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Glucomannan from *Dendrobium officinale* Alleviates Colitis via Modulating Gut Microbiota and Upregulating Deoxycholic Acid Production

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ABSTRACT

Dietary fiber is a bioactive substance that can modulate gut microbiota and exert a relieving effect on inflammatory bowel disease (IBD). *Dendrobium officinale* polysaccharide (DOP) is a type of bioactive dietary fiber that has been proven to have various biological activities on intestinal function. However, the key mechanism underlying DOP-mediated protection against colitis is unclear. In this study, we proved that DOP alleviates colitis induced by dextran sulfate sodium (DSS), and its beneficial effects depend on the gut microbiota. Specifically, DOP supplementation significantly increased the abundance of *Clostridium* and *Ruminococcus* in mice, leading to the upregulated secondary bile acid synthesis pathway and increased deoxycholic acid (DCA) production. Notably, DCA administration alleviated colitis manifestations in DSS-treated mice. Collectively, these results indicate that DOP exerts its mechanism of improving colitis by modulating gut microbiota and promoting the synthesis of DCA.

1 | Introduction

Ulcerative colitis (UC) is one of the main subcategories of inflammatory bowel disease (IBD). It is characterized by chronic, nonspecific inflammation predominantly affecting the colon and rectum (Gros and Kaplan 2023). UC is characterized by recurrent episodes of inflammation and a prolonged disease course, significantly impairing patients' quality of life. With a global prevalence affecting millions, IBD represents a growing healthcare challenge, imposing significant medical, economic, and psychosocial burdens on individuals and society (Berre et al. 2023). Recent epidemiological studies on global IBD trends reveal that the disease typically evolves through four phases: emergence, acceleration in incidence, compounding prevalence, and eventual

prevalence equilibrium (Hracs et al. 2025). Industrialization and the adoption of a Westernized lifestyle, characterized by high-fat, low-fiber diets, are linked to gut microbiota dysbiosis and metabolic imbalances, which impair epithelial barrier function and trigger immune responses, driving the onset and progression of IBD (Adolph et al. 2024; Adolph and Zhang 2022). Recent studies have identified the gut microbiota as a key element in IBD pathogenesis, highlighting its potential as a therapeutic target (Gilliland et al. 2024; Iliev et al. 2025a).

In individuals with IBD, gut microbiota disturbances and alterations in gut metabolite profiles are both observed (Lavelle and Sokol 2020). Gut microbiota produces different kinds of metabolites, including short-chain fatty acids (SCFAs), bile acids,

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and tryptophan metabolites, and is capable of interacting with host targets and modulating host functions (Vila et al. 2024; Zheng et al. 2022). Bile acids are cholesterol-derived molecules mainly produced in the liver, known as primary bile acids. Once entering the intestine, they are metabolized by gut microbes to produce secondary bile acids. Bile acids play a role in immune regulation through the activation of receptors such as farnesoid X receptor (FXR) (Cai et al. 2022). However, patients with IBD are usually accompanied by a decrease in bile salt hydrolase activity, which may lead to an imbalance of bile acids, that is, the decrease of secondary bile acids (Lavelle and Sokol 2020). Increasing the level of specific bile acids can activate specific receptors and regulate different components of the intestinal mucosal barrier, thus regulating the homeostasis of intestinal microorganisms and restoring the function of the intestinal barrier and immune balance. (Fu et al. 2025; Li et al. 2023; Pan et al. 2024; Zhou et al. 2025). Accordingly, approaches focusing on modulating gut microbiota and their metabolites to prevent or manage UC have garnered significant interest (He et al. 2022), with dietary interventions emerging as a promising strategy. For example, carvacrol and thymol have been found to enrich *Bifidobacterium pseudolongum* in mice, elevate hyodeoxycholic acid (HDCA) levels, and alleviate colitis through the cGMP-PKG-mTORC1 pathway (Zhang et al. 2024). Fucoidan modulated the bile acid metabolism by increasing the levels of deoxycholic acid (DCA), lithocholic acid (LCA), cholic acid (CA), and ursodeoxycholic acid (UDCA), while decreasing the level of β -muricholic acid (β MCA). Moreover, it promoted intestinal homeostasis by activating FXR and Takeda G-protein-coupled receptor 5 (TGR5) (Liu et al. 2022; Zhou et al. 2025).

Dietary polysaccharides are often resistant to gastrointestinal digestion and hold significant potential for modulating gut microbiota and metabolic processes. *Dendrobium officinale* polysaccharides (DOP) are glucomannans with a mannose-to-glucose molar ratio around 6.9:1, a molecular weight of roughly 312 kDa, which are a refined glucomannan fraction obtained from the stems of *D. officinale* after extraction and purification (Xing et al. 2014). Our prior research demonstrated that these polysaccharides can enhance gut barrier function and improve insulin resistance by promoting nicotinic acid production by *Parabacteroides distasonis* and subsequently activating host GPR109A (Sun et al. 2023). Although studies have confirmed that various glucomannans can ameliorate colitis by modulating the gut microbiota to exert positive effects on intestinal barrier function and immunoregulation (Li et al. 2022; Zhang et al. 2019, 2023). However, the specific microbial taxa, key functional genes, and downstream bioactive metabolites involved in the action of DOP remain largely unknown. Further mechanistic studies on their effects in colitis are warranted; investigating how gut microbiota and bacterial metabolites mediate these effects could provide valuable insights into developing novel therapeutics or preventive strategies for gastrointestinal disorders.

Therefore, this study investigated DOP's regulation of gut microbiota and metabolites using DSS-induced colitis models with the aim of elucidating the complex interactions among DOP, gut microbiota, and intestinal inflammation.

2 | Methods

2.1 | Preparation of DOP

DOP was isolated from *Dendrobium officinale* as per the procedure given in our previous work (Xing et al. 2015b). Briefly, the stem of *Dendrobium officinale* was powdered and degreased twice with n-hexane (1:5, w/v) for 24 h, followed by two extractions with ethanol (1:5, w/v) for 24 h each. The dried powder was subjected to aqueous extraction (1:20 w/v, 70°C, 4 h), and then centrifuged (10,000×g, 20 min) to discard the residue. Ethanol was added to the supernatant, and the final concentration was set to 75% (v/v). The resulting precipitate was collected, washed, and re-dissolved in water. It was then freeze-dried, and the resulting powder was reconstituted in water (1:99, w/v). The sample was subjected to an enzymatic treatment. After dialysis (8–12 kDa), the supernatant was precipitated by adding ethanol at a ratio of 1:3 (w/v). The resulting precipitate was reconstituted in aqueous solution, thoroughly dialyzed against distilled water, and finally freeze-dried to acquire DOP. According to a previous study, DOP comprises 1,4- β -D-mannopyranosyl and 1,4- β -D-glucopyranosyl units situated in the linear core of its glucomannan structure, with O-acetyl groups attached to the O-2 or O-3 positions of the mannose residue (Xing et al. 2014). Total sugar content was up to 90.41% for DOP, and its weight-average molecular weight (Mw) was 312 kDa.

