

Exploring the Role of Proanthocyanidins in Mitigating Ulcerative Colitis in Mice

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ABSTRACT

Aim: To determine the role of Proanthocyanidins (Pros) in mitigating Ulcerative Colitis (UC) in mice. **Materials and Methods:** A UC mouse model was constructed using dextran sulfate sodium induction in male adult Balb/c mice. Mice were randomly divided into Control, Model, Pro and Mesalazine groups. The pathological morphology of the colon was evaluated using the Disease Activity Index (DAI), colon appearance and length, IL-6, TNF- α and TGF- β levels and Hematoxylin and Eosin (HE) staining. Immunohistochemistry, western blotting and qRT-PCR were used to detect TLR4 and NF-KB p65 protein and mRNA levels. **Results:** DAI scores were significantly increased, and colonic length and HE scores were significantly reduced in the Model group compared with the Control group ($p < 0.001$ for all). IL-6, TGF- β and TNF- α levels increased significantly in the Model group compared with the Control group ($p < 0.001$ for all). The number of apoptotic cells and TLR4 and NF-KB p65 protein and mRNA levels increased significantly in the Model group compared with the Control group ($p < 0.001$ for all). UC improved significantly in the Pro-group compared with the Model group, including suppression of the TLR4/NF-KB p65 pathway. **Conclusion:** Pro-treatment improved UC by depressing the TLR4/NF-KB p65 signalling pathway.

Keywords: NF-kB(p65), Pro, TLR4, UC.

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INTRODUCTION

Ulcerative Colitis (UC), which can potentially escalate into colorectal cancer, is a chronic inflammatory bowel disease characterised by abdominal pain, rectal bleeding and persistent diarrhoea.¹ The pathophysiological processes that underpin the initiation and progression of UC are unclear. Numerous studies suggest that disruption of the intestinal immune system equilibrium and impairment of the mucosal barrier contribute to the pathogenesis of UC.² Dysregulation of the mucosal immune response triggers the release of proinflammatory cytokines, leading to sustained inflammation, ulceration and damage to the mucosal lining of the colon. This cascade of events exacerbates intestinal barrier dysfunction, resulting in dysbiosis and endotoxemia.³ Proanthocyanidins (Pros), a class of polyphenolic compounds derived from grape seeds, have potent anti-inflammatory and antioxidant activities and regulatory effects on glucose and lipid metabolism.⁴ Previous studies^{5,6} demonstrated the beneficial effects of Pros in diabetic retinopathy, nephropathy, cardiovascular complications of

diabetes and periodontitis. However, the underlying mechanisms for Pro-mediated suppression of UC are unclear. Thus, the purpose of this study was to elucidate the mechanisms for the therapeutic effects of Pros on UC in mice.

MATERIALS AND METHODS

Animals

Male adult Balb/c mice ($n=40$), weighing approximately 50g, were housed in a specific pathogen-free laboratory animal facility, which was maintained at a constant temperature ($25^{\circ}\text{C} \pm 2^{\circ}\text{C}$) and humidity ($45\% \pm 5\%$), a 12-hr light-dark cycle and noise levels below 50 decibels. The mice had unrestricted access to water and standard feed and underwent an acclimatisation period before conducting experiments.

Drugs and Reagents

Dextran Sulfate Sodium (DSS) was obtained from MP Biomedicals, LLC (USA) and Grape Seed Extract (GSE) with 22.1% catechin and 19.2% epicatechin (mass fractions) was obtained from Tianjin Jianfeng Natural Product R and D Co., Ltd. Mesalazine (MES) was obtained from Shanghai Fuda Pharmaceutical Co., Ltd. and 4% paraformaldehyde was obtained from Tianjin Dejuren Biotechnology Co., Ltd. ELISA kits for Interleukin-6 (IL-6), Tumour Necrosis Factor- α (TNF- α) and Transforming Growth Factor- β (TGF- β) detection were from Nanjing Jiancheng Bioengineering Institute Co., Ltd.



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Trizol, Prime Script™ and Dual-Luciferase reporter assays were supplied by Takara Bio Inc. (Dalian, China).

Equipment

The following equipment was used: REBEL 2 IN 1 upright/inverted Hybrid microscope (Discover Echo, USA), a ZF-288 automatic gel imaging system (Shanghai Jiapeng Technology Co., Ltd.), a real-time qRT-PCR amplifier and vertical electrophoresis apparatus (Bio-Rad, USA), an ultra-low temperature freezer (Sanyo, Japan), Image-Pro Plus 6.0 image analysis software (Media Cybernetics, USA) and a NanoDrop 2000/2000C microvolume spectrophotometer (Thermo, USA).

Treatment Groups

Balb/c male mice were randomly divided ($n=6$ per group) into Control, Model, Pro and MES groups. On days 1-5, the Control group had unlimited access to standard tap water, while the other three groups received standard tap water infused with 3% DSS. On day 5, faecal samples were collected from 3 mice in each group for gut microbiota analysis. On days 6-10, the Model group continued to receive 2.0% (w/v) DSS with their feed and were gavaged with the corresponding volume of solvent for GSE/MES. In addition to the 2.0% (w/v) DSS in their feed, the Pro-group received a daily 500 mg/kg oral dose of GSE on days 6-10. The MES group received 2.0% (w/v) DSS with their feed and a daily 67mg/kg oral dose of MES on days 6-10.

