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Lactiplantibacillus plantarum LP-315 ameliorates DSS-induced colitis in mice by regulating gut microbiota and metabolites

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ABSTRACT: Ulcerative colitis is a globally prevalent chronic disease that continues to attract significant attention. 5-aminosalicylicacid (5-ASA) is the primary treatment for mild to moderate colitis, but its use may be compromised by side effects and dependency. *Lactiplantibacillus* (*L.*) *plantarum* has shown promise as a remission strategy for alleviating colitis. Our previous study demonstrated that supplementation with *L. plantarum* LP-315 (LP-315) effectively alleviated dextran sulfate sodium (DSS)-induced colitis in mice, though its effects on the gut microbiota and metabolism remained unexplored. In this follow-up study, we analyzed the fecal metagenome, gut metabolic modules (GMMs), and bioactive metabolites in four groups of mice (n = 8 per group): normal control group, DSS group, LP group (LP-315 intervention), and ME group (5-ASA intervention). A correlation network analysis was performed to investigate the associations between key differential gut microbial species, GMMs, metabolites, and the significantly improved phenotypic indicators identified in previous study. The results revealed that LP-315 ameliorated colitis symptoms by modulating the gut microbiota (increasing *Duncaniella newyorkensis*), bioactive metabolites (reducing serotonin, while increasing indole-3-acetic acid, xanthurenic acid, and indole-3-carboxylic acid), and the inflammation-associated Glutamine degradation pathway. Compared to 5-ASA, which primarily reduced the abundance of the harmful bacterium *Parasutterella excrementihominis*, LP-315 exhibited superior efficacy in ameliorating DSS-induced colitis symptoms. Besides, 25 bacterial species and 14 GMMs, closely linked to colitis but unchanged by the intervention, were identified as worthy of further targeted investigation. These findings provide rigorous preclinical evidence supporting the potential and feasibility of *L. plantarum* in colitis amelioration.

Keywords: *Lactiplantibacillus plantarum* LP-315; Ulcerative colitis; Gut microbiota; Gut bioactive metabolites

1. Introduction

Ulcerative colitis (UC) is a chronic inflammatory condition and a subtype of inflammatory bowel disease, characterized by abdominal pain, diarrhea, and rectal bleeding[1, 2]. UC is typically a long-term

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disease that significantly impacts the quality of life of affected individuals[3]. Unfortunately, the incidence and prevalence of UC continue to rise globally[4]. Although the exact etiology of UC remains unclear, it is generally believed that genetic susceptibility, environmental exposures, immune dysregulation, and gut microbiota imbalance collectively contribute to the onset and progression of the disease[5]. Currently, the majority of UC patients present with mild to moderate disease and are treated with a combination of 5-aminosalicylicacid (5-ASA), along with dietary and lifestyle interventions[6]. However, the potential side effects of these medications, their impact on the gut microbiota, and the risk of dependency make them unsustainable solutions[7, 8]. It is worth noting that recent reports suggest that probiotics, owing to their high safety profile and beneficial effects in regulating gut homeostasis, could serve as a valuable adjunctive approach for the effective management of colitis[9-12].

Recently, the beneficial effects of probiotics in alleviating colitis have gained widespread attention and been continuously reported. *Lactiplantibacillus* (*L.*) *plantarum* has shown promising beneficial effects on gut health, positioning it as a substantial potential candidate bacterium for the prevention and improvement of colitis[13-15]. Evidences have indicated that *L.plantarum* effectively ameliorated intestinal inflammation, mucosal barrier function, gut microbiota dysbiosis, and metabolic disturbances by modulating the gut microbiota, metabolic pathways, and bioactive metabolites. Studies have reported that supplementation with *L. plantarum*, by restoring gut microbiota balance, increasing the abundance of short-chain fatty acids (SCFAs)-producing bacteria, and regulating inflammation-related metabolic pathways, significantly reduced the disease activity index (DAI), inflammation, and histopathological scores in DSS-induced colitis mice[16-19]. Furthermore, *L. plantarum* intervention could mitigate colitis by modulating gut homeostasis and affecting microbial-derived tryptophan (Trp) metabolism pathways[20-23]. Therefore, *L. plantarum* administration represents a promising approach for improving colitis. However, there remains a lack of understanding regarding the mechanism differences between *L. plantarum* and conventional drug interventions in regulating gut microbiota and metabolism. Additionally, given that the functional effects of probiotics are strain-specific and that host responses to probiotics can vary individually, continued extensive and high-quality preclinical research to explore novel strains and expand the resource pool of candidate strains, as well as to elucidate their mechanisms, is of significant importance for future clinical prevention and treatment of colitis.

L. plantarum LP-315 (LP-315) is a probiotic strain isolated from pickles in Dayi County, Sichuan Province, known for its excellent acid tolerance, bile tolerance, and bioactivity. A previous study has shown that supplementation with LP-315 significantly reduced the DAI, histopathological scores, and pro-inflammatory cytokine IFN-γ levels in DSS-induced colitis mice, while significantly increasing the levels of the anti-inflammatory cytokine IL-4 and the expression of occludin, thereby effectively alleviating colitis-related symptoms. In comparison, treatment with 5-ASA significantly decreased the histopathological scores as well as the levels of the pro-inflammatory cytokines IL-6 and IL-1β, in colitis mice[24]. However, the beneficial effects of LP-315 on gut microbiota and metabolism in DSS-induced colitis have not been

further investigated. Moreover, whether the more beneficial effects of LP-315 supplementation compared to 5-ASA on colitis symptoms are related to the modulation of gut microbiota and metabolism remains to be explored in more depth.

This study hypothesized that supplementation with LP-315 could alleviate the adverse symptoms in DSS-induced colitis mice by regulating gut microbiota and metabolism, with regulatory targets distinct from those of 5-ASA treatment. As a follow-up study, the aim was to systematically investigate the effects of LP-315 administration on the gut microbiota and metabolism in DSS-induced colitic mice for the first time by analyzing gut microbiota, gut metabolic modules (GMMs), and gut bioactive metabolites. Furthermore, the positive effects of LP-315 supplementation, compared to those of 5-ASA, was further elucidated by correlating the identified key gut microbiota and metabolic biomarkers with the significantly improved colitis-related phenotypic indicators observed in prior study (Fig. 1). This study provides a scientific foundation for the precise probiotic treatment for colitis and offers valuable preclinical insights with potential clinical relevance.

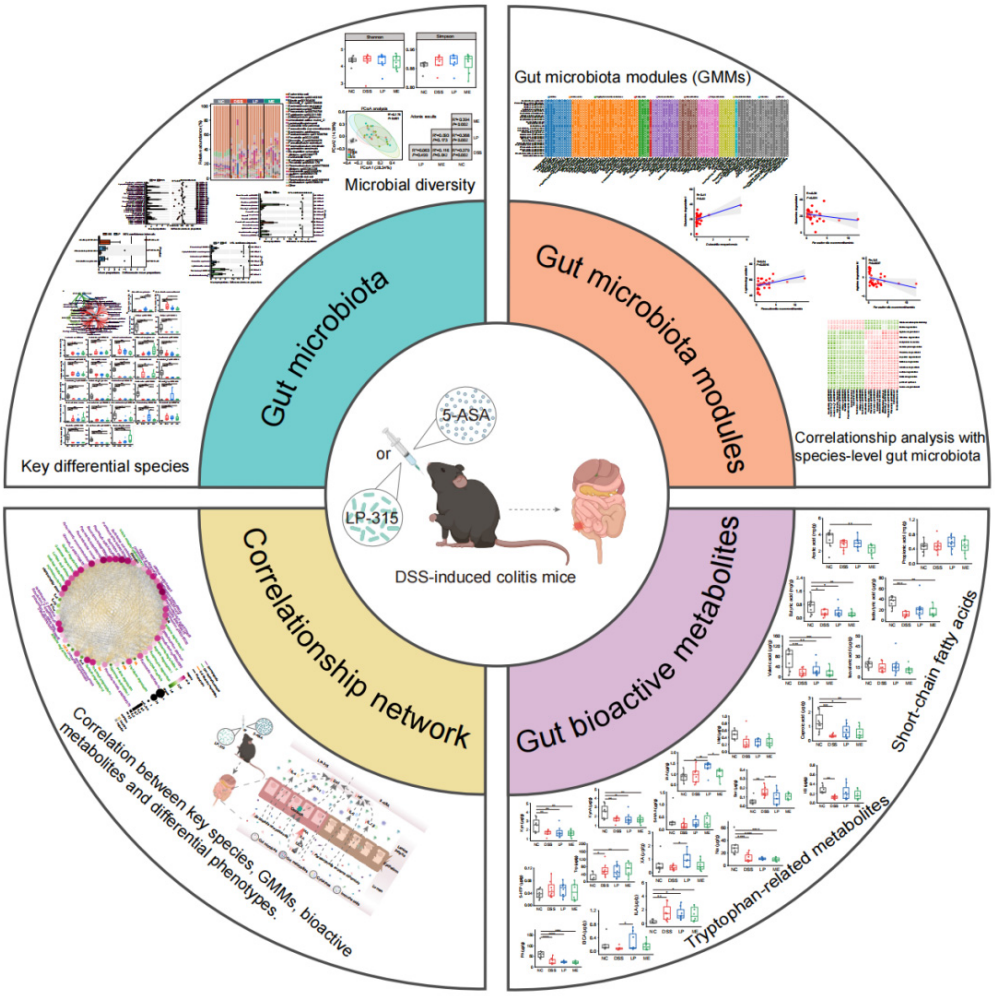

Figure 1. Schematic diagram of the study. This study systematically evaluated the effects of *L. plantarum* LP-315 (LP-315) intervention on gut microbiota and metabolites in DSS-induced colitis mice. Using LP-315 as the experimental group and 5-aminosalicylic acid (5-ASA) as the positive control, we conducted comprehensive analysis including gut microbiota, gut metabolic modules (GMMs), and bioactive metabolites. Correlation network analysis was subsequently established between key differential species-level gut microbiota, GMMs, bioactive metabolites, and previously studied critical phenotypic parameters. Finally, a potential pathway through which LP-315 alleviates DSS-induced colitis in mice was proposed.