2.2 | Animal Experiments

Male C57BL/6J mice (5 weeks old) were purchased from Gem-Pharmatech LLC (Jiangsu, China). Mice were maintained in specific pathogen-free (SPF) conditions on a 12-h light/dark cycle, with ad libitum access to standard chow and water; temperature and humidity were kept constant (22 ± 2°C, 55 ± 10% relative humidity). The mice were acclimatized for one week before any treatment. Mice were randomly assigned to a control group or an intervention group. A sample size of six mice per group was utilized to ensure statistical power. All animal procedures were strictly followed by the National Institutes of Health (NIH) Guide for Care and Use of Laboratory Animals and were approved by the Experimental Animal Care and Use Committee of Nanchang University (approval #IACUC-20221030001). Study design and reporting are compliant with the Animal Research: Reporting of In Vivo Experiments (ARRIVE) 2.0 guideline.

In the assessment of DOP efficacy in colitic mice, mice received daily oral gavage of DOP (400 mg/kg) for 14 days. 3% (w/v) DSS (MW 36,000–50,000; MP Biochemical, USA) was co-administered in drinking water from days 7 to 14. The vehicle control group received equivalent volumes of PBS via gavage.

To explore whether DOP relieved the colitis by targeting the gut microbiota, we used mice treated with an antibiotic cocktail. The mice received daily oral gavage of DOP (400 mg/kg) for 14 days. From days 7 to 14, 3% (w/v) DSS was given in their drinking water. In the vehicle group, PBS solution was administered by gavage in an equivalent volume.

For the DCA efficiency assay in colitic mice, mice received daily oral gavage of DCA (50 mg/kg) for 14 days. From days 7 to 14, 3% (w/v) DSS was co-administered in drinking water. In the vehicle

group, PBS solution was administered by gavage in an equivalent volume.

2.3 | Antibiotic Treatment

To deplete the gut microbiota, mice were orally gavaged with a cocktail of four antibiotics: ampicillin (100 mg/kg), metronidazole (100 mg/kg), vancomycin (50 mg/kg), and neomycin (100 mg/kg) for 7 consecutive days (Sun et al. 2023).

2.4 | Histopathological and Immunohistochemical Analysis

Colon tissue samples were fixed with 4% paraformaldehyde, embedded in paraffin, and sectioned into 4 μ m slices for hematoxylin-eosin (H&E) and Alcian blue/periodic acid-Schiff (AB/PAS) staining. Tissue sections were observed and imaged using a digital pathology platform (Leica Aperio LV1). H&E staining was evaluated according to the scoring methods outlined in earlier studies (Dieleman et al. 1998; Katakura et al. 2005). The scoring system assessed three parameters, each graded on a scale of 0 to 4: the severity of epithelial damage, the degree of inflammatory infiltration, and the depth of the lesion. The overall histological scores were calculated as the sum of the three parameter scores. For AB/PAS staining, at least 20 crypts from each section were subjected to the process with the objective of viewing and enumerating the number of goblet cells. Only crypts with a complete longitudinal section from opening to base were counted. As for the immunohistochemistry (IHC) experiment, paraffin-embedded sections were stained with antibodies that specifically targeted Claudin-1, Occludin, ZO-1, and Muc-2. The proportion of positive regions was calculated with ImageJ (version 1.53k).

2.5 | Quantitative Analysis of Cytokines

The colon tissues were homogenized in PBS and centrifuged at 10,000 rpm, 4°C for 10 min, and the supernatants were extracted for subsequent analysis. Cytokine levels were determined using ELISA kits (Fcmacs, Nanjing, China) according to the instructions, and protein concentrations were detected using the BCA assay kit (Beyotime, Shanghai, China). The cytokine levels were then normalized to the total protein concentration.

2.6 | 16S rRNA Gene Sequencing and Data Analysis

Fecal total DNA was extracted with the Tiangen (Beijing, China) fecal DNA extraction kit, and the V4 region of the 16S rRNA gene was amplified using 515F/806R primers. The amplified products were separated by 2% agarose gel electrophoresis and subsequently purified using the Universal Agarose Gel DNA Recovery Kit (Tiangen). The concentration of the purified PCR product was measured using a Qubit 3.0 fluorometer (Life Invitrogen). DNA samples were mixed in equal amounts according to the manufacturer's protocol. DNA library preparation included end repair, size selection, adenylation of the 3' ends, adapter ligation, and enrichment of DNA fragments. Library quality control was

carried out by Agilent 2100 Bioanalyzer (high-sensitivity DNA chip). Following the standard procedures described, genomic DNA was paired-end-sequenced using Illumina MiSeq (Nie et al. 2021).

2.7 | Gene Expression Analysis

Colonic tissue sample total RNA was extracted with TRIzol reagent (Takara Bio Inc., Otsu, Shiga, Japan). After reverse transcription using the PrimeScript RT kit (Takara Bio Inc.), mRNA levels were quantified by quantitative real-time PCR with the TB Green Premix Ex Taq II (Takara Bio Inc.) on a QuantStudio 7 Flex System (Thermo Fisher Scientific, Waltham, MA, USA). β -Actin served as the endogenous control; mRNA relative expression was calculated using the $2^{-\Delta\Delta C_t}$ quantification method.

2.8 | Nontargeted Metabolomics

Metabolite extraction from the feces of mice was performed based on a previous report with slight modification (Nie et al. 2022). Briefly, 50 mg of feces were suspended in 400 μ L of ice-precooled 50% methanol (v/v) and homogenized with homogenizer KZ-II (Servicebio, Wuhan, China). After ice-bath sonication (20 min), samples were centrifuged at 18,000 $\times$ g for 20 min at 4°C. The resulting supernatant was then analyzed using a Shimadzu Nexera X2 UPLC system (Shimadzu Corporation, Kyoto, Japan) coupled to an AB SCIEX TripleTOF 5600 mass spectrometer (Nie et al. 2024). Chromatographic separation was performed at 40°C using an ACQUITY UPLC HSS T3 column (2.1 $\times$ 100 mm, 1.8 μ m). Raw MS data were processed with Progenesis QI (v2.0; Waters). Metabolites were annotated by matching MS/MS spectra against the HMDB (v4.0) and METLIN (v1.0.6499.51447) databases.

2.9 | Quantification of Bile Acids

To quantify fecal bile acids in mice, precisely 20 mg of feces was weighed into tubes. An ice-cold methanol solution (400 μ L) containing 0.2 mM internal standard was added. Samples were homogenized using a tissue homogenizer for 70 s with intermittent cooling. Samples were then rotary centrifuged for 20 min to extract metabolites, and then all samples were centrifuged at 14,000 rpm for 20 min at 4°C. As for LC-MS/MS analysis, the supernatant was filtered through a membrane filter of pore size 0.22 μ m. Bile acid levels were analyzed via an LC-MS/MS system comprising the Shimadzu Nexera X2 HPLC system (Shimadzu Corporation) and SCIEX 6500 QTRAP quadrupole linear ion trap mass spectrometry (AB SCIEX, Framingham, MA, USA). An ACQUITY UPLC HSS T3 column (2.1 mm $\times$ 100 mm, 1.8 μ m) was used for the separation process. Complete information details were provided in our previous publication (Nie et al. 2024).