Measurement of Disease Activity Index

Mice were meticulously observed and behavioural activity, mental state, dietary patterns, weight fluctuations and faecal consistency were recorded throughout the experiment. Clinical symptoms were scored using the criteria shown in Table 1⁷ to statistically compare the Disease Activity Index (DAI) between groups.

Mouse Colon Morphology and Length

A key indicator of mouse colitis is a significant reduction in colon length, which manifests alongside noticeable swelling. Consequently, the extent of colon shortening serves as a marker for the severity of inflammation. After sacrifice, the abdomen was carefully opened with sterile scissors, cutting downwards to reveal the muscle and peritoneal layers. The colon, cecum and rectum were gently extracted with sterile forceps. After identifying the anus, the surrounding muscles were incised along the rectum to facilitate the removal of the terminal colon segment. Excessive force was avoided to prevent colonic rupture, which can compromise imaging results. The entire intestinal tract from the anus to the cecal junction was excised, examined for morphological integrity and contents and documented. The excised colon was rinsed in 4°C Phosphate-Buffered Saline (PBS). Excess water was blotted with filter paper. The colon was laid straight using forceps, with the anal end serving as the origin

for measurements and photographs were taken to document the length.

IL-6, TNF- α and TGF- β Detection

Peritoneal venous blood was anticoagulated and centrifuged at 2000 rpm for 15 min to obtain plasma. The supernatant was carefully collected for IL-6, TNF- α and TGF- β detection via ELISAs. ELISAs were conducted according to the manufacturer's instructions. The ELISA kit and serum samples were equilibrated to room temperature for 30 min. Blank wells in the ELISA plate were prepared and 100 μ L of standard or sample diluents were added. The plates were sealed and incubated at 37°C for 90 min. After five washes, 100 μ L of a biotinylated antibody diluent and 100 μ L of enzyme conjugate were added to each well and incubated at 37°C for 1 hr. Reactions were terminated with 100 μ L stop solution and absorbance was measured at 450 nm using an ELISA reader. Levels of IL-6, TNF- α and TGF- β were quantified based on the standard curve.

Histological Examination of Mouse Colon

Tissue samples from each group were longitudinally sectioned, rinsed in chilled PBS, fixed in 10% formalin, embedded in paraffin, sectioned and stained with Hematoxylin and Eosin (HE). The pathological morphology of the mouse colon was assessed under a light microscope. Damage grading was based on Wirtz's scoring system for colon injury.

Immunohistochemical Analysis

Colon tissue was washed in chilled PBS, fixed in 10% formalin, embedded in paraffin and longitudinally sectioned before being rehydrated. Sections were treated with citrate buffer (pH 6.0) for antigen retrieval. After blocking with 5% BSA at 37°C for 30 min, sections were incubated with primary antibodies against Toll-Like Receptor 4 (TLR4) and nuclear factor kappa B (NF- κ B p65) (1:100 dilution) overnight at 4°C. Samples were warmed to 37°C for 45 min and incubated with biotin-labelled secondary antibodies at room temperature for 30 min. Antibodies were visualised with DAB and counterstained with hematoxylin for 20 min before mounting the samples with neutral resin. Microscopic images were captured and the integrated optical density values were determined using ImageJ.

TUNEL Assay for Apoptosis Detection

Apoptosis was measured using a TdT-mediated dUTP Nick-End Labelling (TUNEL) apoptosis detection kit, following the manufacturer's instructions. Apoptotic cells were counted in 5 fields from each high-magnification image with no overlap.

TLR4 and NF- κ B p65 Gene Expression

Colon tissues were lysed in 1 mL of Trizol. Total RNA was extracted following the manufacturer's instructions. RNA purity and concentration were determined using a NanoDrop 2000/2000C

spectrophotometer. A Prime Script™ kit was used to synthesise cDNA. The following conditions were used for the qRT-PCR: initial denaturation at 95°C for 5 sec, 40 cycles of denaturation at 95°C for 5 sec and annealing at 60°C for 60 sec. The $2^{-\Delta\Delta CT}$ method was employed to determine the relative gene expression levels, with GAPDH serving as the reference gene. Primer sequences are shown in Table 2.

TLR4 and p-NF- κ B p65 Protein Expression

Proteins were extracted from colon tissue using RIPA buffer and equal quantities (30 μ g) of protein lysates were separated by SDS-PAGE and transferred to membranes. After blocking, the membranes were incubated overnight at 4°C with primary antibodies against TLR4, NF- κ B p65 and GAPDH (all 1:1000 dilution). The membranes were washed and incubated with secondary antibodies (1:5000 dilution) at room temperature for 2 hr. Antibody binding was detected using chemiluminescence and ImageJ software was used to analyse the grayscale values of the protein bands.

Statistical Analysis

All statistical analyses were performed using GraphPad Prism Version 6. Quantitative data are presented as Means $\pm$ Standard

deviations. Differences between the two groups were assessed using paired *t*-tests. Differences between more than two groups were determined using one-way analysis of variance followed by least significant difference *posthoc* tests. A *p*-value < 0.05 was considered statistically significant.

RESULTS

Effect of Pros on DAI in DSS-Induced UC

Normal behaviour and health were maintained in the Control group, with no signs of anorexia, lethargy or hunching. In contrast, appetite loss, listlessness, increased frequency of defecation, loose stools and instances of prolapse and bloody faeces were detected in the Model group. In the advanced UC stages, mice exhibited dull fur, heightened lethargy and increased ocular discharge. More lustrous fur, firmer stools and a reduction in bloody faeces frequency were detected in the Pro and MES groups compared with the Model group, indicating that Pros significantly attenuated UC symptoms in mice. The DAI scores for the Model group were markedly higher compared to the Control group (*p* < 0.01). However, DAI scores were significantly reduced in the Pro and MES groups compared with the scores in the Model group (*p* < 0.01 for both), as depicted in Figure 1A.

