572-020-0205-x.

[3] T. Hibi, H. Ogata, Novel pathophysiological concepts of inflammatory bowel disease, J. Gastroenterol. 41 (2006) 10–16. https://pubmed.ncbi.nlm.nih.gov/16501852.

[4] M.L. Chen, H. Yao, H.Z. Tan, W.Q. Huang, Q.Y. Wu, S.P. Nie, Impact of Bifidobacterium longum NSP001 on DSS-induced colitis in conventional and humanised mice, Food Sci. Hum. Wellness 12 (2023) 1109–1118, https://doi.org/10.1016/j.fshw.2022.10.028.

[5] L.Y. Li, N. Qiu, Y.Q. Meng, C.Y. Wang, Y. Mine, R. Keast, V. Guyonnet, Preserved egg white alleviates DSS-induced colitis in mice through the reduction of oxidative stress, modulation of inflammatory cytokines, NF-κB, MAPK and gut microbiota composition, Food Sci. Hum. Wellness 12 (2023) 312–323, https://doi.org/10.1016/j.fshw.2022.07.021.

[6] M. Harbord, R. Eliakim, D. Bettenworth, K. Karmiris, K. Katsanos, U. Kopylov, T. Kucharzik, T. Molnar, T. Raine, S. Sebastian, H.T. de Sousa, A. Dignass, F. Carbonnel, E.C.C.O. Ecco, Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management, J. CROHNS COLITIS. 11 (2017) 769–784, https://doi.org/10.1093/ecco-jcc/jjx009.

[7] Y. Gao, Y. Wei, Y. Wang, F. Gao, Z. Chen, Lycium barbarum: a traditional Chinese herb and A promising anti-aging agent, Aging Dis 8 (2017) 778–791, https://doi.org/10.14336/AD.2017.0725.

[8] B. Kulczynski, A. Gramza-Michalowska, Goji berry (Lycium barbarum): composition and health effects - a review, POLISH J. FOOD Nutr. Sci. 66 (2016) 67–75, https://doi.org/10.1515/pjfns-2015-0040.

[9] J. Cheng, Z.W. Zhou, H.P. Sheng, L.J. He, X.W. Fan, Z.X. He, T. Sun, X.J. Zhang, R.J. Zhao, L. Gu, C.H. Cao, S.F. Zhou, An evidence-based update on the pharmacological activities and possible molecular targets of Lycium barbarum polysaccharides, Drug Des. Dev. Ther. 9 (2015) 33–78, https://doi.org/10.2147/DDDT.572892.

[10] L.L. Zhang, Y.J. Gong, L. Zhang, B. Liang, H. Xu, W.M. Hu, Z. Jin, X. Wu, X.B. Chen, M. Li, L.Q. Shi, Y.P. Shi, M.J. Li, Y. Huang, Y. Wang, L. Yang, Gou Qi Zi inhibits proliferation and induces apoptosis through the PI3K/AKT1 signaling pathway in non-small cell lung cancer, Front. Oncol. 12 (2022) 1034750, https://doi.org/10.3389/fonc.2022.1034750.

[11] W. Li, M. Gao, T. Han, Lycium barbarum polysaccharides ameliorate intestinal barrier dysfunction and inflammation through the MLCK-MLC signaling pathway in Caco-2 cells, Food Funct. 11 (2020) 3741–3748, https://doi.org/10.1039/d0fo00030b.

[12] C. Li, Y.Y. Cai, Z.X. Yan, Brain-derived neurotrophic factor preserves intestinal mucosal barrier function and alters gut microbiota in mice, Kaohsiung J. Med. Sci. 34 (2018) 134–141, https://doi.org/10.1016/j.kjms.2017.11.002.

[13] J. Martel, S.H. Chang, Y.F. Ko, T.L. Hwang, J.D. Young, D.M. Ojcius, Gut barrier disruption and chronic disease, TRENDS Endocrinol. Metab. 33 (2022) 247–265, https://doi.org/10.1016/j.tem.2022.01.002.