2. Materials and methods

2.1 Experimental design and animals

This study extended the design of the previous work by incorporating 5-ASA as a positive control group[24]. In brief, after 1 week of acclimation, mice were randomly divided into four treatment groups (n = 8 per group), as follows: (1) Control group (NC): sterile water *ad libitum* + oral administration of 0.2 mL saline daily for 21 days; (2) DSS group (DSS): sterile water with 2.3% DSS (w/v; molecular mass 36–50 kDa; MP Biomedicals, Solon, USA) *ad libitum* for 7 days, followed by sterile water with 0.8% DSS *ad libitum* for 14 days + oral administration of 0.2 mL saline daily for 21 days; (3) LP-315 group (LP): sterile water with 2.3% DSS *ad libitum* for 7 days, followed by sterile water with 0.8% DSS *ad libitum* for 14 days + oral administration of 0.2 mL LP-315 (4×10^9 CFU/mouse/day) daily for 21 days; (4) 5-ASA group (ME): sterile water with 2.3% DSS *ad libitum* for 7 days, followed by sterile water with 0.8% DSS *ad libitum* for 14 days + oral administration of 0.2 mL 5-ASA (0.1 g/mouse/kg) daily for 21 days. LP-315 powder (2.8×10^{11} CFU/g) was provided by the Key Laboratory of Dairy Biotechnology and Engineering, Ministry of Education, Inner Mongolia Agricultural University, China. For administration, the powder was freshly suspended in sterile saline each day, and the final suspension was adjusted to 4×10^9 CFU/0.2mL. 5-ASA powder was purchased from Sigma-Aldrich, St. Louis, USA. Mice were sacrificed after anesthesia on day 21, and fecal samples were collected aseptically and stored at -80°C for subsequent metagenomics sequencing and metabolomic determination.

2.2 DNA extraction, metagenomic sequencing, and quality control

As previously stated, fecal genomic DNA was collected and sequenced[25]. The QIAamp Fast DNA Stool Mini Kit (Qiagen, Hilden, Germany) was applied to isolate DNA from fecal samples. Agarose gel electrophoresis and a NanoDrop One spectrophotometer (Thermo, Waltham, USA) were utilized to determine the DNA's purity and integrity. The NEB Next® UltraTM DNA Library Prep Kit (New England Biolabs, Inc., Ipswich, USA) was employed to set up the library and generate 350 bp DNA fragments. Then, the Illumina NovaSeq PE150 platform (Beijing Novogene Technology Co., Ltd., Beijing, China) was employed to carry out paired-end metagenomic sequencing. Afterwards, the KneadData pipeline (http://huttenhower.sph.harvard.edu/kneaddata) was implemented to conduct quality control on raw metagenomic reads. Furthermore, Bowtie2 was used to eliminate reads contaminated by mouse DNA. Subsequently, the clean data was retained for further analysis.

2.3 Metagenomic assembly, binning, and genome dereplication

The clean reads of each sample were compiled into contigs via MEGAHIT[26]. MetaBAT2, DAS Tool, and VAMB were employed to selected contigs larger than 2,000 bp for binning with default parameters[27-29]. Metagenome-assembled genomes (MAGs) were obtained by combined with all the bins. Then, BWA-MEM2 was applied to align the reads with corresponding contigs, and contig depth was measured by Samtools and jgi_summarize_bam_contig_depths[30]. The completeness and contamination of MAGs were evaluated by

CheckM, and the high-quality MAGs (completeness ≥ 80%, contamination ≤ 5%) were clustered then. The most representative genomes from each replicate set were selected ultimately to extract species-level genomic bins (SGBs) using dRep with the options -pa 0.95 and -sa 0.95[31, 32].

2.4 Taxonomic annotation and abundance of SGBs

The SGBs were annotated via Kraken2 and the NCBI non-redundant Nucleotide Sequence Database[33]. Prodigal was used to predict putative genes in the contigs[34]. The predicted genes were searched against the UniProt Knowledgebase (UniProtKB, version 2020) based on the blastp of DIAMOND with the default settings. The relative abundance of each SGB was assessed using CoverM (https://github.com/wwood/CoverM) with the options "–minread-percent-identity 0.95 –min-covered-fraction 0.4".

2.5 Prediction of gut metabolic modules (GMMs)

A module-based analytical framework and MetaCyc metabolic database were used to predict SGBs encoding related GMMs[35]. The predicted open reading frames were aligned with the Kyoto Encyclopedia of Genes and Genomes Orthologies database to annotate the key metabolic modules for each SGB. OmixerRPM was employed to identified the SGBs encoding related modules with the setting -c 0.66[36].

2.6 Measurement of fecal SCFAs via gas chromatography–mass spectrometry (GC-MS)

Fecal SCFAs was measured as previously described[37]. 50 mg samples were combined with 500 μL of water (Milipore, MA, USA) and 100 mg of glass beads. The mixture was homogenized for 1 min, followed by centrifugation at 4℃ for 10 min at 12000 r/min. Afterwards, 200 μL of the supernatant was collected and mixed with 100 μL of 15% phosphoric acid (≥ 85% purity; Sinopharm, Beijing, Chian), 20 μL 375 μg/mL 4-methylvaleric acid (Sigma-Aldrich, St. Louis, USA), and 280 μL ether (≥ 99.5% purity; Greagent, Shanghai, China). The mixture was vortexed for 1 minute, then centrifuged again at 4℃ and 12,000 r/min for 10 minutes. The supernatant was carefully transferred into a sample vial for subsequent GC-MS analysis.

GC analysis was performed on a Trace 1310 gas chromatograph (Thermo Fisher, Waltham, USA) equipped with an HP-INNOWAX capillary column (30 m × 0.25 mm ID × 0.25 μm; Agilent, Inc., Santa Clara, USA)[38]. A 1 μL sample was injected in split mode with a 10:1 ratio, and the injector temperature was set to 250℃. Mass spectrometry was carried out on an ISQ 7000 system (Thermo Fisher, Waltham, USA) operating in electron impact ionization mode. The ion source temperature was maintained at 300℃, while the MS transfer line was kept at 250℃. Data acquisition was performed using single ion monitoring with an electron energy of 70 eV.

2.7 Detection of fecal metabolites related to Trp metabolism via liquid chromatography–mass spectrometry (LC-MS)

Fecal Trp-related metabolites was measured as previously described[39]. 50 mg samples were combined with 100 μL of 80% methanol (≥ 99.9% purity; Thermo Fisher, Waltham, USA) and 100 mg of glass beads, then vortexed for 60 s. The mixture was ground for 1 min at 55 Hz after which 900 μL 10% methanol (≥

99.9% purity; Thermo Fisher, Waltham, USA) was added. The sample was then centrifuged at 4℃ and 12,000 r/min for 5 minutes, and the supernatant was diluted five-fold with 10% methanol (≥ 99.9% purity; Thermo Fisher, Waltham, USA). Next, a 10 ppb solution of Trp-d3 (CDN, Ontario, Canada) was added to the diluent in a 1:1 ratio, and the mixture was vortexed for 10 s. Finally, 150 μL of the supernatant was transferred into a sample vial for subsequent LC-MS analysis.