2.10 | Statistical Analysis

Statistical analyses were performed using GraphPad Prism 10.1.0. and SPSS 26.0; data are presented as mean $\pm$ SEM. The normality of the data was examined to determine the appropriate statistical tests. Two-group comparisons used Student's *t*-tests (equal

variances) or Welch's *t*-tests (unequal variances). Multigroup comparisons used one-way ANOVA followed by Tukey's or Dunnett's post hoc test. Nonparametric data used Mann–Whitney *U* (two groups) or Kruskal–Wallis (multigroup) tests. A *p*-value of less than 0.05 was considered statistically significant.

3 | Results

3.1 | DOP Alleviates DSS-Induced Colitis

To evaluate the effect of DOP on DSS-induced colitis, mice received an oral gavage of DOP once daily for 7 days, followed by concurrent administration of 3.0 % (w/v) DSS and DOP for an additional 7 days. Over the course of the colitis treatment, DOP supplementation significantly attenuated body weight loss and eased diarrhea and rectal bleeding, and avoided colon shortening as well (Figure 1A–C). Additionally, the colons of the mice were histologically examined, and it was found that DOP could alleviate the injury to the intestinal epithelial cells and inhibit the infiltration of inflammatory cells (Figure 1D,E). AB/PAS staining showed a decrease in goblet cell loss in the DOP + DSS group relative to the DSS group (Figure 1D,F). Compared with the DSS group, the DOP + DSS group exhibited significantly decreased myeloperoxidase (MPO) activity and lower levels of the proinflammatory cytokines TNF- α and IL-6 (Figure 1G). Compared with the DSS group, the DOP + DSS group showed increased expression of tight junctions (Claudin-1, Occludin, ZO-1) and mucin secretion (Muc-2) compared to the DSS group (Figure 1H). Moreover, the proportion of positively stained regions of the four proteins was also increased (Figure 1I). These data suggest that DOP could alleviate colitis triggered by DSS.

3.2 | Alleviation of Colitis by DOP is Microbiota-Dependent

UC is commonly associated with an abnormal gut microbiota, and DOP supplementation may exert anticolitis effects via altering gut microbiota (Zeng et al. 2024). To test this hypothesis, we investigated the role of the gut microbiota in DOP-mediated amelioration of colitis by performing antibiotic-induced microbiota ablation in mice. During the course of the colitis treatment, DOP supplementation could not prevent weight loss, diarrhea, rectal bleeding, and colonic shortening caused by DSS (Figure 2A–C). Histological analysis showed that DOP could not reverse the epithelial destruction and inflammatory infiltration induced by DSS (Figure 2D,E). The loss of goblet cells showed no significant difference between the Abx-DOP group and the Abx-DSS group, as determined by AB/PAS staining (Figure 2D,F). The levels of MPO, TNF- α , and IL-6 showed no significant differences between Abx-DOP and Abx-DSS groups (Figure 2G). These findings suggest that gut microbiota is indispensable for DOP's therapeutic efficacy against colitis.

3.3 | DOP Alters the Composition of Gut Microbiota and Increases the Abundance of *Clostridium* and *Ruminococcus* in Colitic Mice

Fecal microbiota structure was analyzed by 16S rRNA sequencing to assess the effects of DOP. Compared with the NC group, neither the DSS nor the DOP + DSS group exhibited significant alterations in community-wide species richness or evenness indices (Figure 3A). However, DSS administration significantly altered gut microbiota composition in mice, while DOP supplementation modulated these microbiota changes in colitic mice (Figure 3B). The relative abundances of *Muribaculum*, *Oscillibacter*, *Lactobacillus*, *Eisenbergiella*, *Alistipes*, and *Clostridium* were decreased in the DSS group compared to the NC group. In contrast, the relative abundance of *Prevotella* and *Akkermansia* was upregulated. Furthermore, DOP supplementation markedly increased the abundances of *Parabacteroides*, *Clostridium*, and *Ruminococcus*, as compared with the DSS group (Figure 3C,D).

The volcano plot showed that, compared with the DSS group, the levels of *Ruminococcus* and *Clostridium* were significantly increased in the DOP + DSS group, with *Ruminococcus* showing a greater increase than *Clostridium* (Figure 3E). Spearman's rank correlation analysis demonstrated that *Ruminococcus* abundance exhibited significant positive correlations with goblet cell counts, body weight, and colon length, while showing negative correlations with DAI scores and the levels of MPO, TNF- α , and IL-6. Similar correlation patterns were observed for *Clostridium*. Notably, *Parabacteroides* abundance displayed strong negative correlations with DAI scores and IL-6 levels. In parallel, significant negative correlations were detected between goblet cell counts and the abundances of *Kiloniella*, *Limosilactobacillus*, *Monoglobus*, and *Streptococcus* (Figure 3F). Notably, histological scores showed a negative correlation with *Clostridium* and *Ruminococcus* abundance, whereas colon length exhibited a positive correlation with these bacterial taxa, suggesting that increased abundance of these bacteria may contribute to intestinal structural improvement in colitis (Figure 3G). The mBodyMap database is a curated database focusing on the human microbiome and its association with health and disease (Jinet al. 2022). Compared with the healthy population, the proportions of *Clostridium* and *Ruminococcus* were significantly lower in patients with Crohn's disease. These results suggest that *Clostridium* spp. and *Ruminococcus* spp. may be the main microbial taxa mediating the protective effects of DOP against inflammatory responses in the colon (Figure 3H,I). These results suggest that *Clostridium* and *Ruminococcus* may be the key bacterial genera through which DOP alleviates colitis.

PICRUSt-based analysis was used to predict the possible functional effect of DOP on gut microbiota. DOP supplementation was positively associated with secondary bile acid biosynthesis, pyrimidine metabolism, tryptophan metabolism, and fructose and mannose metabolism, while negatively associated with bacterial epithelial cell invasiveness and sphingolipid metabolism activity. Among these metabolic pathways, the biosynthesis of secondary bile acid was most strongly affected (Figure 3J). A central step included in this biosynthesis is 7 α -dehydroxylation, which plays an important role in secondary bile acid biosynthesis (W.-B. Jin, Li, et al. 2022). This process is accomplished primarily