[14] K. Parikh, A. Antanaviciute, D. Fawkner-Corbett, M. Jagielowicz, A. Aulicino, C. Lagerholm, S. Davis, J. Kinchen, H.H. Chen, N.K. Alham, N. Ashley, E. Johnson, P. Hublitz, L.Y. Bao, J. Lukomska, R.S. Andev, E. Bjorklund, B.M. Kessler, R. Fischer, R. Goldin, H. Koohy, A. Simmons, Colonic epithelial cell diversity in health and inflammatory bowel disease, Nature 567 (2019) 49–55, https://doi.org/10.1038/s41586-019-0992-y.
[15] S. van der Post, K.S. Jabbar, G. Birchenough, L. Arike, N. Akhtar, H. Sjovall, M.E. V Johansson, G.C. Hansson, Structural weakening of the colonic mucus barrier is an early event in ulcerative colitis pathogenesis, Gut 68 (2019) 2142–2151, https://doi.org/10.1136/gutjnl-2018-317571.
[16] R. Huang, Z.J. Zhu, S.J. Wu, J. Wang, M.F. Chen, W. Liu, A.H. Huang, J.M. Zhang, Q.P. Wu, Y. Ding, Polysaccharides from Cordyceps militaris prevent obesity in association with modulating gut microbiota and metabolites in high-fat diet-fed mice, Food Res. Int. 157 (2022) 111197, https://doi.org/10.1016/j.foodres.2022.111197.
[17] X.M. Ren, Y.Y. Zhu, Y. Gamallat, S.H. Ma, G. Chiwala, A. Meyiah, Y. Xin, E. coli O124 K72 alters the intestinal barrier and the tight junctions proteins of Guinea pig intestine, Biomed. Pharmacother. 94 (2017) 468–473, https://doi.org/10.1016/j.biopha.2017.07.123.
[18] A. Lavelle, H. Sokol, Gut microbiota-derived metabolites as key actors in inflammatory bowel disease, Nat. Rev. Gastroenterol. Hepatol. 17 (2020) 223–237, https://doi.org/10.1038/s41575-019-0258-z.
[19] J.M. Ridlon, D.-J. Kang, P.B. Hylemon, Bile salt biotransformations by human intestinal bacteria, J. Lipid Res. 47 (2006) 241–259, https://doi.org/10.1194/jlr.R500013-JLR200.
[20] S.R. Sinha, Y. Haileselassie, L.P. Nguyen, C. Tropini, M. Wang, L.S. Becker, D. Sim, K. Jarr, E.T. Spear, G. Singh, H. Namkoong, K. Bittinger, M.A. Fischbach, J. L. Sonnenburg, A. Habtezion, Dysbiosis-induced secondary bile acid deficiency promotes intestinal inflammation, Cell Host Microbe 27 (2020) 659–670, https://doi.org/10.1016/j.chom.2020.01.021.
[21] G. Sorrentino, A. Perino, E. Yildiz, G. El Alam, M.B. Sleiman, A. Gioiello, R. Pellicciari, K. Schoonjans, Bile acids signal via TGR5 to activate intestinal stem cells and epithelial regeneration, Gastroenterology 159 (2020) 956–968, https://doi.org/10.1053/j.gastro.2020.05.067.
[22] Q. Zou, X. Zhang, X. Liu, Y. Li, Q. Tan, Q. Dan, T. Yuan, X. Liu, R.H. Liu, Z. Liu, Ficus carica polysaccharide attenuates DSS-induced ulcerative colitis in C57BL/6 mice, Food Funct. 11 (2020) 6666–6679, https://doi.org/10.1039/d0fo01162b.
[23] G. Ahmad, B. Chami, Y. Liu, A.L. Schroder, P.T. San Gabriel, A. Gao, G. Fong, X. Wang, P.K. Witting, The synthetic myeloperoxidase inhibitor AZD3241 ameliorates dextran sodium sulfate stimulated experimental colitis, Front. Pharmacol. 11 (2020) 556020, https://doi.org/10.3389/fphar.2020.556020.
[24] G. Cao, K. Wang, Z. Li, F. Tao, Y. Xu, J. Lan, G. Chen, C. Yang, Bacillus amyloliquefaciens ameliorates dextran sulfate sodium-induced colitis by improving gut microbial dysbiosis in mice model, Front. Microbiol. 9 (2018) 3260, https://doi.org/10.3389/fmicb.2018.03260.