LC analysis was performed on an ExionLC system fitted with an ACQUITY UPLC® HSS T3 column (2.1 mm × 150 mm, 1.8 μm; Waters, Milford, USA). A 5 μL injection volume was employed, and the column temperature was maintained at 40℃. Mobile phase A consisted of water (Millipore, MA, USA) with 0.1% formic acid (≥ 98% purity; TCI, Tokyo, Japan), while mobile phase B was composed of methanol (≥ 99.9% purity; Thermo Fisher, Waltham, USA) with 0.1% formic acid (≥ 98% purity; TCI, Tokyo, Japan). The gradient elution program was as follows: (0–1) min, 5% B; (1–3) min, 5%–30% B; (3–4.5) min, 30% B; (4.5–10) min, 30%–95% B; (10–11) min, 95% B; (11–11.5) min, 95%–5% B; (11.5–15) min, 5% B. The flow rate was set to 0.1 mL/min for (0–3) min, 0.3 mL/min for (3–11.5) min, and 0.1 mL/min for (11.5–15) min. Mass spectrometric detection was performed on a 6500+ system (AB SCIEX, Redwood City, USA) with an electrospray ionization (ESI) source operating in both positive and negative ion modes. The ion source temperature was set to 450℃, and the ion source voltage was 4500 V. The pressures of the collision gas, curtain gas, atomizing gas, and auxiliary gas were 10 psi, 30 psi, 50 psi, and 50 psi, respectively. Multiple reaction monitoring was used for scanning.

2.8 Statistical analysis

Statistical analysis and graphical visualization were performed using Origin 2024, R (v.4.2.2) and Adobe Illustrator. Venn plot was conducted by Omicshare (https://www.omicshare.com). Stamp and correlation network analysis was employed via Omicstudio (https://www.omicstudio.cn) with the cut-off $r > 0.4$ or < -0.4 based on Spearman correlation coefficients. The Wilcoxon rank-sum test was used to assess differences in variables between groups. All *P*-values were corrected using the Benjamini-Hochberg procedure, and $P < 0.05$ was considered statistically significant.

3. Results

3.1 Effects of L. plantarum LP-315 on the diversity of gut microbiota in DSS-induced colitis mice

To explore gut microbiota changes in colitis mice and determine the effects of LP-315 and 5-ASA intervention, feces samples were obtained at the endpoint of the experiment for metagenomic analysis based on whole-metagenome shotgun sequencing and performed alpha (Shannon and Simpson) and beta (PCoA, Bray–Curtis distance) diversity analysis. No significant difference was observed in both Shannon and Simpson indexes between groups ($P < 0.05$) (Fig. 2a). PCoA analysis revealed significant differences in gut microbiota structure between NC group and DSS-treated group (Adonis test, NC vs DSS, $R^2 = 0.379$, $P = 0.002$; NC vs LP, $R^2 = 0.368$, $P = 0.002$; NC vs ME, $R^2 = 0.394$, $P = 0.002$). In addition, compared to the LP group, a more pronounced difference in beta diversity was observed between the ME and DSS groups (LP vs

DSS, $R^2 = 0.063$, $P = 0.499$; ME vs DSS, $R^2 = 0.116$, $P = 0.042$) (Fig. 2b). These results indicated that DSS induction altered the structure of the gut microbiota in mice, and LP-315 administration led to fewer changes in gut microbiota structure compared to 5-ASA treatment in mice with DSS-induced colitis.

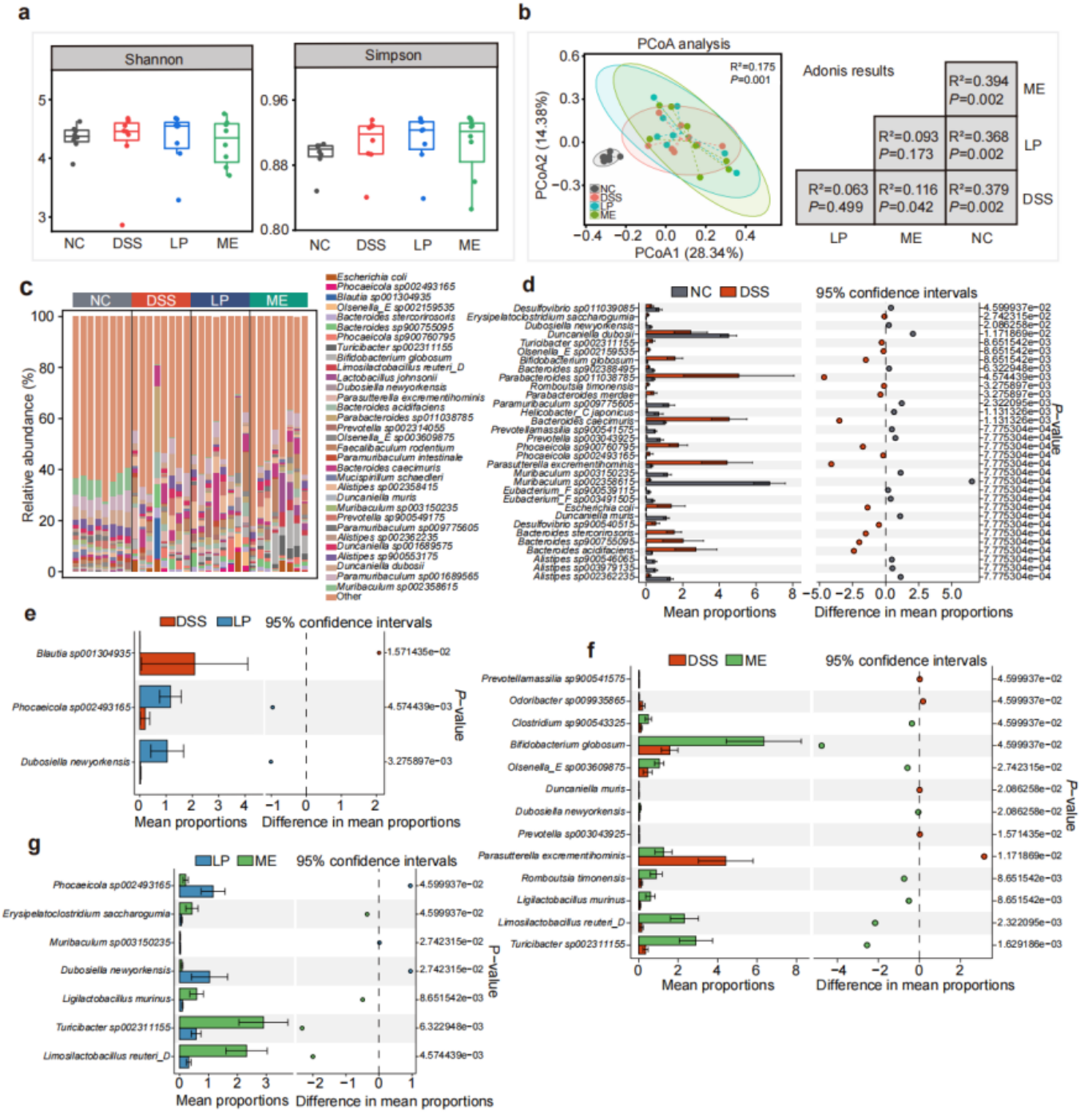

Figure 2. Microbial diversity and composition differences of gut microbiota in DSS-induced colitis mice. a Shannon and Simpson diversity index. **b** Principal coordinates analysis (PCoA; Bray–Curtis distance) score plots and Adonis test results. **c** Composition and relative abundance of species-level gut microbiota. Different colors represent different species. The color corresponding to the vertical coordinate in bar plot is the relative abundance of the corresponding species. Stamp analysis indicates the differential species between **(d)** control group (NC) vs dextran sulfate sodium group (DSS), **(e)** DSS group vs *L. plantarum* LP-315 group (LP), **(f)** DSS group vs 5-aminosalicylic acid group (ME), and **(g)** LP group vs ME group. The central line in the box plot denotes the median, while the box edges correspond to the interquartile range. The whiskers extend to values outside the upper and lower quartiles. Wilcoxon test was used to compare the differences between groups with the adjusted *P* value using Benjamini-Hochberg.