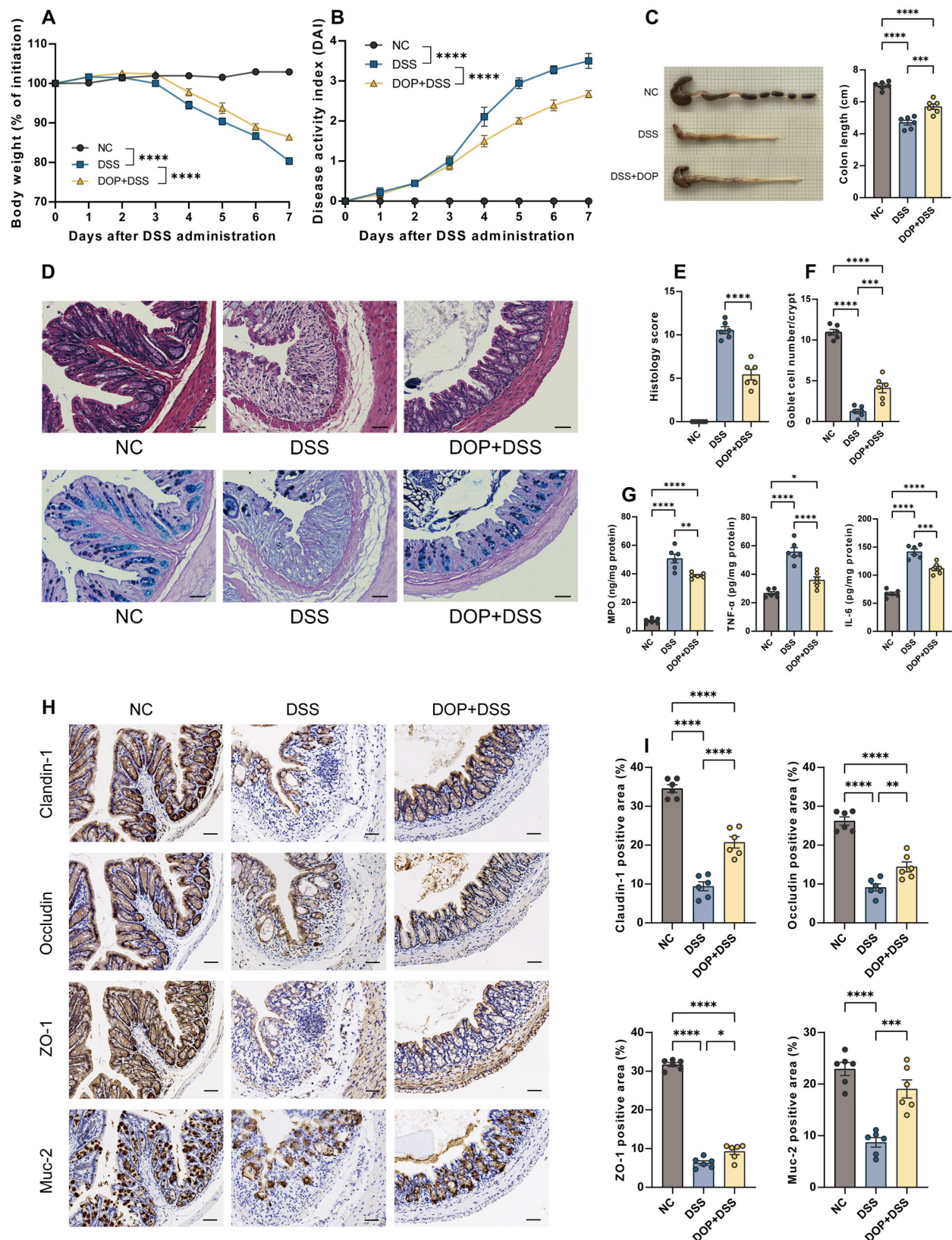


FIGURE 1 | DOP treatment alleviates colitis-associated phenotype. (A) Body weight dynamics during DSS administration. (B) Disease activity index (DAI). (C) Representative photographs of the colon and colon length. (D) Representative H&E-stained and AB/PAS-stained colon sections (scale bar: 50 μ m). (E) Histology score. (F) Counting of goblet cells per crypt. (G) Colonic levels of MPO, TNF- α , and IL-6 in colon. (H) Representative images of immunohistochemical staining for Claudin-1, Occludin, ZO-1, and Muc-2 (scale bar: 50 μ m). (I) The positive areas of Claudin-1, Occludin, ZO-1, and Muc-2 were calculated by ImageJ. Values are presented as mean $\pm$ SEM. $n = 6$ mice per group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

