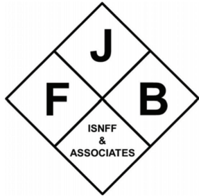

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Dietary flavonoid tectochrysin ameliorates dextran sodium sulfate-induced intestinal barrier dysfunction relevant to MAPK-NF-κB-MLCK signaling pathway

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Abstract

Intestinal barrier exerts a fundamental role in homeostasis and loss of barrier integrity is often implicated in diseases. In this study, we investigated the protective effect of tectochrysin (TEC), a flavonoid broadly existing in dietary plants, on the intestinal barrier dysfunction in DSS-induced colitis mice. TEC treatment significantly improved DSS-induced clinical performances and intestinal pathological alterations including high scores of disease activity index (DAI), shortened colon length, apoptosis of intestinal epithelial cells and loss of tight junction (TJ) molecules. As for the mechanism, TEC suppressed pro-inflammatory cytokines (TNF-α, IFN-γ), alleviated macrophage infiltration, and shifted macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype. Furthermore, TEC targeted DSS-induced MAPK-NF-κB-MLCK signal cascade in inflamed intestine. Consequently, our findings suggested that administration of dietary flavonoid TEC effectively ameliorated DSS-induced intestinal barrier damage and offered a potential therapeutic strategy for intestinal barrier dysfunction.

Keywords: Tectochrysin; Ulcerative colitis; Intestinal barrier; Inflammation; Macrophage polarization.

1. Introduction

The intestinal barrier is of importance on health and disease. The barrier provides the space where millions of microbes and ingested substances come together to interact with the host immune system (Lv et al., 2024; Vancamelbeke and Vermeire, 2017). Defects of the barrier have been involved in a broad spectrum of diseases (Du et al., 2022; Wang et al., 2021c). Diet and lifestyle are the most frequent factors impacting on intestinal barrier function (Ananthakrishnan, 2015). For example, the Western-style diet, high in saturated fat and sugar and rich in ultra-processed foods, may impair the intestinal barrier function and link to the occurrence, development and prognosis of inflammatory bowel disease (IBD) mainly including ulcerative colitis (UC) and Crohn's disease (CD) (Gadaleta et al., 2011; Rogler et al., 2021). This condition has become increasingly prevalent worldwide (Kassam et al., 2014; Kobayashi et al., 2020). In particular, the incidence of IBD in China has risen annually in recent decades, correlating with rapid economic development and lifestyle changes, and the affected population is becoming younger (Zhang et al., 2022).

Although the etiology and the mechanisms of IBD are not fully illustrated at the present, intestinal barrier dysfunction represents the convincing evidence towards increased tight junction permeability in IBD patients (Saha et al., 2025). Mechanistic studies have pointed out that the intestine of IBD patients displays dys-

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regulation of signal pathways such as MAPK and NF-κB and an imbalance of pro-inflammatory and anti-inflammatory cytokine profile characterized by highly upregulated tumor necrosis factor (TNF)-α and interleukin (IL)-1β and downregulated IL-10 leading to inflammation initiation and progression (Horowitz et al., 2023; Saha et al., 2025; Wei and Feng, 2010). The altered cytokine profiles further stimulate the production of reactive oxygen species (ROS), resulting in intestinal barrier damage and the development of UC (Feng et al., 2024; Saber et al., 2019). Consequently, the insights into inflammatory pathways promote novel therapeutic approaches such as cytokine blockers ustekinumab, vedolizumab and JAK inhibitors (Neurath, 2017). While neither the above novelty medications nor traditional drugs are non-fully-efficient due to adverse effects and refractory IBD that impair their long-term use (Li et al., 2023a). Therefore, it is urgent to find a new treatment scheme with higher efficacy, lower cost, and fewer side effects.