Table 1: DAI Scoring Details.

Scores	Weight Loss (%)	Fecal Consistency	Hematochezia
0	None	Normal	None
1	1-5	Soft but formed	Stool without visible blood.
2	6-10	Very soft	Stool with small amounts of visible blood.
3	11-20	Diarrhea	Obvious rectal bleeding.
4	>20	Diarrhea	Prolapse with severe bleeding.

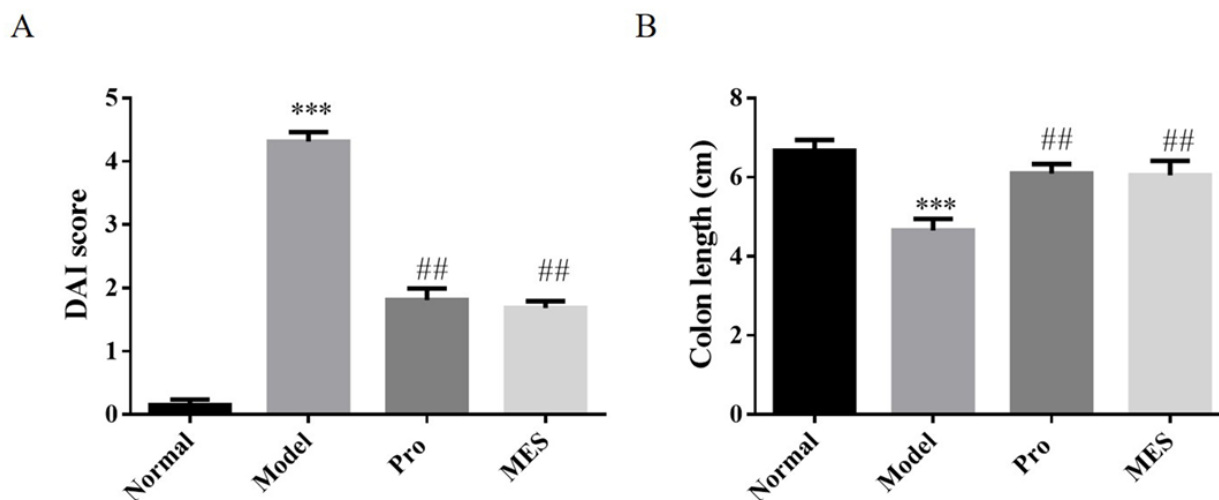


Figure 1: Effect of Pro on DAI, Colon Morphology and Length in DSS-Induced UC in Mice.

Effect of Pro on Colon Morphology and Length in DSS-Induced UC in Mice.

***: *p* < 0.001, compared with Normal group; ##: *p* < 0.01, compared with Model group.

Effects of Pros on Colon Morphology and Length in DSS-Induced UC

As shown in Figure 1B, colon tissue from the Control group appeared normal in colour with appropriate elasticity. In contrast, colon tissue from the Model group was darkened, swollen and exhibited visible blood streaks. Colon tissue from the Pro and MES groups exhibited less swelling compared with the Model group and no blood streaks were observed on the colon surface. Colons from the Model group were significantly shorter compared with colons from the Control group ($p < 0.01$). In contrast, colons from the Pro and MES groups were significantly longer than colons from the Model group ($p < 0.01$).

Effects of Pros on Colonic Histopathology in DSS-Induced UC

The assessment of HE-stained colonic tissue revealed that tissue integrity was preserved in the Control group; colonic mucosal epithelial cells, crypt structures and goblet cells were complete and distinctly visible. The glands were orderly, and no oedema was detected in the submucosal layer of colonic tissue in the Control group. In addition, no inflammatory cell infiltration was detected in the colons from the Control group. Conversely, the

Model group displayed pronounced inflammation, a decrease in goblet cell numbers, disarray in the colonic gland arrangement and tissue disruption extending into cryptitis and the glandular tubular structures. Elevated lymphocyte and eosinophil infiltration were also observed in the Model group. The Pro and MES groups exhibited more preserved goblet cell and crypt structures, with only slight damage to the glandular structure, compared with the Model group. Minimal inflammatory cell invasion was detected in the Pro and MES groups.

The HE scores for the Model group were significantly elevated compared with the scores in the Control group ($p < 0.05$). The HE scores were significantly lower in the Pro and MES groups compared with the scores in the Model group ($p < 0.01$), as shown in Figure 2.

Effects of Pros on Serum IL-6, TNF- α and TGF- β in DSS-Induced UC

As shown in Figure 3, serum IL-6, TNF- α and TGF- β levels were significantly higher in the Model group compared with the levels in the Control group ($p < 0.01$). In contrast, serum IL-6, TNF- α and TGF- β levels were significantly lower in the Pro and MES groups compared with the levels in the Model group ($p < 0.01$),

Table 2: Primer sequence.