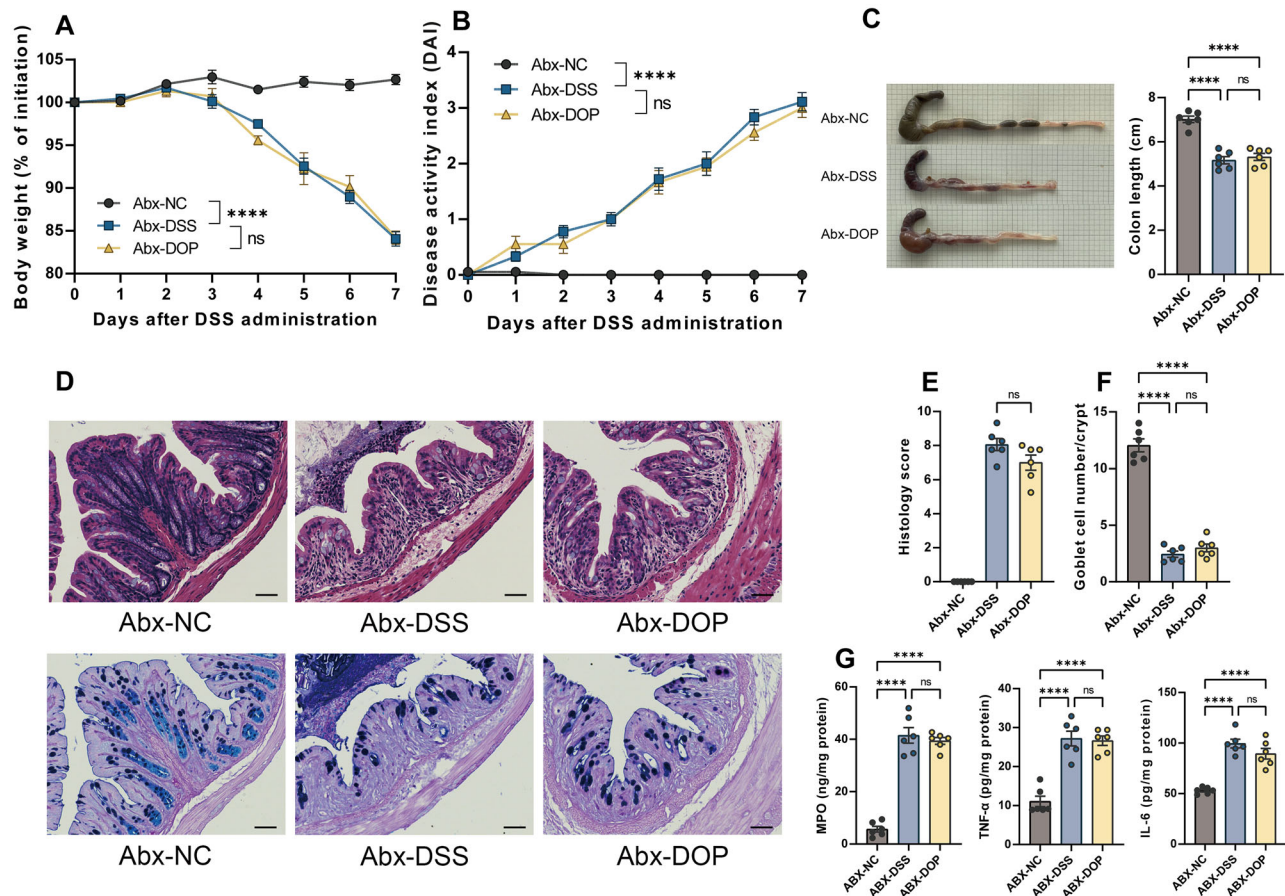


FIGURE 2 | Gut microbiota mediates the protective effects of DOP against colitis development. (A) Body weight dynamics during DSS administration. (B) Disease activity index (DAI). (C) Representative photographs of the colon and colon length. (D) Representative H&E-stained and AB/PAS-stained colon sections (scale bar: 50 μ m). (E) Histology score. (F) Counting of goblet cells per crypt. (G) Colonic levels of MPO, TNF- α , and IL-6 in colon. Values are presented as mean $\pm$ SEM. $n = 6$ mice per group. **** $p < 0.0001$. No significant (ns) for $p > 0.05$.

by enzymes encoded by the bile acid-inducible (*bai*) gene cluster in the gut microbiota. Analysis of *bai* gene expression revealed that DOP significantly upregulated the expression levels of both *baiCD* and *baiH* in mice with DSS-induced colitis compared to the DSS group (Figure 3K).

3.4 | DOP Supplementation Promotes Deoxycholic Acid (DCA) Production

Gut microbiota systematically regulate host metabolic homeostasis by synthesizing a wide variety of metabolites through diverse metabolic pathways (Lavelle and Sokol 2020; Rooks and Garrett 2016). To measure the key metabolites, we used nontargeted LC-MS/MS metabolomics technology to analyze the feces of mice. The PCA plot with scores of the pos and neg model showed that DOP significantly altered metabolite distribution in colitis mice, and the effect was robust in both positive and negative ion modes (Figure 4A,B). DOP supplementation significantly upregulated 21 metabolites, including L-pyrrolidic acid, genistein, and DCA, while five metabolites, including oleamide, histamine, and 10, 11-dihydroxystearic acid, were significantly downregulated (Figure 4C). Furthermore, the pathways mostly affected by DOP mainly included metabolism of primary bile acids, biosynthetic pathways of phenylalanine, tyrosine, and tryptophan, as well as

phenylalanine metabolism (Figure 4D). Based on the abundance levels of the metabolites altered by DOP treatment, DCA was the most abundant (Figure 4E).

To elucidate the correlation between DCA levels and colitis severity, we assessed their relationship with key disease parameters. The results revealed that DCA abundance was significantly negatively correlated with the histologic damage score, TNF- α levels, and MPO levels, while positively correlated with colon length (Figure 4F). Furthermore, we collected feces from mice in the PBS and DOP groups, and then bacteria from these feces were incubated in BHI media supplemented with cholic acid. DOP-influenced bacteria also exhibited stronger DCA synthesis capability in vitro (Figure 4G–I). In conclusion, the results indicate that DOP may relieve colitis by promoting the synthesis of secondary bile acids, and DCA is the key metabolite involved.

3.5 | DCA Relieves DSS-Induced Colitis

Based on the results from metabolomics and gut microbiota analysis, we hypothesized that the gut microbiota influenced by DOP is associated with bile acid metabolism. Notably, DOP intervention enriched *Clostridia* and *Ruminococcus*, known converters of primary to secondary bile acids. Given these significant