Diet interference significantly impacts the frequency and severity of IBD. Given the pathogenesis, diets with anti-inflammatory and antioxidant properties are of great utility in therapeutic management of patients with IBD (Pereira et al., 2024; Shaoul and Day, 2019). Dietary flavonoids, widely found in edible plants, present the anti-inflammatory properties and ability to alleviation of oxidative stress. In consequence, flavonoids clearly meet the demand for therapeutic strategies for IBD. Here, we center on tectochrysin (TEC), a flavonoid broadly existing in plants, displaying the capabilities against inflammation, oxidative stress, and cancers (Li et al., 2023c; Liu et al., 2024). For example, TEC ameliorated shrimp tropomyosin-induced allergic airway inflammation by suppressing Th2 response and oxidative stress (Fang et al., 2021). Additionally, TEC inhibited release of TNF-α, and IL-6 in the supernatant of LPS-primed macrophages (Hou et al., 2018). TEC isolated from propolis showed the maximal lipid antioxidant activity in comparison of the other isolated flavonoids (Rapta et al., 1995). Therefore, given bioactive properties of TEC and the pathogenesis of IBD, TEC could be taken into consideration as a candidate phytochemical targeting IBD. Thus, based on the aforementioned bioactivity of TEC, it can be speculated that TEC may have the potential to resist UC and inhibit its development. However, there is currently no research on TEC for the treatment of UC, and the mechanism is still unclear.

To determine the protective role of TEC on IBD and the mechanisms behind it, we utilized dextran sulfate sodium (DSS)-induced colitis model manifesting significant inflammation associated with dysfunction of intestinal mucosal barrier (Vowinkel et al., 2004; Yang and Merlin, 2024a; Zeng et al., 2022). Our results revealed that oral gavage of TEC was capable of alleviating the clinical and pathological performances in DSS-induced colitis mice. Moreover, investigation of mechanisms reflected that oral gavage of TEC led to the decreased production of inflammatory cytokines, bluntly activated of the MAPK/NF-κB signaling pathway, and the infiltration and M2 polarization of macrophages in the intestine. This study addressed our understanding of dietary flavonoid in alleviation of intestinal barrier dysfunction and suggested that food highly containing TEC might be promising in modulation of intestinal barrier homeostasis.

2. Materials and methods

2.1. Chemicals and reagents

DSS was purchased from Aladdin Holdings Group Co., Ltd (Shanghai, China), TEC (99.7% purity) was purchased from Purification Technology Development Co., Ltd (Chengdu, China), 4% paraformaldehyde and Bicinchoninic acid (BCA) protein assay kit were purchased from Beyotime Biological Co., Ltd (Shanghai, China), TRIzol, PBS and enhanced-chemiluminescence (ECL) reagent were purchased from Biosharp Co., Ltd (Beijing, China), Transcriptor cDNA Synthesis Kit was obtained from Vazyme Biotech Co., Ltd (Nanjing, China), MonAmp™ SYBR®Green qPCR Mix(Low ROX) were obtained from Mona Biotechnology Co., Ltd (Wuhan, China). For more information about the materials please refer to Table S1.

2.2. Animals and treatment

For animal experiments, TEC was dissolved in commercially available carboxymethyl cellulose (CMC) which also acted as the vehicle in some groups. 6–8 weeks-old C57BL/6J mice (male, 20–22 g) were purchased from Vital River Laboratory Animal Technology Co. Ltd. (Beijing, China). All mice were kept under controlled conditions of temperature (22 ± 3 °C), humidity (50 ± 10%), and 12 h alternating light and dark cycle for a week to adapt to the environment before the experiment. After one week of acclimation, experiments were performed as illustrated in Figure 1a according to previous methods (Chassaing et al., 2014; Wen et al., 2020; Wirtz et al., 2007). Briefly, the mice were assigned into 3 groups with 8 mice per group including Control (regular water plus CMC as vehicle), DSS (3% DSS water for 10days), and TEC (3% DSS water for 10 days and 2.5 mg/kg TEC for 14 days) groups. The dose of 2.5 mg/kg TEC was selected based on previous studies that confirmed its efficacy, safety, and appropriate dose–response range in multiple inflammatory and intestinal disease models (Hou et al., 2018; Fang et al., 2021; Zhang et al., 2024). On day 14, the intestinal tissue samples were collected and the lengths were measured and photographed. Then, a 1 cm section of the colon tissue near the anal end was cut after thoroughly cleaning and stored at −80 °C for subsequent experiments. The spleen tissues of mice were weighed and then stored at −80 °C. All animal experiments were approved by the Experimental Animals Ethics Committee of Tianjin University of Commerce (TKLFB-2023YJS-1).

2.3. Disease activity index (DAI) Score

The weight and stool characteristics of mice were recorded daily, and the disease activity index (DAI) was calculated according to Murano's methods (Murano et al., 2000): weight loss score + stool character score + bloody score)/3.