3.2 L. plantarum LP-315 intervention alters the composition of gut microbiota in DSS-induced colitis mice

The overall fecal microbiota comprised eight phyla, mainly Bacteroidota, Firmicutes, Deferribacterota, Actinobacteriota, and Proteobacteria (relative abundance > 1%). Bacteroidetes (47.23%) and Firmicutes (20.53%) were the two common major phyla among the NC, DSS, LP, and ME groups (Fig. S1a). The number of dominant genera (relative abundance > 1%) in the NC, DSS, LP, and ME groups were 7, 12, 13, and 15, respectively (Fig. S1b), demonstrating the clear differences in gut microbiota composition among these groups. Therefore, species-level differences were further evaluated to identify the specific microbes associated with colitis and determine how the state and progression of colitis can be controlled. 32 of the 58 identified species were ascertained to be preponderant (relative abundance > 1%) (Fig. 2c). The differential species among the NC, DSS, LP, and ME groups were identified via stamp analysis. Specifically, 32 species (DSS group vs. NC group), 3 species (LP group vs. DSS group), 13 species (ME group vs. DSS group), and 7 species (LP group vs. ME group) were detected, respectively. (Fig. 2d-g). Interestingly, among the dominant species, an obviously lower abundance of *Duncaniella* (*D.*) *dubosii* ($P < 0.05$) and a higher abundance of *Bacteroides* (*B.*) *caecimuris* ($P < 0.01$) was detected in the DSS group when compared to the NC group (Fig. 2d). Meanwhile, among the low-abundance species, *D. newyorkensis* showed a lower abundance in the DSS group than in the NC group ($P < 0.05$). The abundance of *D. newyorkensis* was remarkably higher after LP-315 supplementation ($P < 0.01$) or 5-ASA intervention ($P < 0.05$) compared to DSS group, with a more pronounced effect observed in LP group ($P < 0.05$, vs. ME group) (Fig. 2e-g). In addition, the abundance of *Parasutterella* (*P.*) *excrementihominis* was significantly higher in the DSS group than in the NC group ($P < 0.001$), but lower in the LP group ($P > 0.05$) and ME group ($P < 0.05$) (Fig. 2d, f). Additionally, 39 differential species were identified in the comparisons of NC vs. LP and NC vs. ME groups (Fig. S1c, d). Among them, 25 recalcitrant species exhibited significant ($P < 0.05$) differences between the NC and DSS groups and remained significantly ($P < 0.05$) different from the NC group even after LP-315 or 5-ASA intervention, indicating that these alterations were not ameliorated by the treatments. Then, venn diagrams were used to illustrate the interactions between the differential abundant bacterial species in the NC, DSS, LP, and ME groups for unearthing the gut microbiota species most closely associated with colitis and its treatment (Fig. 3a). Collectively, 27 key species (Fig. 3b), which were closely linked to DSS-induced colitis were identified. *D. newyorkensis* and *P. excrementihominis* could serve as target species involved in the therapeutic effects of LP-315 or 5-ASA intervention. These results suggested that supplementation with LP-315 or 5-ASA could modulate DSS-induced colitis symptoms in mice by mediating different gut microbiota.

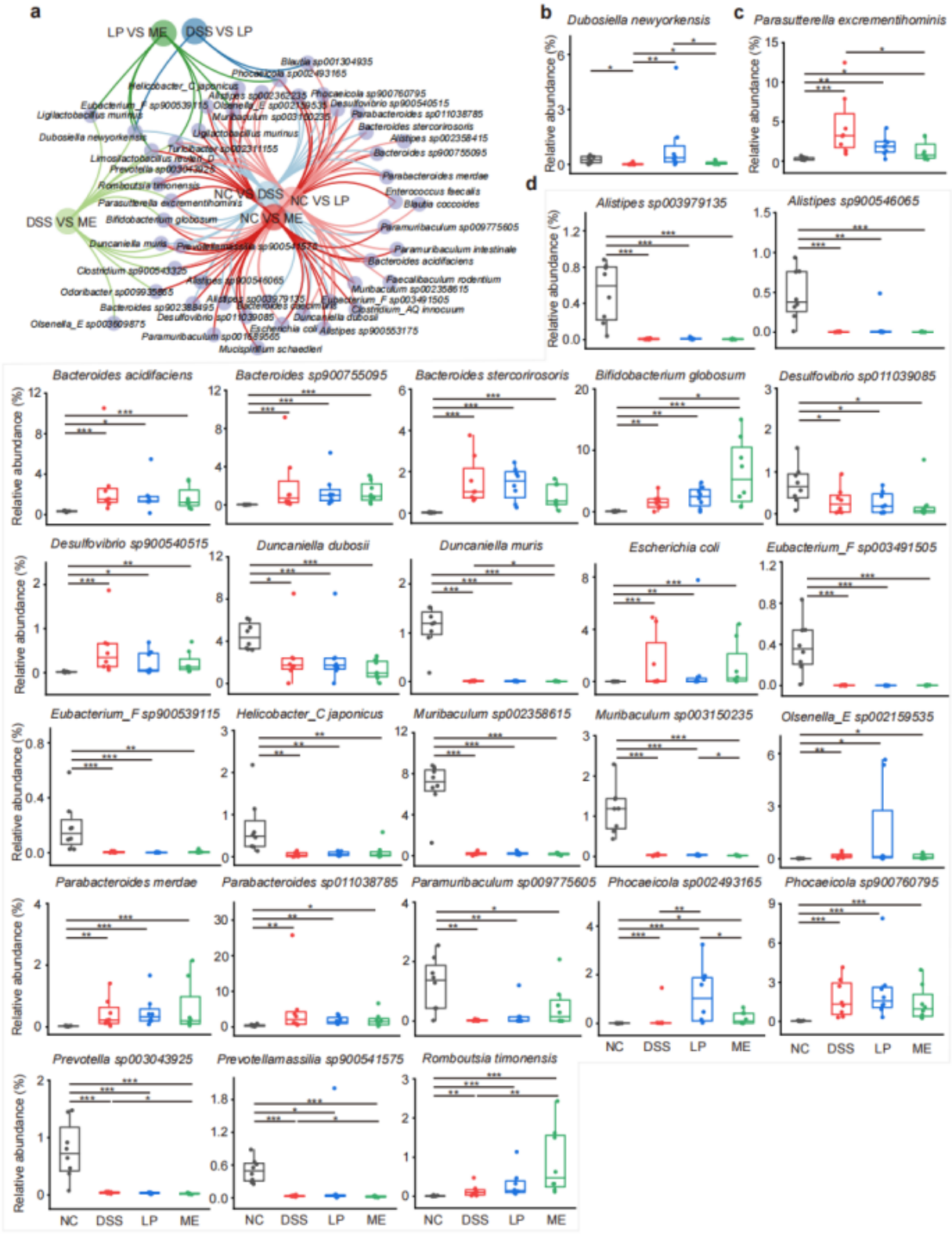

Figure 3. Important differential species related to DSS-induced colitis, *L. plantarum* LP-315, and 5-aminosalicylic acid intervention. a Venn plot of differential species of each two groups. Light blue, light red, dark red, dark blue, light green, and dark green represent the differential species of control group (NC) vs dextran sulfate sodium group (DSS), NC group vs *L. plantarum* LP-315 group (LP), NC group vs 5-aminosalicylic acid group (ME), DSS group vs LP group, DSS group vs ME group, and LP group vs ME group, respectively. Each purple circle represents a species. Essential species related to (b) LP-315 intervention, (c) 5-ASA intervention, and (d) DSS induced colitis. Data were presented as means ± sem. The central line in the box plot denotes the median, while the box edges correspond to the interquartile range. The whiskers extend to values outside the upper and lower quartiles. Wilcoxon test was used to compare the differences between groups with the adjusted *P* value using Benjamini-Hochberg. **P* < 0.05, ***P* < 0.01, ****P* < 0.001.

3.3 L. plantarum LP-315 intervention regulates the GMMs in DSS-induced colitis mice

The compositional heterogeneity of gut microbiota fundamentally governs gut metabolic features. Leveraging the MetaCyc and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases, a genome-centric metabolic reconstruction was established to systematically dissect intervention-induced alterations in GMMs across distinct SGBs. A total of 91 GMMs spanning 10 metabolite categories were identified, including SCFAs, amino acids, Trp derivatives, fatty acids, monosaccharides, disaccharides, polysaccharides, neurotransmitters, vitamins, and other specialized metabolic modules (Fig. 4a). These modules were encoded by 27 previously screened key differential SGBs. Notably, *D. newyorkensis* (significantly enriched post LP-315 intervention), *P. excrementihominis* (markedly depleted post 5-ASA intervention), and 25 recalcitrant species (unchanged under both LP-315 and 5-ASA interventions) exhibited distinct metabolic modules, validating the impact of gut microbiota shifts on GMMs.