Gene Name	F:(5'-3')	R:(5'-3')
TLR4	TCCAGAGCCGT'TGGTGTATCTT	ACAATTTCGACCTGCTGCCTCA
NF- κ B(p65)	TCATCTTCCCGGCAGAGCCAG	GTGGGTCTTGGTGGTAGCTGT
GAPDH	TCTGACTTCAACAGGGACACC	CTGTTGGTGTAGCCAAATTCGT

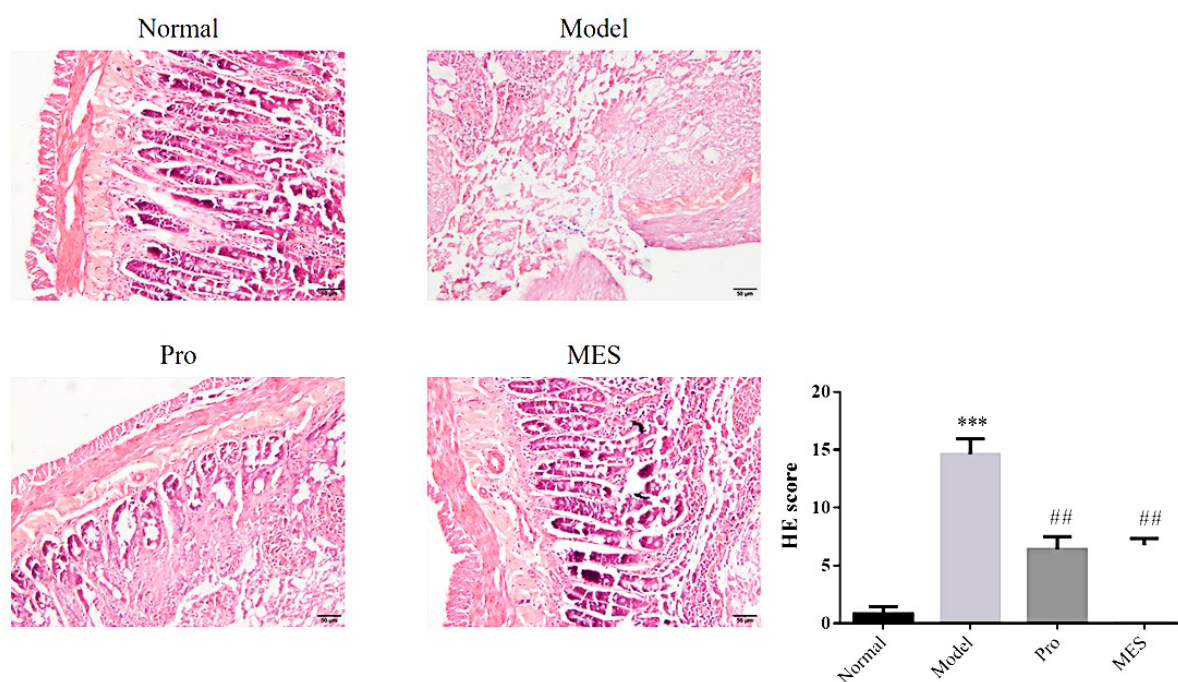


Figure 2: Effect of Pro on Colonic Histopathology in DSS-Induced UC in Mice.

***: $p < 0.001$, compared with Normal group; ##: $p < 0.01$, compared with Model group

suggesting that DSS induces an inflammatory response in mice that is mitigated by Pros and MES.

Effects of Pros on Cellular Apoptosis in Colon Tissues of DSS-Induced UC

Based on the TUNEL assay results, the number of apoptotic cells in the colon increased significantly in the Model group compared with the number of apoptotic cells in the Control group ($p<0.01$) (Figure 4). In contrast, the numbers of apoptotic cells in the Pro and MES groups were significantly lower than the number of apoptotic cells in the Model group ($p<0.01$).

Effects of Pros on TLR4 and NF- κ B p65 mRNA Levels in DSS-Induced UC

TLR4 and NF- κ B p65 mRNA levels were significantly elevated in the Model group compared with the mRNA levels in the Control group ($p<0.01$), as shown in Figure 5. The mRNA levels for TLR4 and NF- κ B p65 were significantly lower in the Pro and MES groups compared with the expression levels in the Model group ($p<0.01$).

Effects of Pros on TLR4 and NF- κ B p65 Protein Levels in DSS-Induced UC

Immunohistochemical analysis of colon tissues revealed that TLR4 and NF- κ B p65 were predominantly localised to the cytoplasm. TLR4 and NF- κ B p65 protein levels were significantly higher in the Model group compared with levels in the Control group ($p<0.01$), as shown in Figures 6 and 7. Conversely, TLR4 and NF- κ B p65 protein levels in the Pro and MES groups were significantly lower compared with the levels in the Model group ($p<0.01$).

Western blot analysis revealed that TLR4 and phosphorylated NF- κ B p65 were significantly elevated in the Model group compared with the levels in the Control group ($p<0.01$), as illustrated in Figure 8. TLR4 and phosphorylated NF- κ B p65 levels in the Pro and MES groups were significantly lower compared with the levels in the Model group ($p<0.01$).

DISCUSSION

The development of a DSS-induced UC model is influenced by multiple factors. For example, the choice of animal species (mice, rats or hamsters) introduces variations, particularly in the initial site of the disease.^{8,9} In our Balb/c male mouse model, UC predominantly manifested in the middle to distal colon.