2.4. Histological analysis

The colon tissues were fixed in 4% paraformaldehyde for paraffin embedding, and the colon paraffin-embedded sections were cut into 4 μm thickness. Then, the colon sections were deparaffinized, rehydrated, and stained, following a standard procedure. Finally, the slides were examined using light microscopy.

2.5. Immunohistochemistry analysis

Immunohistochemistry analysis was performed using colon sections obtained from mice. The colon tissue slides were stained with antibodies and microwaved 3 times for 3 min each. Then the slides were treated with hydrogen peroxidase in methanol at

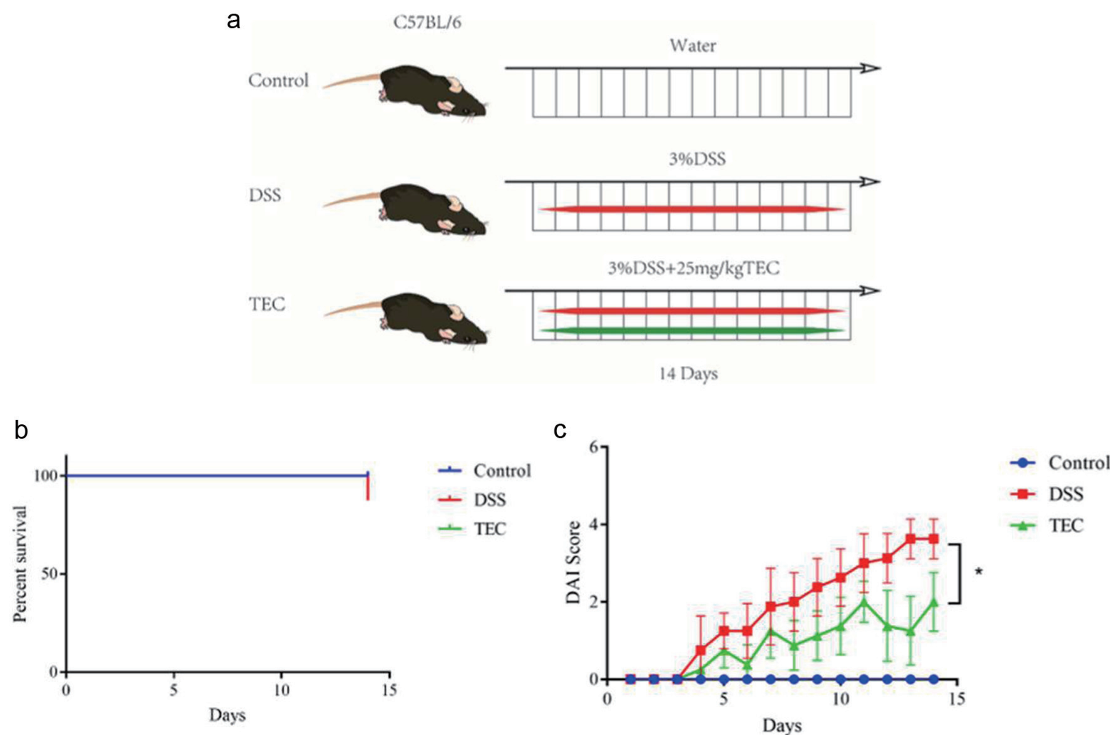

Figure 1. TEC improved the survival status of DSS-induced mice. (a) Study design of in vivo experiments in mice, (b) survival rate of mice, (c) DAI scores of mice. All data represented as mean ± SD (n = 8, *P < 0.05 for TEC group vs DSS group).

room temperature for 15 min to remove endogenous peroxidase. Subsequently, the slides were subjected to incubation with primary antibodies at 4 °C overnight. Then, the slides were incubated with biotinylated secondary antibody at 37 °C for 20 min. Thereafter, 5 min of incubation with DAB was done and the sections were then counterstained with hematoxylin for 8 min and examined by a light microscope. The positive area of proteins was analyzed by Image J software (National Institutes of Health, Bethesda, MD, USA).

2.6. qRT-PCR analysis

The TRIzol reagent was used to isolate total RNA from colon tissue. The total RNA was transcribed into cDNA by a transcriptor cDNA synthesis kit. MonAmp™ SYBR®Green qPCR Mix (Low ROX) was used to perform qRT-PCR analysis, and the primers were listed in Table S2.