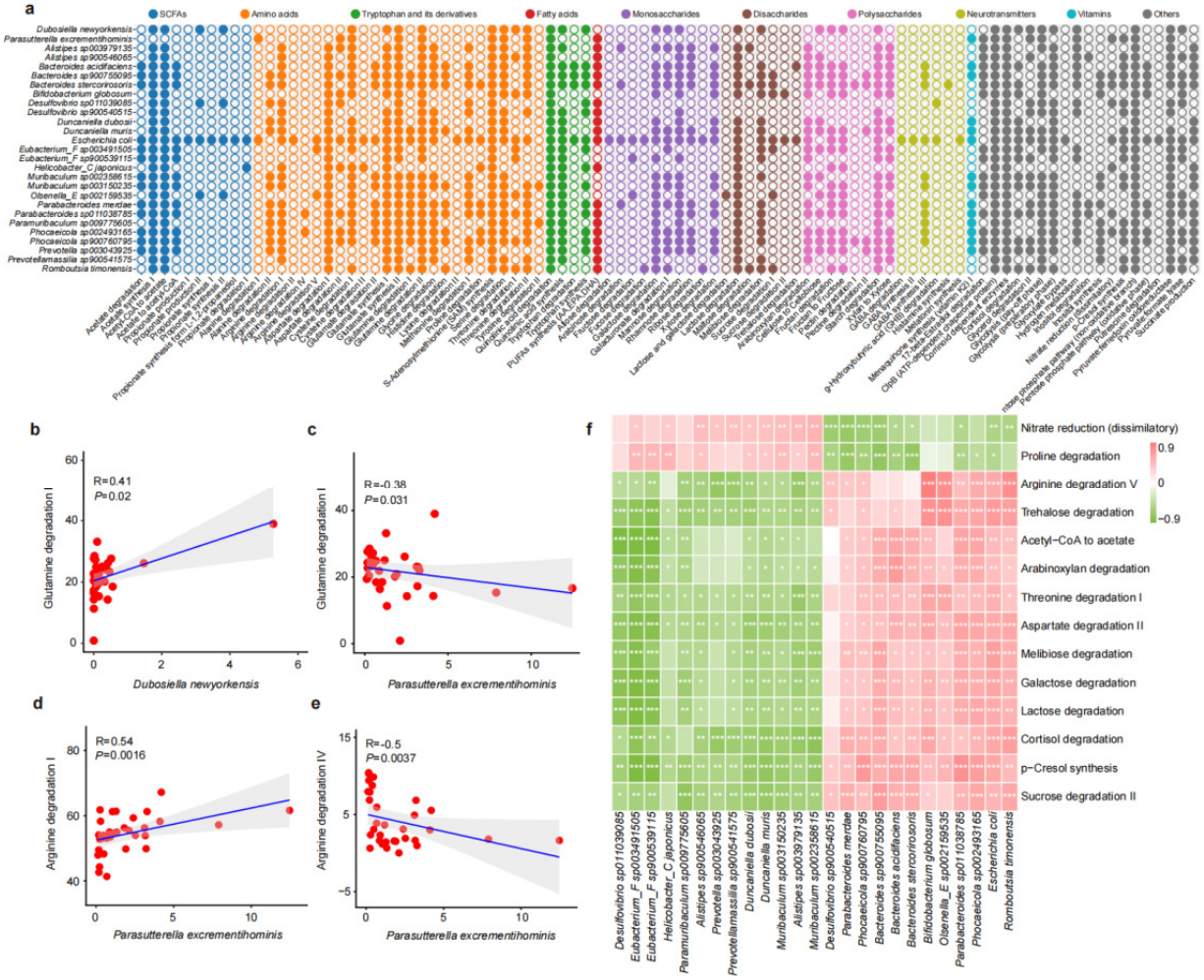

Figure 4. Predicted gut metabolic modules (GMMs) and correlation analysis with key species-level gut microbiota. a Distinction of 91 GMMs belonging to 10 metabolic modules, including short-chain fatty acids (SCFAs), amino acids, Trp and its derivatives, fatty acids, monosaccharides, disaccharides, polysaccharides, neurotransmitters, vitamins, and other metabolic modules across 27 bacterial species. Different colors is used to distinguish metabolic module classes. **b** Correlation scatter plot between *Dubosiella newyorkensis* and glutamine degradation I closed to LP-315 intervention. **c-e** Correlation scatter plot between *Parasutterella excrementihominis* and glutamine degradation I, arginine degradation I, and arginine degradation IV related to 5-ASA intervention. **f** Correlation heatmap of 14 GMMs and 25 species associated with DSS-induced colitis. Datasets were evaluated based on Spearman correlation coefficient. The intensity of the color reflects the strength of the correlation. * $P < 0.05$, ** $P < 0.01$.

3.4 Correlation analysis of key differential GMMs and species-level gut microbiota

Then, differential GMMs between groups were further explored (Fig. S2). Notably, Glutamine degradation I demonstrated a significant positive correlation with *D. newyorkensis* (R = 0.41, $P = 0.02$; Fig. 4b) but an inverse association with *P. excrementihominis* (R = -0.38, $P = 0.03$; Fig. 4c), suggesting their opposing regulatory roles in suppressing this metabolic pathway within DSS-induced colitis in mice. Additionally, Arginine degradation I showed a significant positive correlation with *P. excrementihominis* (R = 0.54, $P = 0.002$; Fig. 4d), while Arginine degradation IV displayed inverse trends (R = -0.50, $P = 0.004$; Fig. 4e). Interestingly, 14 GMMs remained unperturbed by either LP-315 or 5-ASA interventions. Compared to NC group, 12 GMMs were significantly upregulated ($P < 0.05$) in the DSS, LP, and ME groups, except for nitrate reduction (dissimilatory) and proline degradation, which were significantly downregulated ($P < 0.05$). Correlation network analysis revealed heterogeneous associations between the 14 GMMs and the aforementioned 25 recalcitrant species (Fig. 4f). Furthermore, Trehalose degradation, Threonine degradation I, Aspartate degradation II, and *p*-Cresol synthesis modules exhibited significant ($P < 0.05$) negative correlations with 13 species-level gut microbiota (Supplementary Table 1), whereas *p*-Cresol synthesis demonstrated significant positive ($P < 0.05$) associations with another 12 species (Supplementary Table 2). These findings validated that gut microbiota significantly drove the difference in gut metabolic profiles, suggesting that LP-315 or 5-ASA intervention likely ameliorated DSS-induced colitis through distinct regulatory axes.

3.5 Effects of L. plantarum LP-315 intervention on the production of SCFAs in DSS-induced colitis mice

SCFAs are metabolites produced by intestinal bacteria through the fermentation of dietary fiber. Acetic, propionic, butyric, isobutyric, valeric, isovaleric, and caproic acids are the primary SCFAs produced in the intestinal tract. Evidence has demonstrated that the colitis-induced decrease in beneficial gut bacteria and increase in harmful gut bacteria are closely associated with low intestinal levels of SCFAs, exacerbating inflammation. Accordingly, with the exception of acetic acid ($P > 0.05$), propionic acid ($P > 0.05$), and isovaleric acid ($P > 0.05$), the levels of butyric acid ($P < 0.05$), isobutyric acid ($P < 0.001$), valeric acid ($P < 0.001$), and caproic acid ($P < 0.001$) were significantly lower in the DSS group than NC group (Fig. 5a). LP-315 intervention increased the levels of SCFAs to some extent—except for butyric acid—more effectively than 5-ASA treatment, although these changes were not statistically significant ($P > 0.05$) (Fig. 5a).