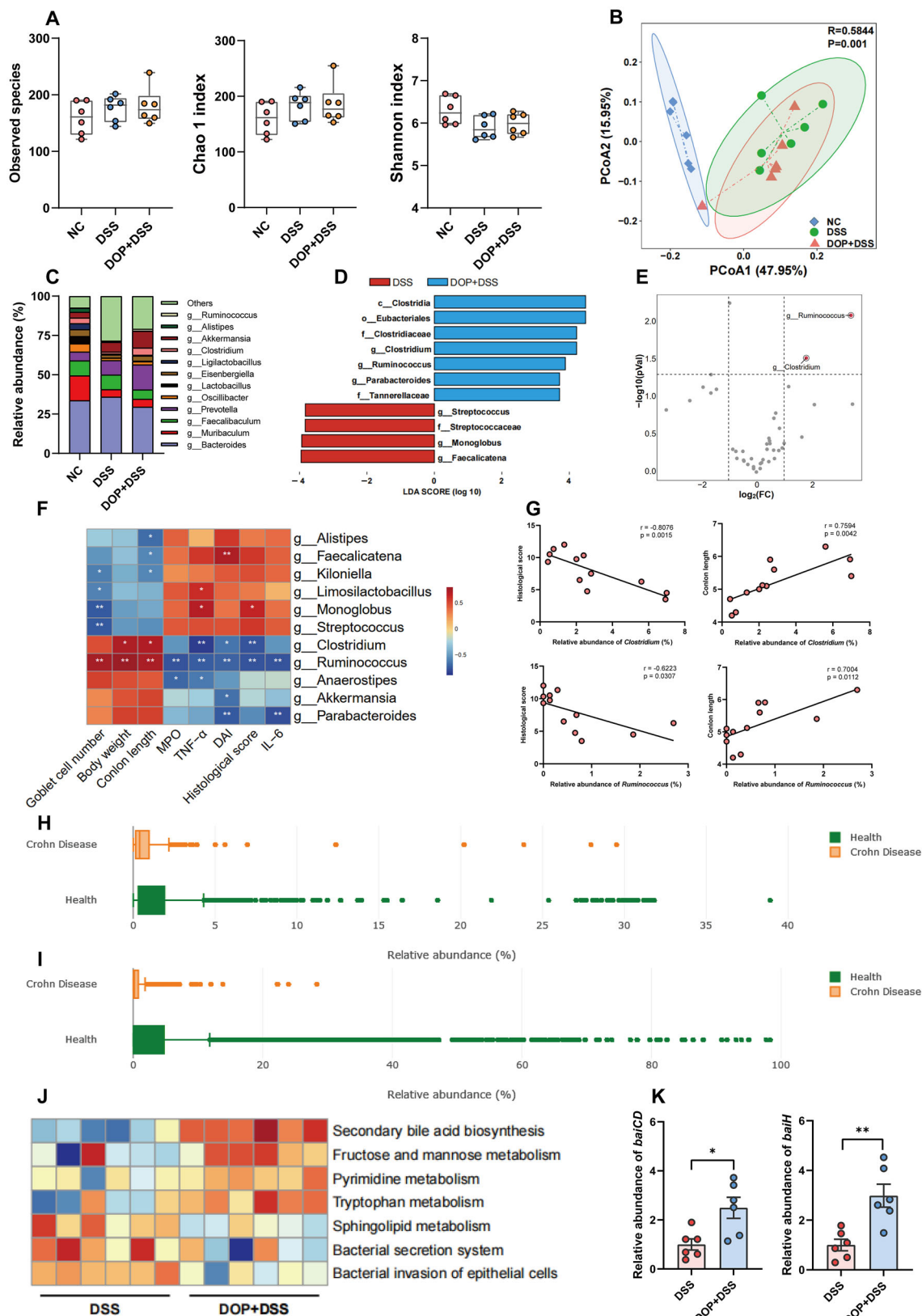


FIGURE 3 | DOP alters gut microbiota composition and increases *Clostridium* and *Ruminococcus* abundance in colitic mice. (A) Gut microbiota α -diversity in each of the varying groups represented by the Observed species, Chao1, and Shannon index. (B) PCoA graph based on unweighted UniFrac. (C) Genus-level taxonomic abundance. (D) LefSe for determining the comparative bacterial relative abundance comparing DSS and DOP + DSS groups. (E) Volcano plot for displaying bacteria from the DSS and DOP + DSS group. (F) Heatmap for illustrating the correlation between bacteria and colitis—related parameters. (G) Correlation analysis of the abundance of *Clostridium* and *Ruminococcus* with histological score and colon length, the relationships between variables were studied via linear regression analysis. Calculation of the linear correlation index R and p-values.

microbial shifts, we subsequently analyzed the fecal bile acid profile. Consistent with the alterations in the gut microbiota described above, DOP led to increased levels of DCA in the feces of colitic mice (Figure 5A). Subsequently, we examined the impact of DCA on mice suffering from colitis. During the induction of colitis, the addition of DCA markedly reduced body weight loss, alleviated symptoms of diarrhea and rectal bleeding, and suppressed colon shortening (Figure 5B–D). Histological evaluations of the mouse colon revealed that DCA significantly decreased intestinal epithelial damage and restricted the infiltration of inflammatory cells (Figure 5E,F). AB/PAS staining showed that DCA supplementation alleviated DSS-induced generation of cupped cell loss (Figure 5G,H). In the DCA + DSS group of mice, the levels of MPO, TNF- α , and IL-6 were markedly lower than those in the DSS group (Figure 5I). Furthermore, the addition of DCA markedly enhanced the relative mRNA expression levels of *Claudin-1*, *Occludin*, *ZO-1*, and *Muc-2* in the colon of mice (Figure 5J). DOP and DCA supplementation could significantly upregulate the mRNA expression level of TGR5 (Figure 5K,L). These findings indicate that DCA has the potential to mitigate colitis triggered by DSS and might serve as a critical therapeutic metabolite mediating the protective effects of DOP.

4 | Discussion

Dietary fiber is widely found in everyday foods, and it is considered to be the seventh most important nutrient for humans. Bioactive dietary fibers, resistant to digestion and absorption in the upper gastrointestinal tract, undergo microbial fermentation and selectively promote the growth and activity of beneficial bacterial populations in the intestine (Nie et al. 2019). *Dendrobium officinale* is an important traditional Chinese medicine and functional food, with a variety of health benefits (Xing et al. 2015a). Glucomannan is an important bioactive component in *Dendrobium officinale* and has been reported to have many biological properties, including antioxidant, hypoglycemic, anti-inflammatory, anticancer, immunomodulatory, and gastrointestinal protective effects (Shi et al. 2020). Prior investigations have established that DOP can regulate gut microbiota composition and exert immunoregulatory effects, as well as increase colon length and reduce colonic pH, thereby improving the colonic microenvironment in mice (Zhang et al. 2016). Furthermore, DOP intervention significantly alleviated colitis in mouse models, as evidenced by a reduction in pro-inflammatory cytokine levels (TNF- α , IL-6, and IL-1 β) and an increased number of goblet cells in the colon (Zhang et al. 2019, 2020). In the present study, we found administration of DOP significantly reduced colonic inflammation, intestinal epithelial destruction, and limited inflammatory cell infiltration, suggesting that DOP could protect against DSS-induced colitis in mice.

Gut microbial dysbiosis is a pivotal driver in the pathogenesis of IBD, and we also found alleviation of colitis by DOP is

microbiota-dependent based on the antibiotic-induced gut microbiota depletion experiment (Figure 2). Generally, IBD-associated gut dysbiosis is characterized by an elevated ratio of pathobionts to beneficial bacteria coupled with reduced microbial overall diversity (Iliev et al. 2025a). Regarding specific bacterial species, multiple large-scale cohort studies have revealed significant microbial imbalances in IBD, including the increased abundance of *Streptococcus anginosus*, *Clostridium innocuum*, *Fusobacterium* spp., along with a reduction in beneficial groups such as *Faecalibacterium prausnitzii*, *Ruminococcus* spp., and *Eubacterium rectale* (Iliev et al. 2025a; Pascal et al. 2017; Vila et al. 2018). In the presented study, we found that the abundance of *Muribaculum*, *Oscillibacter*, *Lactobacillus*, *Eisenbergiella*, *Alistipes*, and *Clostridium* was decreased in colitic mice. A recent study revealed that the levels of *Muribaculum* decreased significantly in colitic mice but rebounded with the improvement of colitis (Gu et al. 2022). As a key mucin monosaccharide utilizer, *Muribaculum* may play a protective role by inhibiting *Clostridioides difficile* colonization (Pereira et al. 2020). *Lactobacillus*, a well-known probiotic, enhances host health via nutritional, physiological, microbiological, and immunomodulatory mechanisms. The mechanism of *Lactobacillus* on the amelioration of colitis is mainly associated with the regulation of the immunological barrier, intestinal epithelial cell barrier, intestinal mucus barrier, as well as improvement of the intestinal microbiota microenvironment (C. Li, Peng et al. 2023). Importantly, the clinical research results show that the level of AhR ligand in the intestine of patients with IBD is significantly lower than that of healthy controls. The elevation of AhR ligands in the intestinal environment is facilitated by *Lactobacillus*, thus activating the receptor and stimulating the production of anti-inflammatory cytokine IL-22 (Laursen et al. 2021; Zhang, et al. 2024). *Alistipes* is a butyrate-producing bacterium that is thought to be linked to host health status, exhibits anti-inflammatory effects, and may prevent UC (Mancabelli et al. 2017). *Clostridium* is closely associated with pathogenesis and amelioration of IBD. *C. difficile* infection is an important cause of colitis, whereas certain *Clostridium* species (e.g., *Clostridium* clusters XIVa and XIV) are reported to protect against colitis, mainly through SCFAs production, amino acid metabolism, and bile acid metabolism (Iliev et al. 2025a). DOP treatment also elevated the abundance of *Clostridium* and *Ruminococcus*. These results indicate that the dysbiosis of gut microbiota occurs in colitis, and that increased abundance of *Clostridium* and *Ruminococcus* might be associated with improvement of colitis.