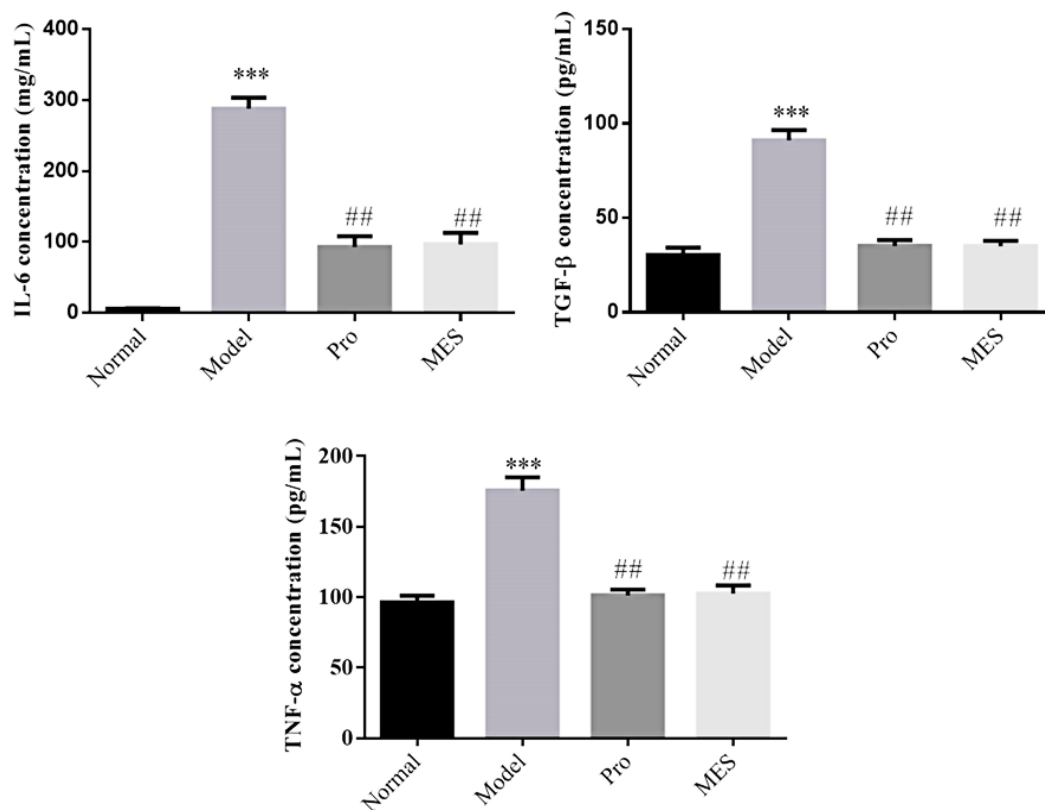


Figure 3: Effect of Pro on Serum IL-6, TNF- α and TGF- β in DSS-Induced UC in Mice.

***: $p<0.001$, compared with Normal group; ##: $p<0.01$, compared with Model group.

The concentration of DSS to induce UC ranges from 1% to 10%. Higher concentrations can be lethal to mice. We opted for a 2-3% concentration, which proved to be non-lethal while still eliciting pronounced UC symptoms. Thus, this DSS concentration range may be ideal for inducing UC in mice. The duration of DSS exposure is also crucial as the pathology exhibits a clear temporal progression, with symptoms intensifying over time, highlighting a dose-response relationship between DSS exposure and colonic damage.

Recent studies have confirmed the anti-inflammatory and antioxidant properties of Pros, highlighting the substantial medicinal potential. Grape seeds are a rich source of proteins,

carbohydrates, lipids and 5%-8% of plant polyphenols, including epicatechins, catechins, gallic acid, epigallocatechin gallate, Pros and other dimers, trimers and polymers. Epicatechins and catechins are lipophilic and Pros are water-soluble, which facilitates their extraction.¹⁰⁻¹²

MES served as the positive control drug in this investigation due to its widespread use in clinical UC treatment. MES suppresses intestinal wall inflammation by inhibiting the synthesis of proinflammatory prostaglandins and leukotrienes. We monitored the general condition of the mice across all groups throughout the study. The Control group maintained normal behaviour, with vitality and no signs of anorexia, lethargy or hunched posture. In