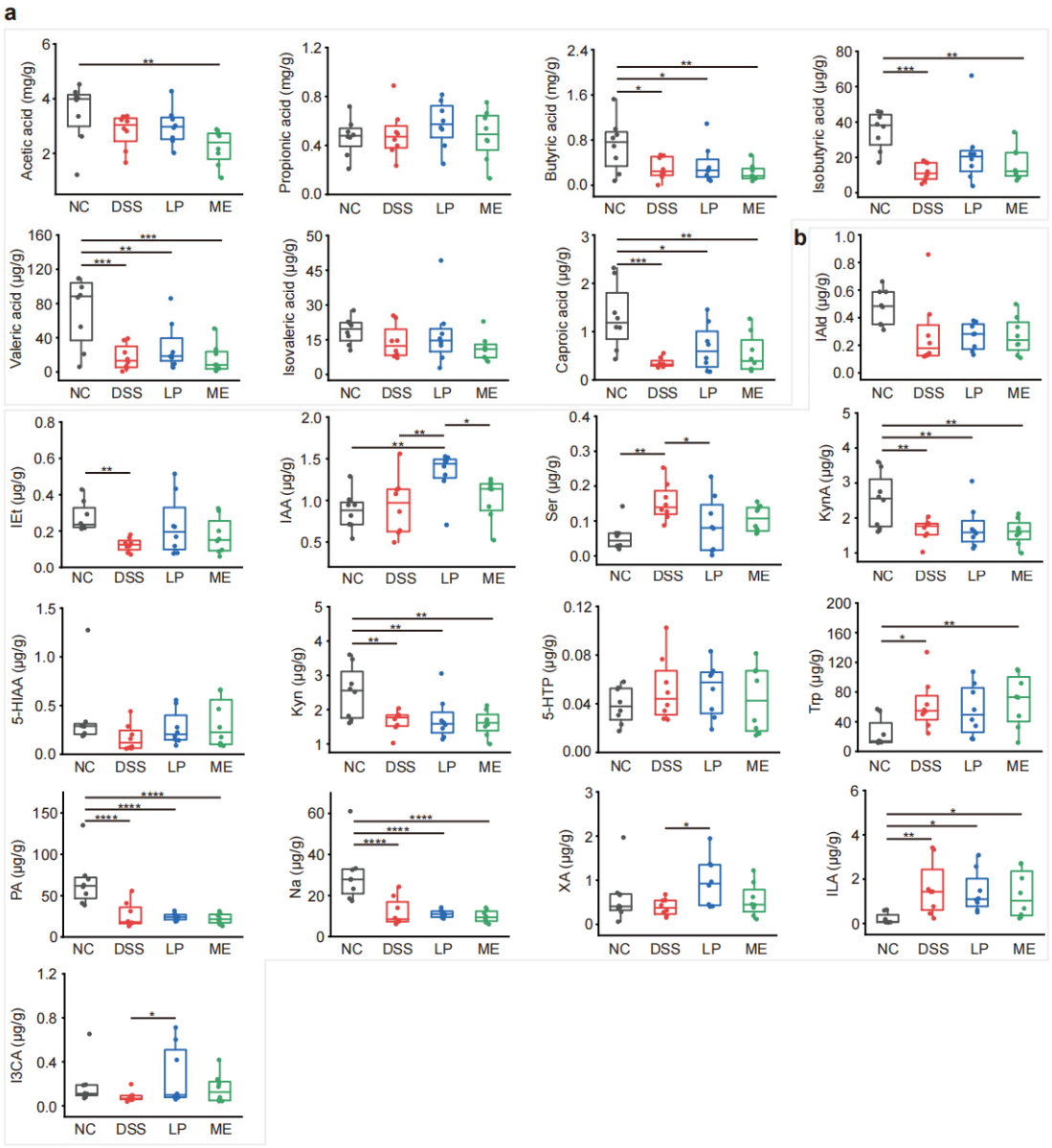

Figure 5. Changes in fecal short-chain fatty acids (SCFAs) and Trp-related metabolites of DSS-induced colitis mice. **a** Comparison of fecal SCFAs in DSS-induced colitis mice. **b** Differential fecal metabolites related to Trp metabolic pathway in DSS-induced colitis mice. Data were presented as means ± sem. The central line in the box plot denotes the median, while the box edges correspond to the interquartile range. The whiskers extend to values outside the upper and lower quartiles. Wilcoxon test was used to compare the differences between groups with the adjusted *P* value using Benjamini-Hochberg. **P* < 0.05, ***P* < 0.01, ****P* < 0.001, *****P* < 0.0001.

3.6 L. plantarum LP-315 intervention modules Trp-related metabolites in in DSS-induced colitis mice

Intestinal dysbiosis during colitis also alters the levels of relevant metabolites derived from Trp metabolic pathways, which play a dual role in maintaining the intestinal barrier and immune balance, mainly via the kynurenine pathway, serotonin pathway, and indole pathway. In this study, the levels of kynurenic acid (KynA; $P < 0.01$), kynurenine (Kyn; $P < 0.01$), picolinic acid (PA; $P < 0.0001$), and niacin (Na; $P < 0.0001$) were significantly lower in DSS-induced colitis mice (including the DSS, LP, and ME groups) than in the NC group, while the levels of indole-3-lactic acid (ILA; $P < 0.01$, DSS group vs NC group; $P < 0.05$, LP group vs NC group; $P < 0.05$, ME group vs NC group) showed the opposite trend (Fig. 5b). Moreover, indole-3-ethanol (IEt; $P < 0.01$) exhibited significantly lower levels in the DSS group than NC group, while serotonin (Ser; $P <$

0.01) and Trp ($P < 0.05$) showed significantly higher levels. Notably, LP-315 supplementation significantly increased indole-3-acetic acid (IAA; $P < 0.01$), xanthurenic acid (XA; $P < 0.05$), and indole-3-carboxylic acid (I3CA; $P < 0.05$) levels and decreased Ser levels ($P < 0.05$) (versus the DSS group), presenting a more significant modulatory effect than 5-ASA (Fig. 5b). These findings suggested that supplementation with LP-315 could regulate DSS-induced colitis in mice through modulation of gut bioactive metabolites and differed from intervention with 5-ASA.

3.7 L. plantarum LP-315 ameliorates DSS-induced colitis in mice by regulating gut microbiota and metabolites

To further investigate the relationship between key differential gut microbiota, GMMs and the phenotypes that previously identified ameliorative effects on colitis, correlation network analysis was performed based on Spearman correlation coefficient (Fig. 6a). Consistent with the differential results observed in the previous comparisons among various indicators, *D. newyorkensis* was significantly negatively correlated with DAI (R = -0.40, $P = 0.04$) and IFN-γ (R = -0.48, $P = 0.01$), and significantly positively correlated with occludin (R = 0.66, $P = 0.01$) and IL-4 (R = 0.43, $P = 0.03$). *P. excrementihominis* exhibited significant positive correlations with HE (R = 0.61, $P = 0.001$), IL-6 (R = 0.56, $P = 0.003$), and IL-1β (R = 0.62, $P = 0.001$). Furthermore, 21 out of the 25 recalcitrant species showed significant correlations with DAI, indicating the involvement in the underlying pathophysiological mechanisms. From the perspective of GMMs, Glutamine degradation I was significantly negatively correlated with IFN-γ (R = -0.44, $P = 0.03$), while Arginine degradation I was significantly positively correlated with IL-6 (R = 0.46, $P = 0.02$), and Arginine degradation IV showed a significant negative correlation with HE (R = -0.71, $P = 8.8e-05$) and IL-1β (R = -0.51, $P = 0.009$). Notably, Glutamine degradation I was significantly positively correlated with Arginine degradation IV (R = 0.49, $P = 0.01$). Additionally, among the 14 GMMs that were unchanged with the interventions, 6 GMMs (Arginine degradation V, Cortisol degradation, Galactose degradation, Melibiose degradation, Sucrose degradation II, Trehalose degradation) were significantly positively correlated with DAI (R = 0.60, $P = 0.001$; R = 0.42, $P = 0.03$; R = 0.46, $P = 0.02$; R = 0.51, $P = 0.009$; R = 0.63, $P = 0.001$; R = 0.48, $P = 0.01$, respectively), while 2 GMMs (Nitrate reduction [dissimilatory], Proline degradation) were significantly negatively correlated with DAI (R = -0.7, $P = 8.5e-05$; R = -0.60, $P = 0.002$, respectively). In addition, among the measured bioactive metabolites, Ser was significantly positively correlated with HE (R = 0.48, $P = 0.01$) and negatively correlated with occludin (R = -0.61, $P = 0.02$) and I3CA (R = -0.42, $P = 0.03$). I3CA was significantly positively correlated with XA (R = 0.73, $P = 3.7e-05$). Therefore, potential pathways through which LP-315 or 5-ASA intervention may ameliorate DSS-induced colitis in mice were presented according to the correlation network analysis (Fig. 6b). The findings suggested that supplementation with LP-315 alleviated DSS-induced colitis more effectively by dual regulation of gut microbiota and metabolites, with distinct regulatory targets compared to 5-ASA intervention.