The gut microbiota regulates host metabolism through microbial-derived metabolites, including SCFAs, lipopolysaccharides (LPS), and bile acids, establishing a key connection between the gastrointestinal tract and distant organs (Lin et al. 2025; Nie et al. 2024). In our study, we found treatment with DOP influenced a series of fecal metabolites, including increased levels of L-pipecolic acid, DCA, genistein, taurine, and 3-indolepropionic acid. Based on the high abundance of DCA in the intestine, we

(H) Relative abundance of *Clostridium* in Crohn's disease patients versus its relative abundance in healthy individuals (from mBodymap). (I) Relative abundance of *Ruminococcus* in Crohn's disease patients compared to their relative abundance in healthy individuals (from mBodyMap). (J) Analysis of the effects of DOP on the potential functions of gut microbiota with PICRUST analysis. (K) Relative abundance of *baiCD* and *baiH* in different groups. Values are presented as mean $\pm$ SEM. * $p < 0.05$, ** $p < 0.01$.

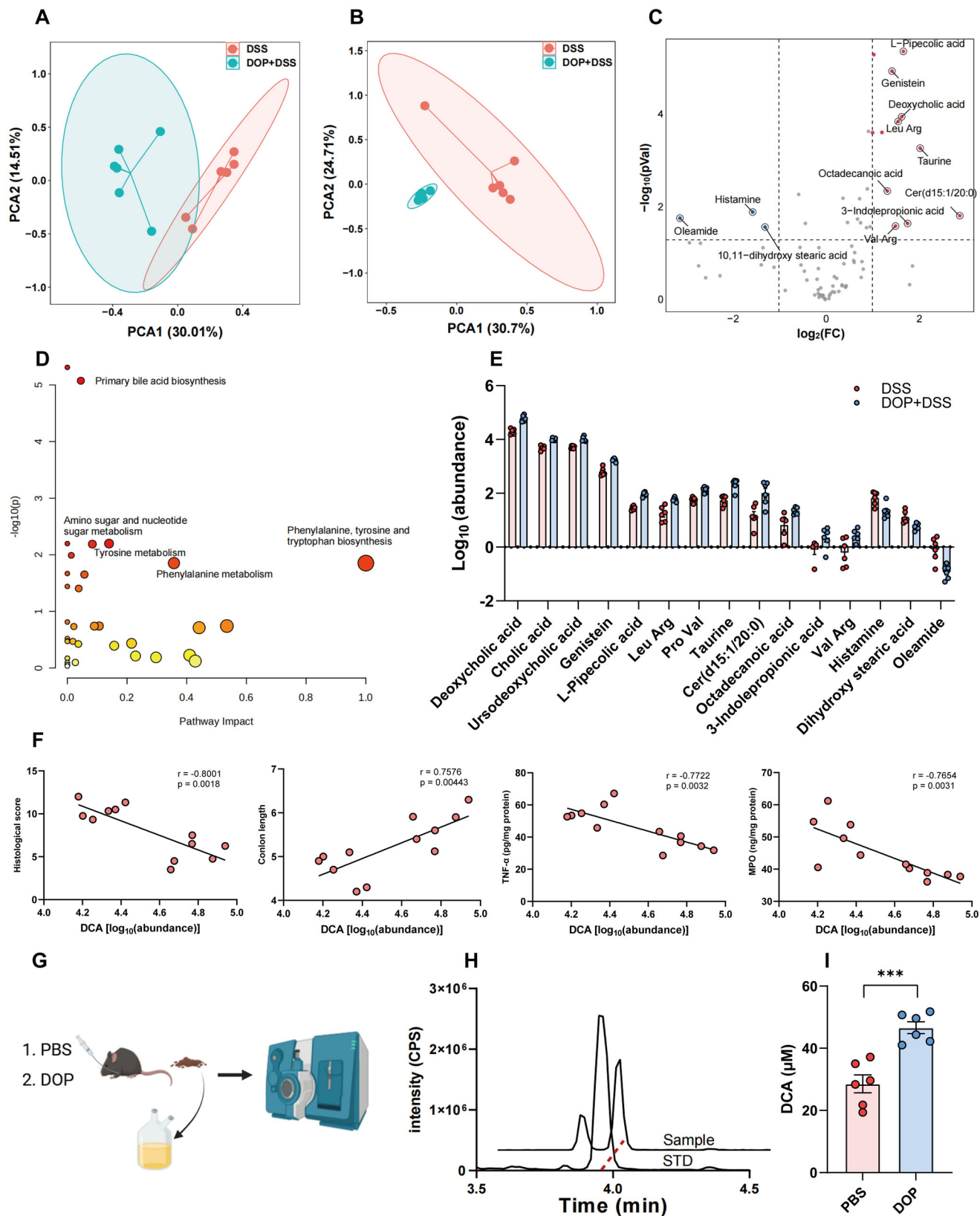


FIGURE 4 | Treatment with DOP increased DCA levels. (A, B) PCA score plots for both positive and negative models in DSS and DOP + DSS group. (C) Volcano plot of the metabolic data between the DSS group and the DOP + DSS group. (D) Pathway enrichment analysis was performed using the mummichog algorithm on fecal metabolomics data from DOP-treated samples. (E) A relatively abundant metabolite significantly changed after DOP treatment, as shown in (C). (F) Correlation analysis of DCA levels with histologic score, colon length, TNF- α , and MPO levels. (G–I) Establishment of the MS method for DCA detection (H) and quantification of DCA from DOP-influenced bacteria incubation (I), as described in the schematic diagram (G). Values are presented as mean $\pm$ SEM. $n = 6$ mice per group. *** $p < 0.001$.