[25] T. Azuma, M. Shigeshiro, M. Kodama, S. Tanabe, T. Suzuki, Supplemental naringenin prevents intestinal barrier defects and inflammation in colitic mice, J. Nutr. 143 (2013) 827–834, https://doi.org/10.3945/jn.113.174508.
[26] M. Shan, M. Gentile, J.R. Yeiser, A.C. Walland, V.U. Bornstein, K. Chen, B. He, L. Cassis, A. Bigas, M. Cols, L. Comerma, B. Huang, J.M. Blander, H. Xiong, L. Mayer, C. Berin, L.H. Augenlicht, A. Velcich, A. Cerutti, Mucus enhances gut homeostasis and oral tolerance by delivering immunoregulatory signals, Science 342 (2013) 447–453, https://doi.org/10.1126/science.1237910.
[27] X. He, Z. Wei, J. Wang, J. Kou, W. Liu, Y. Fu, Z. Yang, Alpinetin attenuates inflammatory responses by suppressing TLR4 and NLRP3 signaling pathways in DSS-induced acute colitis, Sci. Rep. 6 (2016) 28370, https://doi.org/10.1038/srep28370.
[28] N.A. Molodecky, I.S. Soon, D.M. Rabi, W.A. Ghali, M. Ferris, G. Chernoff, E.I. Benchimol, R. Panaccione, S. Ghosh, H.W. Barkema, G.G. Kaplan, Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review, Gastroenterology 142 (2012) 46–54, https://doi.org/10.1053/j.gastro.2011.10.001.
[29] S.C. Ng, H.Y. Shi, N. Hamidi, F.E. Underwood, W. Tang, E.I. Benchimol, R. Panaccione, S. Ghosh, J.C.Y. Wu, F.K.L. Chan, J.J.Y. Sung, G.G. Kaplan, Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies, Lancet (London, England) 390 (2017) 2769–2778, https://doi.org/10.1016/S0140-6736(17)32448-0.
[30] C.R. Choi, I. Al Bakir, N.J. Ding, G. Lee, A. Askari, J. Warusavitarne, M. Moorghen, A. Humphries, A. Ignjatovic-Wilson, S. Thomas-Gibson, B.P. Saunders, M. D. Rutter, T.A. Graham, A.L. Hart, Cumulative burden of inflammation predicts colorectal neoplasia risk in ulcerative colitis: a large single-centre study, Gut 68 (2019) 414–422, https://doi.org/10.1136/gutjnl-2017-314190.
[31] M. Eisenstein, Ulcerative colitis: towards remission, Nature 563 (2018) S33, https://doi.org/10.1038/d41586-018-07276-2.
[32] J. Durack, S. V Lynch, The gut microbiome: relationships with disease and opportunities for therapy, J. Exp. Med. 216 (2019) 20–40, https://doi.org/10.1084/jem.20180448.
[33] Y. Liu, J. Lv, B. Yang, F. Liu, Z. Tian, Y. Cai, D. Yang, J. Ouyang, F. Sun, Y. Shi, P. Xia, Lycium barbarum polysaccharide attenuates type II collagen-induced arthritis in mice, Int. J. Biol. Macromol. 78 (2015) 318–323, https://doi.org/10.1016/j.ijbiomac.2015.04.025.
[34] L.L. Gao, J.M. Ma, Y.N. Fan, Y.N. Zhang, R. Ge, X.J. Tao, M.W. Zhang, Q.H. Gao, J.J. Yang, Lycium barbarum polysaccharide combined with aerobic exercise ameliorated nonalcoholic fatty liver disease through restoring gut microbiota, intestinal barrier and inhibiting hepatic inflammation, Int. J. Biol. Macromol. 183 (2021) 1379–1392, https://doi.org/10.1016/j.ijbiomac.2021.05.066.
[35] W. Liu, W.J. Guo, J. Wu, Q. Luo, F.F. Tao, Y.H. Gu, Y. Shen, J.X. Li, R.X. Tan, Q. Xu, Y. Sun, A novel benzo[d]imidazole derivate prevents the development of dextran sulfate sodium-induced murine experimental colitis via inhibition of NLRP3 inflammasome, Biochem. Pharmacol. 85 (2013) 1504–1512, https://doi.org/10.1016/j.bcp.2013.03.008.