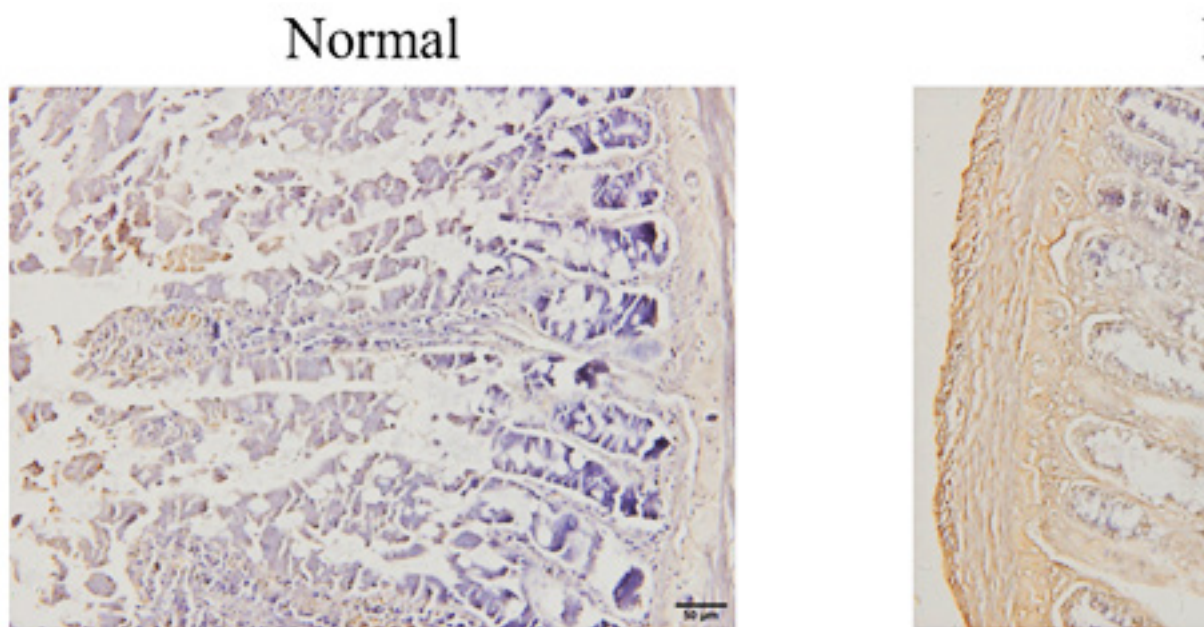


Figure 4: Effect of Pro on Cellular Apoptosis in Colon Tissues of DSS-Induced UC in Mice.

***: $p < 0.001$, compared with Normal group; #: $p < 0.01$, compared with Model group.

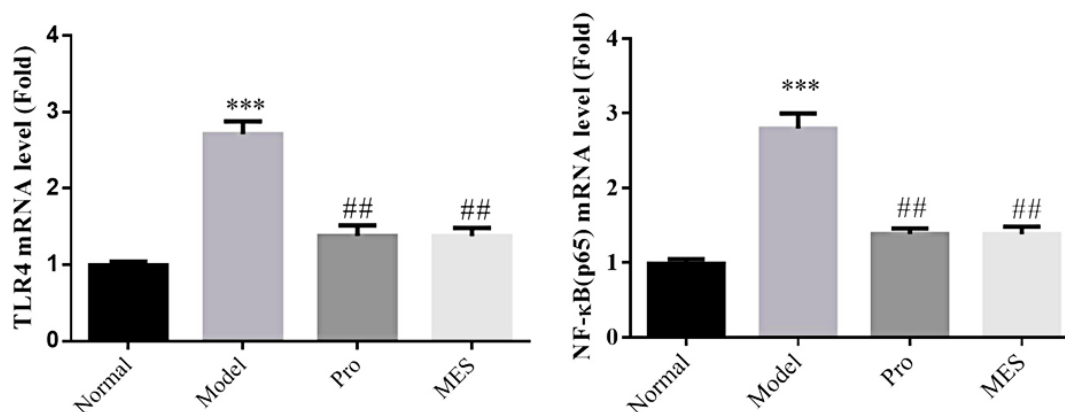


Figure 5: Effect of Pro on Gene Expression of TLR4 and NF-κB(p65) in Colon of DSS-Induced UC in Mice.

***: $p < 0.001$, compared with Normal group; #: $p < 0.01$, compared with Model group.

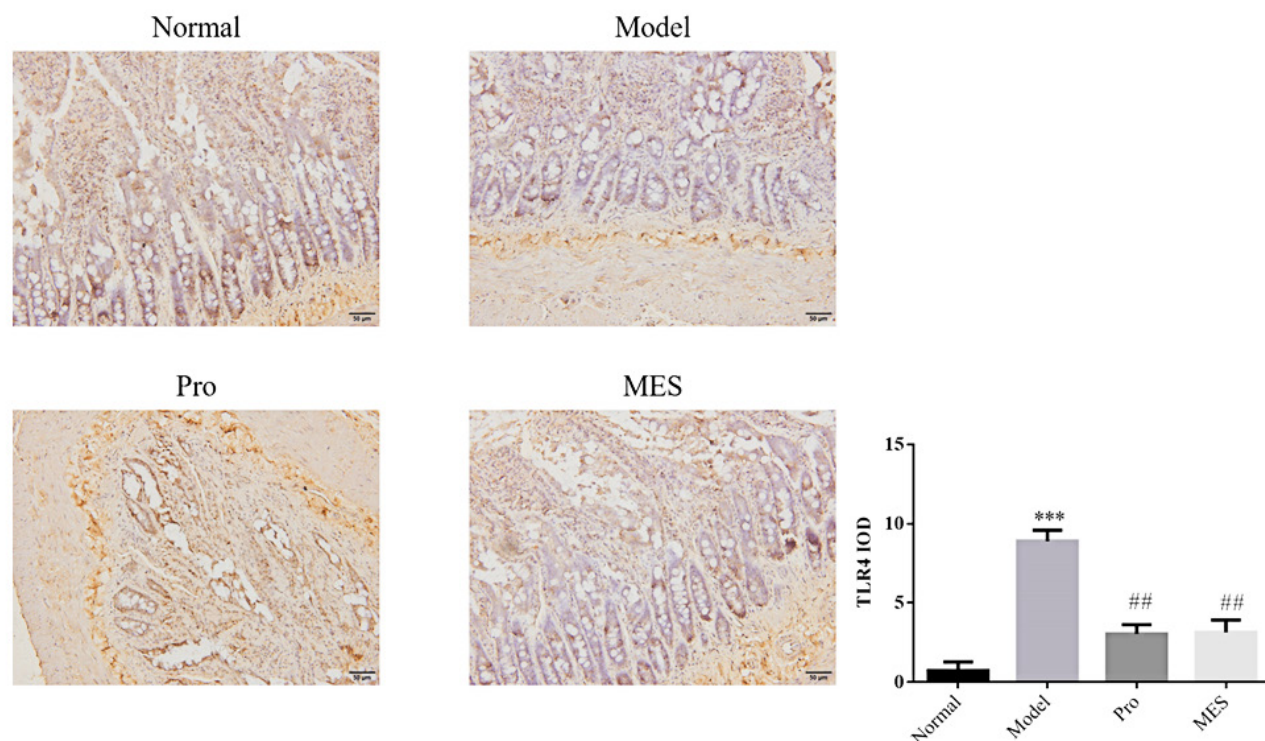


Figure 6: Effect of Pro on the Expression of TLR4 in Colon of DSS-Induced UC in Mice.