2.7. Western blot analysis

The colonic proteins were extracted using a radioimmunoprecipitation assay buffer, and the total amount of proteins was measured using the Pierce™BCA Protein Quantification Kit. Equal amounts of proteins in each group were loaded on 10% SDS polyacrylamide gels using a vertical electrophoresis system (Tanon-EPS 300, Tanon, Shanghai, China), and then wet-transferred on polyvinylidene fluoride (PVDF) membranes. These membranes were blocked for 1 h and then incubated into the primary antibodies at 4 °C overnight. Subsequently, the membranes were washed using TBST 4 times (10 mins each time) and then incubated with a secondary antibody at room temperature for 1 h. The detailed information on primary and secondary antibodies was listed in Table S1. Afterward, these membranes were washed with TBST 4 times again and detected with a chemiluminescent imaging system. The results were measured by Image J software (National Institutes of Health, Bethesda, MD, USA).

2.8. Statistical analysis

In this study, all data were analyzed using Student's t-test using GraphPad Prism (GraphPad Software, San Diego, CA, USA) and SPSS (SPSS Inc., Armonk, NY, USA). All values were presented as means ± SD.

3. Results

3.1. TEC improved the survival status of DSS-induced mice

Using DSS-induced colitis model, we firstly investigated the protective effects of TEC. We observed that, upon administration of TEC, the mice were well survival (Figure 1b) and exhibited the lower DAI score (Figure 1c) than the mice treated with DSS alone, indicating that TEC improved the quality of life of DSS-induced mice.

3.2. TEC alleviated intestinal barrier damage in DSS-induced mice

Having confirmed TEC improvement of clinical symptoms of DSS-induced colitis, we next investigated the role of TEC in al-