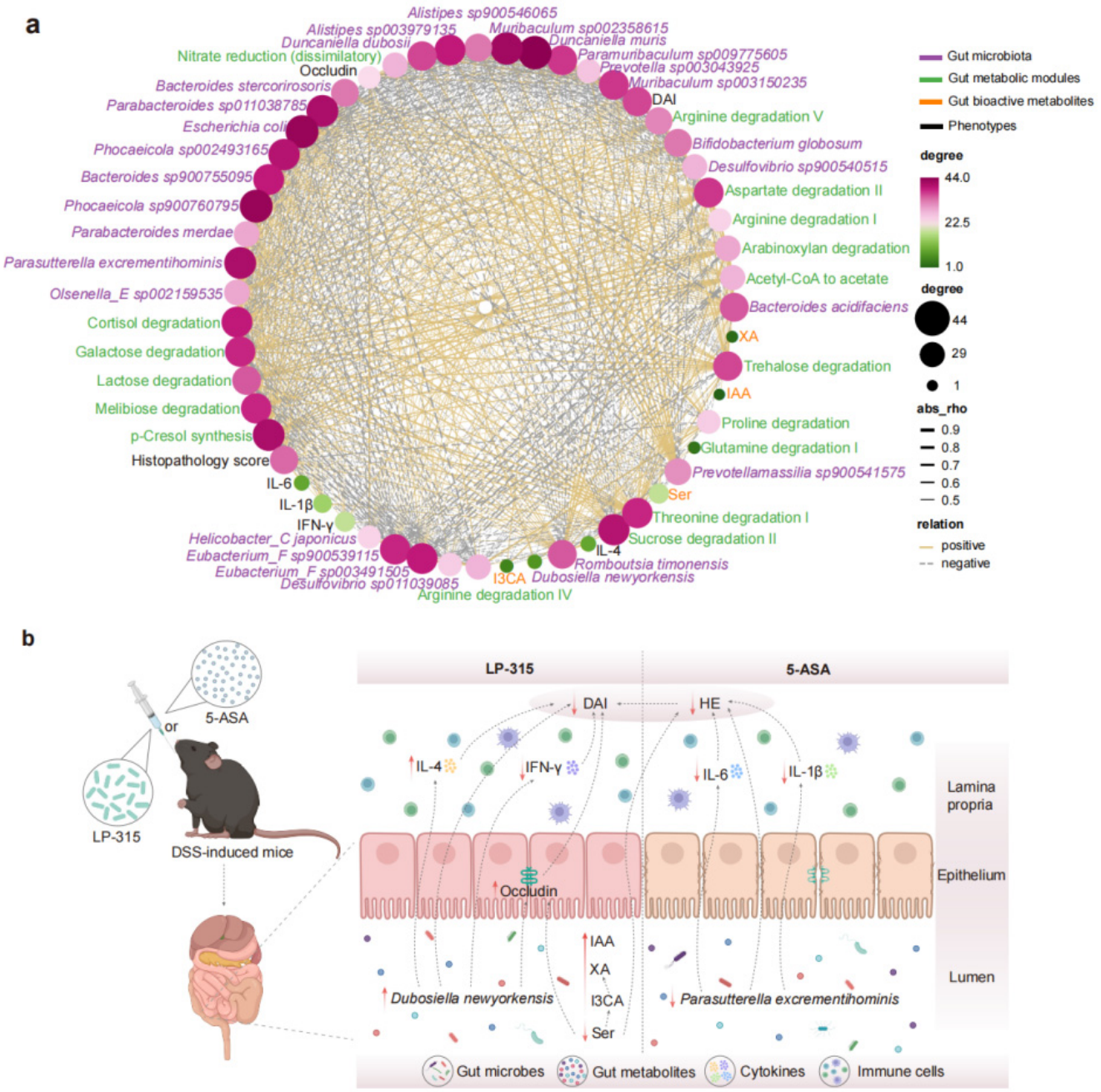

Figure 6. Correlation network of differential indicators and underlying alleviation mechanism of DSS-induced colitis mice with *L. plantarum* LP-315 and 5-aminosalicylic acid intervention. a Integrated correlation analysis of species-level gut microbiota, gut metabolic modules, gut bioactive metabolites, and previously studied differential phenotypes with purple, green, orange and black, respectively. Spearman correlation coefficient was employed to assess the relationship between the two sets, and features with $r > 0.4$ or $r < 0.4$ and $P < 0.05$ were selected for constructing the network plot. Yellow lines indicate positive correlations and gray lines indicate negative correlations. The thickness of the line indicates the absolute value of the correlation coefficient. The larger the circle, the deeper the pink color, and the greater the number of connections. b A proposed differential underlying mechanism of *L. plantarum* LP-315 and 5-aminosalicylic acid on remission of DSS-induced colitis mice symptoms.

4. Discussion

UC is a chronic inflammatory disease that severely impacts patients' quality of life, with its prevalence steadily increasing worldwide. Conventional pharmacological treatments often carry drawbacks such as side effects, drug dependence, and disruption of intestinal homeostasis. Consequently, probiotics have garnered significant attention as a safe and beneficial management approach. Substantial studies have demonstrated

that *L. plantarum* alleviated colitis symptoms by modulating the gut microbiota and metabolites. Given the strain-specific and host-specific nature of probiotic functions, it is imperative to continually identify candidate strains to expand the repository of functional probiotics. Our previous research has shown that 5-ASA intervention reduced colonic histopathological scores and levels of pro-inflammatory cytokines IL-6 and IL-8 in DSS-induced colitis mice. Interestingly, supplementation with LP-315 exhibited more favorable effects in ameliorating colitis symptoms. Specifically, LP-315 intervention decreased DAI, colonic histopathological scores, and levels of the pro-inflammatory cytokine IFN-γ, while increasing the expression of the anti-inflammatory factor IL-4 and the tight junction protein occludin in the colon. However, the beneficial impacts of LP-315 supplementation on gut microbiota and metabolism, which could propose its underlying mechanisms, have not been thoroughly investigated. As a follow-up study, we systematically analyzed the beneficial effects of LP-315 intervention on gut microbiota and metabolic profiles in DSS-induced colitis mice, which were distinct from those observed by 5-ASA intervention. These results indicated that, compared to the conventional drug 5-ASA, which primarily alleviated colitis by inhibiting harmful bacteria, LP-315 ameliorated colitis symptoms more comprehensively and effectively through dual mechanisms—modulating both the gut microbiota and the bioactive metabolites. This study provides novel scientific evidence supporting targeted intervention based on *L. plantarum*, and lays a theoretical foundation for microecological therapeutic strategies against colitis.

The gut microbiota serves as the primary pathway through which probiotics exert their effects, playing a crucial role in maintaining intestinal homeostasis and alleviating colitis symptoms. The results of α and β diversity revealed that LP-315 intervention did not significantly alter the gut microbiota structure in DSS-induced colitis mice ($P > 0.05$). Similarly, intervention with *L. plantarum* CKCC1312 in colitis mice showed no significant differences in the Shannon index and β diversity of the gut microbiota[40]. In contrast, another study found that supplementation with *L. plantarum* L15 shifted the overall gut microbiota structure of DSS-treated mice to the control group[41]. This reflects the individual variation among different bacterial strains. Additionally, other studies have indicated that probiotics may alleviate colitis symptoms without significantly affecting gut microbiota diversity, potentially by modulating specific bacterial populations and altering the intestinal environment[42, 43]. Consistent with these findings, our study observed changes in the gut microbiota composition at the species level in DSS-induced colitis mice, as well as differences following interventions with LP-315 or 5-ASA. Notably, among dominant species with relative abundances greater than 1%, neither LP-315 nor 5-ASA induced significant changes in the gut microbiota of colitis mice. However, among low-abundance species with relative abundances less than 1%, LP-315 supplementation significantly restored DSS-induced reductions in *D. newyorkensis* ($P < 0.05$), while 5-ASA supplementation significantly reduced DSS-induced increases in *P. excrementihominis* ($P < 0.05$). These findings suggested that low-abundance species may play important roles in regulating gut microecology and colitis amelioration. It has been previously reported that *D. newyorkensis* modulates immune tolerance during colitis via producing SCFAs, particularly propionic acid, and the L-lysine-activated AhR-IDO1-Kyn pathway to improve mucosal

barrier damage and ameliorate colitis symptoms[44]. Notably, no earlier studies have reported that a single *L. plantarum* strain intervention can enhance the intestinal abundance of *D. newyorkensis* in DSS-induced mouse models of colitis. This study is the first to propose and provide evidence that LP-315 exerts this beneficial effect. Besides, *P. excrementihominis* exhibits dual properties, generally exacerbating the symptoms of colitis[45, 46]. *Parasutterella* spp. were previously shown to be highly abundant in the ileal submucosa in patients with Crohn's disease and in stool samples from patients with IBD. The increased abundance of *Parasutterella* spp. also appeared to be positively correlated to intestinal inflammation[47-49], consistent with our findings. Whereas, other studies have found that treatment with DSS actually reduced the abundance of *P. excrementihominis* of the gut microbiota[50]. Therefore, this remains controversial and requires extensive in vivo and in vitro experiments, as well as multi-dimensional analysis, to truly elucidate its impact on colitis. Furthermore, the present study identified 25 under-reported recalcitrant species that are strongly associated with colitis but are challenging to regulate. Notably, 21 of these species exhibited a strong correlation with the DAI. If these recalcitrant species can be effectively modulated via intervention with additional probiotics or other microecological preparations, DSS-induced colitis may be alleviated more effectively. Therefore, these strains may represent potential targets and hold promise for further pertinent investigations.

Compositional variations in gut microbiota influence gut metabolic characteristics, thereby modulating host metabolism and immune responses, which in turn affect colitis development and symptom severity[51, 52]. To investigate the impact of LP-315 on gut metabolic pathways in DSS-induced colitis mice, we analyzed differences in GMMs encoded by the 27 key differential species identified above across different groups. Notably, correlation analysis revealed a significant positive association between Glutamine degradation I and *D. newyorkensis* ($P < 0.05$), whereas an inverse relationship was observed with *P. excrementihominis* ($P < 0.05$). Glutamine serves as a primary energy source for intestinal epithelial cells, and its degradation products may support the restoration of intestinal barrier function by promoting energy metabolism, upregulating tight junction protein expression, or enhancing mucin MUC2 synthesis[53]. Additionally, glutamine mediate NF-κB, STAT, or Wnt signaling pathways to inhibit the release of pro-inflammatory factors and promote the production of anti-inflammatory factors, thereby mitigating colonic mucosal damage[54, 55]. Furthermore, correlation analysis identified a significant positive association between *P. excrementihominis* and Arginine degradation I ($P < 0.01$), contrasted by a negative correlation with Arginine degradation IV ($P < 0.01$). The dual modulation of the arginine degradation pathway in the gut by 5-ASA intervention is not coincidental, as there is a close relationship between the degradation products of arginine and its regulatory effects. In colorectal cancer models, gut microbiota accelerated tumor progression through polyamine synthesis, and increased the abundance of *Parasutterella* correlated with intestinal inflammation[49, 56]. Furthermore, when arginine is converted to citrulline via the arginine deiminase pathway, the resultant citrulline may inhibit pathogenic bacterial growth through nitric oxide synthase-dependent nitric oxide generation[57]. Additionally, we identified 14 recalcitrant GMMs unaffected by LP-315 or 5-ASA interventions. Among them, Trehalose degradation, Threonine degradation I, Aspartate degradation II, and *p*-Cresol synthesis were significantly

negatively correlated with 13 recalcitrant species. Moreover, *p*-Cresol synthesis was also significantly positively correlated with another 12 recalcitrant species. Notably, these four metabolic pathways were typically upregulated in colitis, strongly associating with pathogenic bacterial proliferation, beneficial microbiota depletion, exacerbated colonic inflammation, and oxidative stress[58-61]. These findings highlighted the necessity for future colitis research to investigate these microbial species and metabolic modules, potentially informing the development of novel targeted gut intervention strategies.