***: $p < 0.001$, compared with Normal group; ##: $p < 0.01$, compared with Model group.

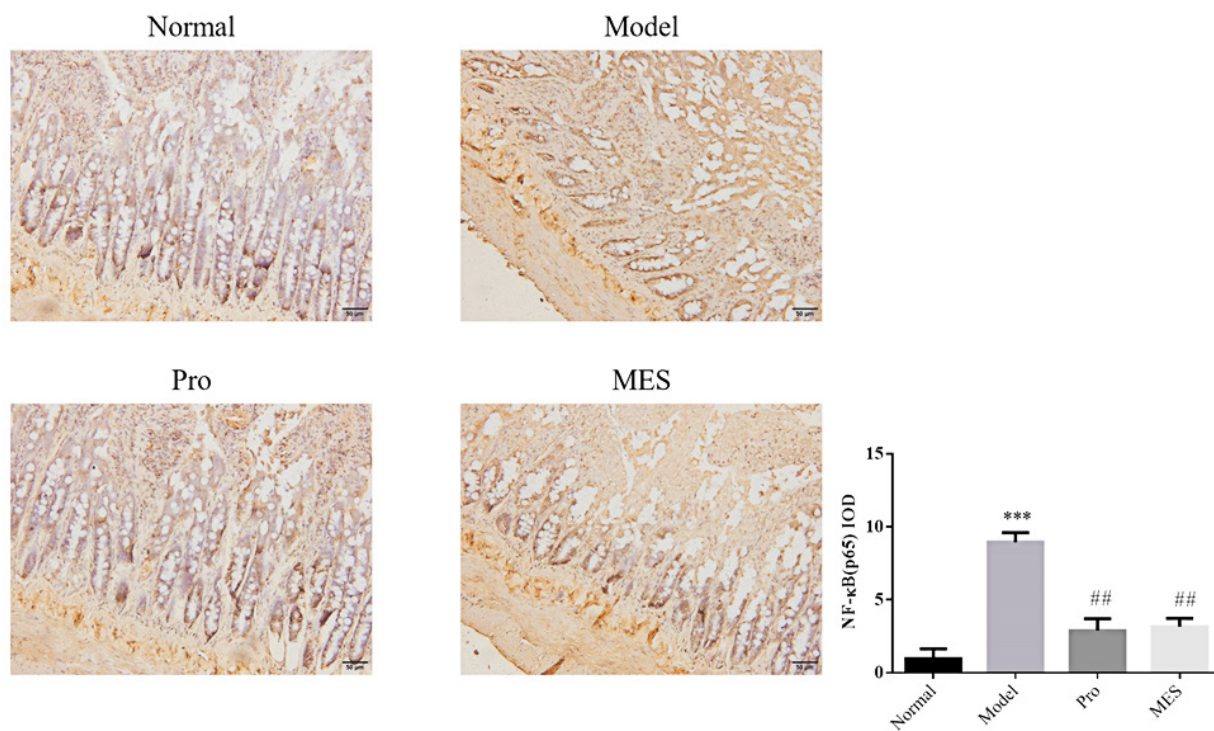


Figure 7: Effect of Pro on the Expression of NF-κB(p65) in Colon of DSS-Induced UC in Mice.