[36] Z. Huang, K. Liu, W. Ma, D. Li, T. Mo, Q. Liu, The gut microbiome in human health and disease-Where are we and where are we going? A bibliometric analysis, Front. Microbiol. 13 (2022) 1018594, https://doi.org/10.3389/fmicb.2022.1018594.
[37] S. Wu, Z.F. Bhat, R.S. Gounder, I.A. Mohamed Ahmed, F.Y. Al-Juhaimi, Y. Ding, A.E.-D.A. Bekhit, Effect of dietary protein and processing on gut microbiota-A systematic review, Nutrients 14 (2022) 453, https://doi.org/10.3390/nu14030453.
[38] K.L. Glassner, B.P. Abraham, E.M.M. Quigley, The microbiome and inflammatory bowel disease, J. Allergy Clin. Immunol. 145 (2020) 16–27, https://doi.org/10.1016/j.jaci.2019.11.003.
[39] E.A. Franzosa, A. Sirota-Madi, J. Avila-Pacheco, N. Fornelos, H.J. Haiser, S. Reinker, T. Vatanen, A.B. Hall, H. Mallick, L.J. McIver, J.S. Sauk, R.G. Wilson, B. W. Stevens, J.M. Scott, K. Pierce, A.A. Deik, K. Bullock, F. Imhann, J.A. Porter, A. Zhernakova, J. Fu, R.K. Weersma, C. Wijmenga, C.B. Clish, H. Vlamakis, C. Huttenhower, R.J. Xavier, Gut microbiome structure and metabolic activity in inflammatory bowel disease, Nat. Microbiol. 4 (2019) 293–305, https://doi.org/10.1038/s41564-018-0306-4.
[40] F. Wan, M. Wang, R. Zhong, L. Chen, H. Han, L. Liu, Y. Zhao, H. Lv, F. Hou, B. Yi, H. Zhang, Supplementation with Chinese medicinal plant extracts from Lonicera hypoglauca and scutellaria baicalensis mitigates colonic inflammation by regulating oxidative stress and gut microbiota in a colitis mouse model, Front. Cell. Infect. Microbiol. 11 (2021) 798052, https://doi.org/10.3389/fcimb.2021.798052.
[41] F. Wan, R. Zhong, M. Wang, Y. Zhou, Y. Chen, B. Yi, F. Hou, L. Liu, Y. Zhao, L. Chen, H. Zhang, Caffeic acid supplement alleviates colonic inflammation and oxidative stress potentially through improved gut microbiota community in mice, Front. Microbiol. 12 (2021) 784211, https://doi.org/10.3389/fmicb.2021.784211.
[42] L. Peng, X. Gao, L. Nie, J. Xie, T. Dai, C. Shi, L. Tao, Y. Wang, Y. Tian, J. Sheng, Astragalin attenuates dextran sulfate sodium (DSS)-Induced acute experimental colitis by alleviating gut microbiota dysbiosis and inhibiting NF-κB activation in mice, Front. Immunol. 11 (2020) 2058, https://doi.org/10.3389/fimmu.2020.02058.
[43] X. Wen, H.-G. Wang, M.-N. Zhang, M.-H. Zhang, H. Wang, X.-Z. Yang, Fecal microbiota transplantation ameliorates experimental colitis via gut microbiota and T-cell modulation, World J. Gastroenterol. 27 (2021) 2834–2849, https://doi.org/10.3748/wjg.v27.i21.2834.
[44] Q. Deng, W. Wang, L. Zhang, L. Chen, Q. Zhang, Y. Zhang, S. He, J. Li, Gougunao tea polysaccharides ameliorate high-fat diet-induced hyperlipidemia and modulate gut microbiota, Food Funct. 14 (2023) 703–719, https://doi.org/10.1039/d2fo01828d.
[45] X. Ye, Y. Liu, J. Hu, Y. Gao, Y. Ma, D. Wen, Chlorogenic acid-induced gut microbiota improves metabolic endotoxemia, Front. Endocrinol. 12 (2021) 762691, https://doi.org/10.3389/fendo.2021.762691.
[46] T. Wilkins, J. Sequoia, Probiotics for gastrointestinal conditions: a summary of the evidence, Am. Fam. Physician 96 (2017) 170–178. https://pubmed.ncbi.nlm.nih.gov/28762696.