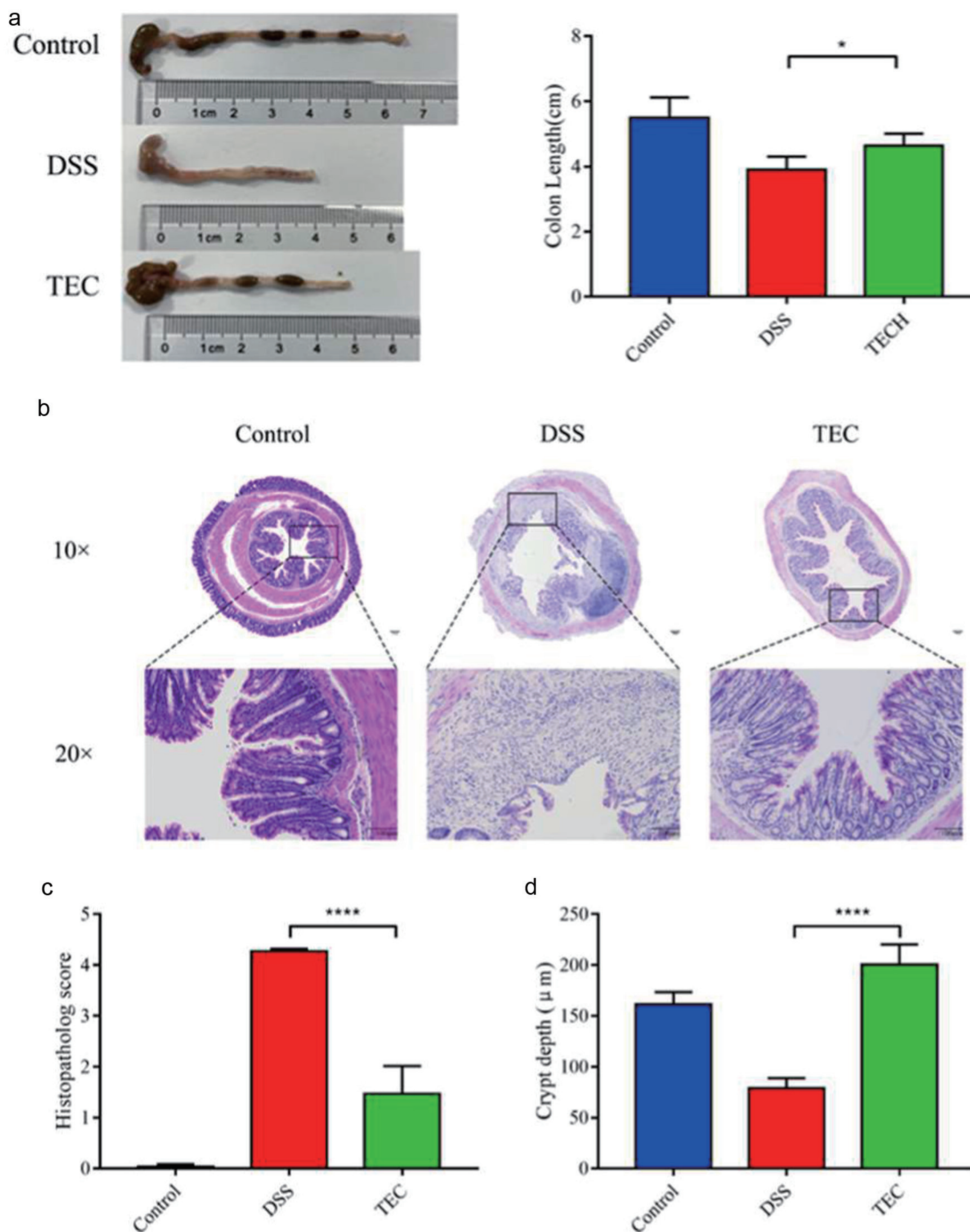

Figure 2. TEC improved colonic histological damage in DSS-induced mice. (a) Appearances and lengths of colon tissues, (b) HE stained of colon tissues, (c) histological scores of colon tissues, (d) crypt depth of colon tissues. All data were represented as mean ± SD. (n = 8, *P < 0.05, ****P < 0.0001 for TEC group vs DSS group).

leviating intestinal barrier damage. As shown in Figure 2a, TEC treatment significantly rescued the colon shortening caused by DSS. Furthermore, the pathological observation in the colon tissues indicated that administration of TEC significantly counteracted DSS-induced intestinal damage including the submucosal edema, mucosal epithelium destruction, inflammatory cells infiltration and loss of crypt and goblet cells (Figure 2b), and accordingly markedly reduced colonic tissue scores (Figure 2c) and inhibited colonic crypt atrophy (Figure 2d). These results provided the pathological evidence that TEC effectively improved DSS-induced intestinal barrier damage.

3.3. TEC inhibited the intestinal epithelial cells apoptosis and TJs loss in DSS-induced mice

The loss of intestinal epithelia and their connector TJs results in intestinal barrier dysfunction (Yang et al., 2024c). Mounting evi-