***: $p < 0.001$, compared with Normal group; ##: $p < 0.01$, compared with Model group.

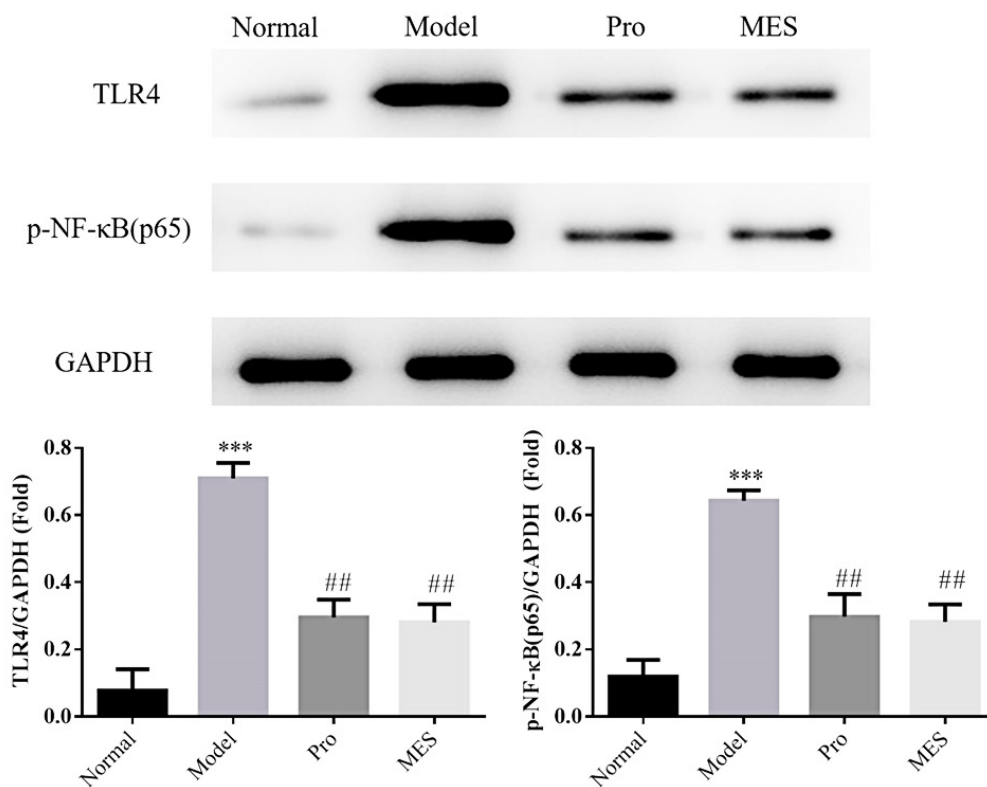


Figure 8: Effect of WB Testing on the Expression of TLR4 and NF-κB(p65) in Colon Tissues of DSS-Induced UC in Mice.

***: $p < 0.001$, compared with Normal group; ##: $p < 0.01$, compared with Model group.

contrast, the Model group exhibited decreased appetite, lethargy, higher defecation frequency and abnormal stools, including prolapse and bloody stools. In the latter stages of the experiment, mice in the Model group exhibited dull fur, increased lethargy and elevated eye secretions. Compared with the Model group, UC symptoms were significantly ameliorated in the Pro and MES groups; mice in the Pro and MES groups exhibited shinier fur, more regular stool formation and reduced bloody stools. The DAI scores were markedly increased in the Model group compared to the Control group ($p < 0.001$). In contrast, DAI scores were lower in the Pro and MES groups compared with the Model group ($p < 0.01$). Colon tissue from mice in the Control group appeared normal in colour and texture, whereas colons were discoloured and swollen, with visible blood streaks in the Model group. Compared with the Model group, the Pro and MES groups exhibited less swelling and no blood streaks on the colon. Colons from the Model group were significantly shorter than colons from the Control group ($p < 0.01$), whereas colons from the Pro and MES groups were significantly longer than colons from the Model group. Apoptotic cells were also reduced in the Pro and MES groups compared with the Model group. This suggests that Pros alleviate symptoms and ameliorate colon tissue damage in

mice with UC. Thus, Pros are promising therapeutic agents for the treatment of UC.

TLR4 is a key member of the TLR family; TLR4 triggers the activation of the transcription factor NF-κB p65 after recognising specific pathogen-associated molecular patterns. Activated NF-κB p65 orchestrates the transcription of various genes involved in immune and inflammatory responses. In UC, overactive NF-κB leads to disproportionate expression of inflammatory mediators. Thus, the balance between proinflammatory and anti-inflammatory factors is disrupted, leading to mucosal immune-inflammatory injury.¹³ TLR4 expressions is low in normal human intestinal mucosa but is significantly upregulated in the mucosa of UC patients and the UC mouse model.¹⁴ Our results demonstrate that Pros markedly downregulate TLR4 and NF-κB p65. Thus, the beneficial effects of Pros may be mediated by attenuating the cytokine imbalance via modulation of the TLR4/NF-κB p65 signalling pathway.

CONCLUSION

In conclusion, Pros significantly mitigated colon tissue damage in a DSS-induced UC mouse model by inhibiting the TLR4/NF-κB p65 signalling pathway. These results lay a robust groundwork for the potential clinical utility of Pros.

ABBREVIATIONS

UC: Ulcerative Colitis; IL-6: Interleukin-6; TNF- α : Tumour Necrosis Factor-Alpha; TGF- β : Transforming Growth Factor-Beta; DSS: Dextran Sulfate Sodium.

FUNDING

This study was supported by the National Natural Science Foundation of China (NO.81770551).

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study was approved by the Ethics Committee of First Affiliated Hospital of Dalian Medical University (No. 20220806-05).

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

To determine the role of Proanthocyanidins (Pros) in mitigating Ulcerative Colitis (UC) in mice. A UC mouse model was constructed using dextran sulfate sodium induction in male adult Balb/c mice. Mice were randomly divided into Control, Model, Pro and Mesalazine groups. The pathological morphology of the colon was evaluated using the Disease Activity Index (DAI), colon appearance and length, IL-6, TNF- α and TGF- β levels and Hematoxylin and Eosin (HE) staining. Immunohistochemistry, western blotting and qRT-PCR were used to detect TLR4 and NF-KB p65 protein and mRNA levels. DAI scores were significantly increased and colonic length and HE scores were significantly reduced in the Model group compared with the Control group ($p < 0.001$ for all). IL-6, TGF- β and TNF- α levels increased significantly in the Model group compared with the Control group ($p < 0.001$ for all). The number of apoptotic cells and TLR4 and NF-KB p65 protein and mRNA levels increased significantly in the Model group compared with the Control group ($p < 0.001$ for all). UC improved significantly in the Pro-group compared with the Model group, including suppression of the

TLR4/NF-KB p65 pathway. Pro-treatment improved UC by depressing the TLR4/NF-KB p65 signaling pathway.

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