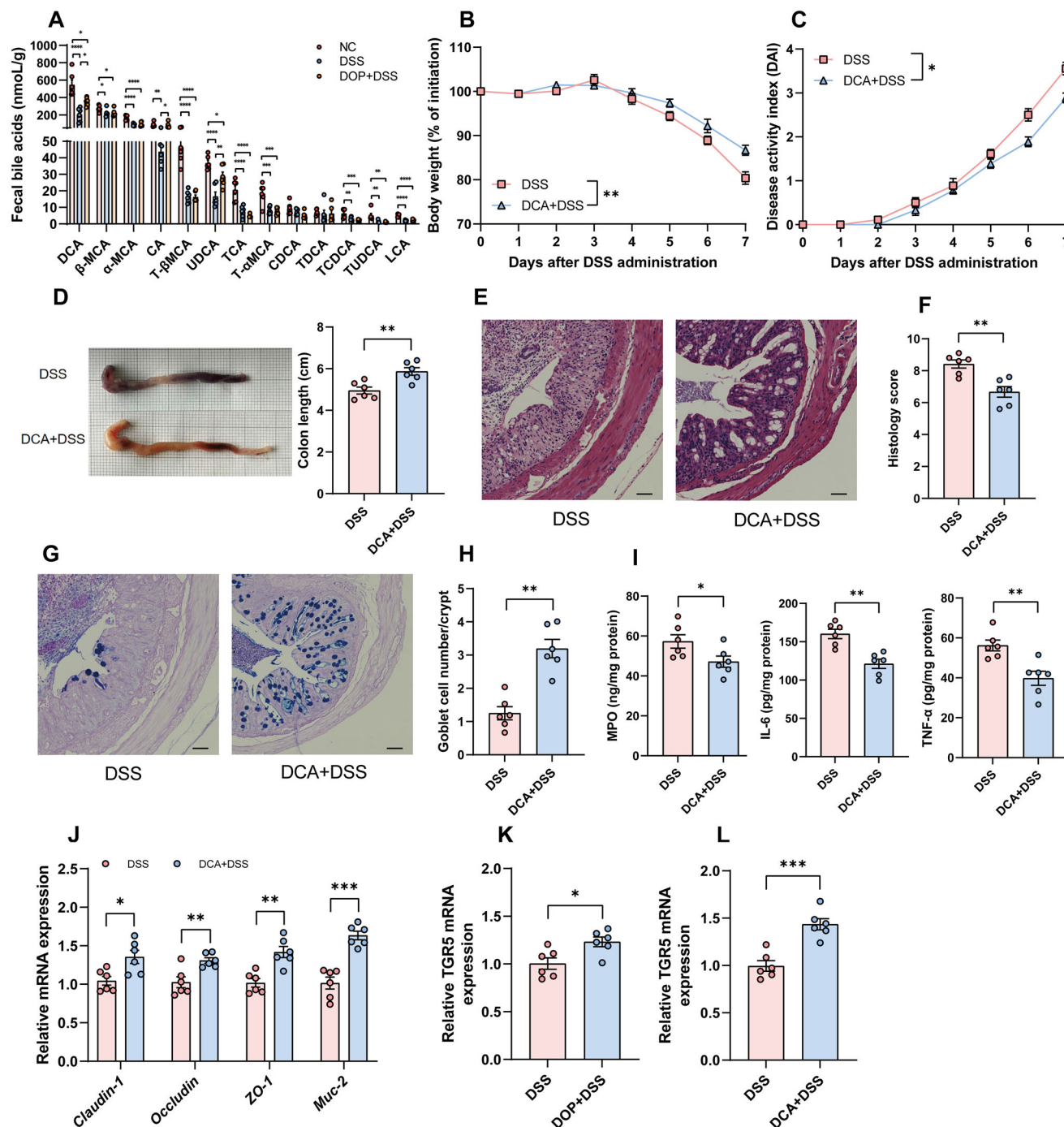


FIGURE 5 | DCA intervention alleviates DSS-induced colitis. (A) Fecal bile acids' profile of different groups of mice. (B) Body weight dynamics during DSS administration. (C) Disease activity index (DAI). (D) Representative photographs of the colon and colon length. (E) Representative H&E-stained colon sections (scale bar: 50 μ m). (F) Histological scoring. (G) Representative AB/PAS-stained colon sections (scale bar: 50 μ m). (H) Counting of goblet cells per crypt. (I) Colonic MPO, TNF- α , and IL-6 levels. (J) Representative gene expression of *Claudin-1*, *Occludin*, *ZO-1*, and *Muc-2*. (K, L) Relative expression level of TGR5 mRNA in colonic tissue in different groups. Values are presented as mean $\pm$ SEM. $n = 6$ mice per group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$.

speculate that DCA might be the key metabolite that mediates the improvement of colitis. In addition, the increase in DCA is directly linked to the enrichment of *Clostridium/Ruminococcus* and the upregulated bai gene with the improvement of IBD, and DCA supplementation successfully reproduced the protective effect on IBD mice observed by DOP supplementation. Primary bile acids (CA and CDCA) are synthesized from cholesterol in

the liver and can be converted to secondary bile acids (DCA and LCA) by gut microbiota. In IBD, bile acid metabolism undergoes significant dysregulation, especially under conditions of microbial dysbiosis. Fecal samples from IBD patients exhibit elevated conjugated bile acid levels alongside depleted secondary bile acids (Franzosa et al. 2019). Manipulation of the bile acid pool can regulate the activation of bile acid receptors such as FXR,

pregnane X receptor (PXR), vitamin D receptor (VDR), and TGR5, among which secondary bile acids have greater affinity for TGR5 activation (Vallim et al. 2013).

TGR5 knockout mice exhibit disrupted colonic mucous cell morphology and tight junction integrity, compromising intestinal barrier function and exacerbating DSS-induced colitis (Cipriani et al. 2011). Similarly, TGR5 agonists have been shown to reduce the inflammatory index in a DSS-induced colitis model. 7-KDCA directly acts on intestinal epithelial cells, activates the TGR5-IP3R signaling axis, induces endoplasmic reticulum calcium release, and enhances colonic mucosal healing in a mouse model of colitis (Zhang et al. 2025). This effect has been detected in other models of intestinal and gastric epithelial injury, such as those induced by acetylsalicylic acid (Cipriani et al. 2013). Furthermore, DCA supplementation significantly improved colonic inflammation in colitic mice, indicating that DOP might ameliorate colitis via increased levels of DCA in mice.

Production of DCA is associated with the function of 7 α -dehydroxylation in gut microbiota. This reaction is catalyzed by an enzyme encoded by the *bai* gene family. 7 α -dehydroxylation is limited to free bile acids and is a multistep pathway carried out by several *bai* genes (*baiB*, *baiCD*, *E*, *A2*, *baiF*, *baiG*, *baiH*, and *baiI*) (Funabashi et al. 2020; Wu et al. 2021). *Clostridium* and *Ruminococcus* species have been identified to harbor the *bai* operon, which mediates the 7 α -dehydroxylation reaction, encoding enzymatic machinery for the bioconversion of primary bile acids to secondary bile acids (Wang et al. 2023; Wu et al. 2021). DOP Supplementation increased the abundance of *Clostridium* and *Ruminococcus*, along with the gene abundance of *baiCD* and *baiH*, which contribute to the up-regulated pathway of secondary bile acid synthesis and increased levels of DCA.

5 | Conclusion

Our study elucidated the mechanism by which DOP exerts beneficial effects on colitis and provided new insights into the alleviation of intestinal inflammation by secondary bile acids. Specifically, we found that DOP could alleviate DSS-induced colitis through changes in the gut microbiota, particularly the enrichment of *Clostridium* and *Ruminococcus*. These microbial changes are associated with the activation of the secondary bile acid synthesis pathway, with DCA emerging as a key bioactive metabolite involved in the alleviation of colitis. Our findings highlight the importance of bioactive dietary components in regulating host health through the secondary bile acid synthesis pathway. Collectively, these results revealed the unique mechanism of DOP in colitis and provided a feasible strategy for treating and preventing colitis with bioactive dietary fiber.

Author Contributions

Jie Xu: conceptualization, methodology, validation, formal analysis, writing – original draft. **Shanshan Zhang:** conceptualization, methodology, validation, formal analysis, writing – original draft. **Qi Chen:** investigation. **Chenqing Xu:** investigation. **Siying Wu:** investigation. **Qiongni Lin:** investigation. **Zhipeng Li:** investigation. **Qixing Nie:** funding acquisition, supervision, validation, writing – review and editing.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data are available from the corresponding author upon reasonable request.

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