[47] S. Qu, L. Fan, Y. Qi, C. Xu, Y. Hu, S. Chen, W. Liu, W. Liu, J. Si, Akkermansia muciniphila alleviates dextran sulfate sodium (DSS)-Induced acute colitis by NLRP3 activation, Microbiol. Spectr. 9 (2021) e0073021, https://doi.org/10.1128/Spectrum.00730-21.
[48] L. Wang, L. Tang, Y. Feng, S. Zhao, M. Han, C. Zhang, G. Yuan, J. Zhu, S. Cao, Q. Wu, L. Li, Z. Zhang, A purified membrane protein from Akkermansia muciniphila or the pasteurised bacterium blunts colitis associated tumourigenesis by modulation of CD8+ T cells in mice, Gut 69 (2020) 1988–1997, https://doi.org/10.1136/gutjnl-2019-320105.
[49] D.J. Jia, Q.W. Wang, Y.Y. Hu, J.M. He, Q.W. Ge, Y.D. Qi, L.Y. Chen, Y. Zhang, L.N. Fan, Y.F. Lin, Y. Sun, Y. Jiang, L. Wang, Y.F. Fang, H.Q. He, X.E. Pi, W. Liu, S. J. Chen, L.J. Wang, Lactobacillus johnsonii alleviates colitis by TLR1/2-STAT3 mediated CD206+ macrophagesIL-10 activation, Gut Microb. 14 (2022) 2145843, https://doi.org/10.1080/19490976.2022.2145843.
[50] D. Ahl, H. Liu, O. Schreiber, S. Roos, M. Phillipson, L. Holm, Lactobacillus reuteri increases mucus thickness and ameliorates dextran sulphate sodium-induced colitis in mice, Acta Physiol. 217 (2016) 300–310, https://doi.org/10.1111/apha.12695.
[51] Z.J. Zhu, R. Huang, A.H. Huang, J. Wang, W. Liu, S.J. Wu, M.F. Chen, M.T. Chen, Y.Z. Xie, C.W. Jiao, J.M. Zhang, Q.P. Wu, Y. Ding, Polysaccharide from Agrocybe cylindracea prevents diet-induced obesity through inhibiting inflammation mediated by gut microbiota and associated metabolites, Int. J. Biol. Macromol. 209 (2022) 1430–1438, https://doi.org/10.1016/j.ijbiomac.2022.04.107.
[52] F. Wan, H. Han, R. Zhong, M. Wang, S. Tang, S. Zhang, F. Hou, B. Yi, H. Zhang, Dihydroquercetin supplement alleviates colonic inflammation potentially through improved gut microbiota community in mice, Food Funct. 12 (2021) 11420–11434, https://doi.org/10.1039/d1fo01422f.
[53] Z. Zhai, F. Zhang, R. Cao, X. Ni, Z. Xin, J. Deng, G. Wu, W. Ren, Y. Yin, B. Deng, Cecropin A alleviates inflammation through modulating the gut microbiota of C57bl/6 mice with DSS-induced IBD, Front. Microbiol. 10 (2019) 1595, https://doi.org/10.3389/fmicb.2019.01595.
[54] F. Dong, F. Xiao, X. Li, Y. Li, X. Wang, G. Yu, T. Zhang, Y. Wang, Pediococcus pentosaceus CECT 8330 protects DSS-induced colitis and regulates the intestinal microbiota and immune responses in mice, J. Transl. Med. 20 (2022) 33, https://doi.org/10.1186/s12967-022-03235-8.