It is worth noting that alterations in the gut microbiota and GMMs are often accompanied by changes in gut metabolites. Studies have shown that *D. newyorkensis* and *P. excrementihominis* are involved in the production of SCFAs and metabolites derived from the Trp metabolic pathway, both of which are closely associated with colitis-related inflammation[44, 49]. Moreover, alterations in glutamine and arginine degradation metabolic modules can indirectly influence intestinal SCFAs and Trp-related boiactive metabolites by affecting gut homeostasis and immune responses[62-65]. Therefore, this study further evaluated the impact of LP-315 or 5-ASA interventions on typical active metabolites in the intestines of colitis mice. In this study, supplementation with LP-315 was found to have a more pronounced effect on fecal SCFAs, particularly propionic acid, in mice with DSS-induced colitis when compared to 5-ASA, although the difference was not statistically significant ($P > 0.05$). This result is presumed to be associated with the significant increase in the abundance of *D. newyorkensis*, a known SCFAs-producing bacterium. Notably, *D. newyorkensis* has been reported to alleviate colitis symptoms through the production of SCFAs, particularly propionic acid, which is consistent with the findings of this study[44]. Furthermore, propionic acid has been shown to specifically induce the activation of $Foxp3^+$ IL-10-producing regulatory T cells, thereby contributing to the amelioration of intestinal inflammation[66]. Besides, study has reported that supplementation with *L. plantarum* ZJ316 can increase SCFA levels in the intestines of mice with DSS-induced colitis, outperforming 5-ASA in alleviating colitis symptoms[17]. Interestingly, LP-315 also significantly increased the levels of IAA ($P < 0.01$), XA ($P < 0.05$), and I3CA ($P < 0.05$) in the feces of colitis mice and notably reduced the DSS-induced elevation of Ser ($P < 0.05$). Consistent with the findings of this study, treatment with *L. plantarum* D266 or *L. fermentum* 016 significantly enhanced fecal levels of IAA[20, 67]. In addition, evidence has investigated that the combination of *L. plantarum* KLDS 1.0386 and Trp can increase IAA concentration in the colon. IAA, acting as an aryl hydrocarbon receptor agonist, is known to activate the immune response and strengthen the intestinal epithelial barrier, thereby exerting anti-inflammatory effects[68]. Although evidence specifically addressing the impact of *L. plantarum* intervention on intestinal XA levels in colitis mice is limited, similar findings have been observed in studies involving multi-strain probiotic supplementation, which significantly increased XA levels in the host intestine[69]. XA has been shown to promote oxidative phosphorylation in intestinal epithelial cells, enhance cell proliferation, support intestinal barrier repair, and reduce oxidative stress-induced damage[70]. Furthermore, *L. plantarum* 06CC2 has been reported to increase the intestinal concentration of I3CA in mice following intervention[71]. I3CA regulates the IDO1/Kyn/AHR axis, inhibits the differentiation of CD4+ Treg cells, and enhances the function of CD8+ T

cells, thereby contributing to the prevention of colorectal cancer progression[72]. Additionally, *L. plantarum* AR495 has been found to improve intestinal health by inhibiting the aberrant proliferation of enterochromaffin cells, suppressing the expression of the rate-limiting enzyme TPH1, and inhibiting the conversion of Trp to Ser[23].

To further elucidate whether the identified key differential species-level gut microbiota, GMMs, and bioactive metabolites are associated with amelioration of colitis, we conducted a correlation network analysis between previously reported significantly different phenotypic indicators and the key differential targets identified in this study. This analysis aimed to delineate the distinct and beneficial pathways exerted by LP-315 and 5-ASA interventions. The results indicated that LP-315 supplementation effectively alleviated DSS-induced colitis mice through a dual modulation of gut microbiota and metabolism. These changes illustrated significant relationship with the reduction in DAI, colonic histopathological scores, and IFN-γ, alongside increased expression of occludin and IL-4. Therefore, we propose a potential mechanism by which LP-315 alleviates symptoms in DSS-induced colitis mice. Supplementation with LP-315 may increase the abundance of beneficial bacteria *D. newyorkensis*, which is involved in SCFAs production and Trp metabolism. This, in turn, modulates the intestinal levels of SCFAs, IAA, XA, I3CA and Ser, and regulates the inflammation-associated Glutamine degradation pathway. These effects collectively contribute to the protection of the intestinal mucosal barrier, mitigation of inflammation, and improvement of colitis symptoms. In contrast, 5-ASA intervention primarily attenuated colonic inflammation through reduction the abundance of pathogenic *P. excrementihominis*, resulting in moderate improvement in histopathological scores in this study. Notably, LP-315 exhibited a more pronounced therapeutic effect on colitis mice compared to 5-ASA. This phenomenon of probiotic superiority over pharmacological agents in colitis management is consistent with emerging research paradigms. Study have found that the beneficial effects of 5-ASA on DAI, body weight, colon length, IL-1β, IL-6, and TNF-α in colitis mice were weaker than those of *L. Plantarum* BW2013[73]. Another study demonstrated that *L. plantarum* ZJ316 significantly outperformed 5-ASA in regulating SCFA contents in the guts of colitis mice[17]. Furthermore, the clinical efficacy of 5-ASA in the treatment of UC can be significantly variable, with more than half of all cases potentially experiencing treatment failure. This “ineffectiveness” may stem from the fact that prolonged DSS-induced colonic injury may surpass the therapeutic scope of 5-ASA for mild-to-moderate colitis. Furthermore, it could be attributed to the propensity of 5-ASA to be absorbed in the stomach and small intestine, or its acetylation and metabolic inactivation via specific gastrointestinal microbes or enzymes. These phenomena may cause drug concentrations at the site of injury to be far below the minimum effective dose, thereby hindering the desired anti-inflammatory effects[8, 74].

This study also acknowledges certain limitations and proposes directions for future research. By integrating gut metagenomic analysis, functional metabolic modules, and bioactive metabolite profiling following LP-315 intervention in DSS-induced colitis mice, and correlating these findings with previously identified phenotypic improvements, we identified key differential bacterial species and metabolites as

potential therapeutic targets. Future studies should include targeted validation of these metabolites, as well as the use of pathway-specific antagonists or receptor-deficient mouse models to further elucidate the molecular mechanisms by which LP-315 alleviates colitis. Moreover, our research highlights the limitations and prospects of probiotics applications in colitis management. First, the variability in DSS dosing protocols across colitis models introduces methodological heterogeneity, potentially confounding outcome interpretation and intervention efficacy evaluation. Establishing standardized modeling protocols would significantly advance therapeutic development for colitis management. Second, the gut microbiome not only consists of large bacteria but also includes viral microorganisms, such as bacteriophages. Increasing evidence suggests that probiotics have beneficial regulatory effects on gut bacteriophages[75-77]. However, research on the impact of probiotics on the intestinal bacteriophage community in colitis mouse models remains limited and warrants further scientific exploration. Moreover, it is essential to gradually expand the types and genomic information of bacteriophages in databases to provide reliable resources for clinical applications. Third, probiotics exhibit strain specificity, and the host's response to probiotics varies individually. The dosage and duration of probiotics also influence the extent of their effect on improving colitis. Therefore, extensive preclinical research is still required to identify novel probiotics and elucidate their mechanisms of action. Large-scale clinical studies are necessary to assess the safety, efficacy, and consistency of probiotics, thereby promoting the development and application of novel targeted formulations for colitis.

5. Conclusion

This study demonstrated that LP-315 exerted superior therapeutic benefits and potential in ameliorating DSS-induced colitis in mice compared to the conventional drug 5-ASA. LP-315 supplementation may alleviate colitis symptoms by enriching *D. newyorkensis*, a beneficial bacterium involved in SCFAs production and Trp metabolism, especially modulating key intestinal metabolites (IAA, XA, I3CA, Ser) and regulating the inflammation-associated Glutamine degradation pathway. These changes contribute to the restoration of the intestinal mucosal barrier and the attenuation of inflammation. Future research should integrate multi-dimensional data, including transcriptomics, immunomics, and single-cell analysis, to elucidate the key molecular targets and pathways. This study provides a strain-specific candidate strategy and novel insights for the microecological management of colitis, establishing scientific support and theoretical foundations for the development of personalized microecological therapies for colitis in clinical application.

Data availability

The raw sequences reported in this article were deposited in the China National GeneBank DataBase under the accession number CNP0006503 (https://db.cngb.org/search/?q=CNP0006503).

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