[55] Y.P. Fu, C.Y. Li, X. Peng, H. Wangensteen, K.T. Inngjerdingen, Y.F. Zou, Pectic polysaccharides from Aconitum carmichaelii leaves protects against DSS-induced ulcerative colitis in mice through modulations of metabolism and microbiota composition, Biomed. Pharmacother. 155 (2022) 113767, https://doi.org/10.1016/j.biopha.2022.113767.
[56] H. Wang, X. Huang, S. Xia, C. Chen, X. Chen, Y. Zhang, M.A. Farag, J. Xiao, S. Nie, Celery soluble dietary fiber antagonizes flavonoids ameliorative effect on dextran-sodium-sulfate-induced colitis in mice, J. Adv. Res. 52 (2023) 73–88, https://doi.org/10.1016/j.jare.2023.01.013.
[57] H. Cheng, D. Zhang, J. Wu, J. Liu, Y. Tan, W. Feng, C. Peng, Atractylodes macrocephala Koidz. volatile oil relieves acute ulcerative colitis via regulating gut microbiota and gut microbiota metabolism, Front. Immunol. 14 (2023) 1127785, https://doi.org/10.3389/fimmu.2023.1127785.
[58] C. Guo, Y. Wang, S. Zhang, X. Zhang, Z. Du, M. Li, K. Ding, Crataegus pinnatifida polysaccharide alleviates colitis via modulation of gut microbiota and SCFAs metabolism, Int. J. Biol. Macromol. 181 (2021) 357–368, https://doi.org/10.1016/j.ijbiomac.2021.03.137.
[59] Y. Chen, J. Wang, J. Li, J. Zhu, R. Wang, Q. Xi, H. Wu, T. Shi, W. Chen, Astragalus polysaccharide prevents ferroptosis in a murine model of experimental colitis and human Caco-2 cells via inhibiting NRF2/HO-1 pathway, Eur. J. Pharmacol. 911 (2021) 174518, https://doi.org/10.1016/j.ejphar.2021.174518.
[60] A. Baars, A. Oosting, J. Knol, J. Garssen, J. van Bergenhenegouwen, The gut microbiota as a therapeutic target in IBD and metabolic disease: a role for the bile acid receptors FXR and TGR5, Microorganisms 3 (2015) 641–666, https://doi.org/10.3390/microorganisms3040641.
[61] K. Gerlach, A.N. McKenzie, M.F. Neurath, B. Weigmann, IL-9 regulates intestinal barrier function in experimental T cell-mediated colitis, Tissue Barriers 3 (2015) e983777, https://doi.org/10.4161/21688370.2014.983777.
[62] K.H. Ling, M.L.Y. Wan, H. El-Nezami, M. Wang, Protective capacity of resveratrol, a natural polyphenolic compound, against deoxynivalenol-induced intestinal barrier dysfunction and bacterial translocation, Chem. Res. Toxicol. 29 (2016) 823–833, https://doi.org/10.1021/acs.chemrestox.6b00001.