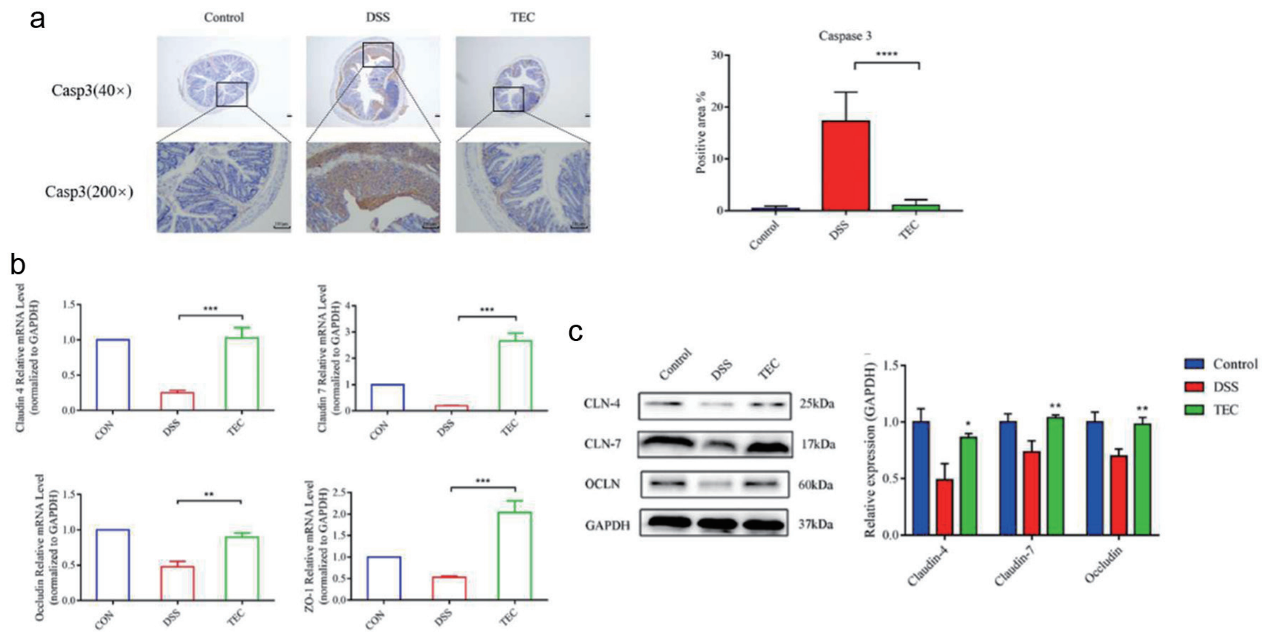

Figure 3. TEC attenuated DSS-induced intestinal barrier dysfunction. (a) Immunohistochemical representation and positive area statistics of caspase-3 in colon tissues, (b) the mRNA levels of representative TJs, (c) representative western blot images and the expressions of TJ proteins. All data were represented as mean ± SD (n = 3, *P < 0.05, **P < 0.01, ***P < 0.001, ****P < 0.0001 for TEC group vs DSS group).

dence have suggested that overexpression of caspase-3, an apoptosis molecule, is an important marker of intestinal barrier injury (Kim et al., 2023). As shown in Figure 3a, TEC significantly inhibited the highly upregulated caspase-3 induced by DSS, supporting that TEC reduced the apoptosis of intestinal epithelial cells. We further examined a panel of TJ molecules including Claudin-4, Claudin-7, Occludin, and ZO-1. As predicted, the DSS-induced loss of TJs was restored upon administration of TEC (Figure 3b and c). The results showed that TEC effectively blunted the death of intestinal epithelium and alleviated the TJs loss induced by DSS.

3.4. TEC ameliorated DSS-induced intestinal barrier damage associated with the inhibition of inflammation activation

On the basis of the above findings, we sought whether TEC administration ameliorate the intestinal inflammation which is key to initiate and furthering intestinal barrier damage. Firstly, we observed that there was increased spleen weight in DSS-treated mice, cueing the system inflammation (Figure 4a). Interestingly, administration of TEC effectively shrank the splenic edema caused by DSS (Figure 4a), prompting the potential anti-inflammatory activity of TEC. We next centered on whether administration of TEC targeted the inflamed intestine. As shown in Figure 4b, TEC largely inhibited the intestinal expression of pro-inflammatory cytokines TNF-α and IFN-γ, thereby suppressing the inflammatory response. Given that macrophages are the important donors of pro-inflammatory cytokines, we tested the intestinal infiltrated macrophages. Indeed, the massively infiltrated macrophages (staining with F4/80) induced by DSS were sharply reduced in the intestine of mice administrated by TEC (Figure 4c). Subsequently, we further explored whether there were phenotype shifts of macrophages because of the macrophages with M1-like shew contributing to inflammation. As shown in Figure 4d, TEC treatment significantly turned over DSS-induced highly expressed M1 phenotype molecules CD86 and IL-6 and conversely increased M2-like molecules CD163 and TGF-β, suggesting that TEC notably counteracted DSS-induced intestinal inflammation involving in suppression of pro-inflammatory macrophages. These results indicated that TEC ameliorated DSS-induced intestinal barrier damage associated with the inhibition of inflammation activation.

3.5. TEC ameliorated the DSS-induced intestinal barrier damage associated with the restraining MAPK-NF-κB-MLCK activation

On the basis of the above observation, we continue to explore the signaling mechanisms regarding the anti-inflammatory effect of TEC on intestinal mucosal barrier. As to DSS-induced colitis, the activation of MAPK and NF-κB signaling pathways exert a crucial pro-inflammatory effect (Zhao et al., 2021). As shown in Figure 5a, administration of TEC strongly inhibited DSS-induced the phosphorylation of ERK, p38, and JNK in intestine. Likewise, we found that TEC inhibited the DSS-induced intestinal activation of NF-κB manifesting the reduced nuclear locations of p65 (Figure 5b). The above results indicated that TEC possessed remarkable anti-inflammatory potency associated with MAPK and NF-κB pathway activation. Given that the activated MAPK and NF-κB pathways promote myosin light chain kinase (MLCK) to pull the strings of epithelial TJs (Cunningham and Turner, 2012), we performed immunohistological testing on intestinal MLCK expressions. In agreement, administration of TEC significantly led to the reversal of DSS-induced upregulation of MLCK (Figure 5c). Taken together, these results suggested that TEC prevented DSS-induced intestinal barrier damage by restraining MAPK-NF-κB-MLCK activation.

4. Discussions

Accumulating researches center on the bioactivities of TEC such

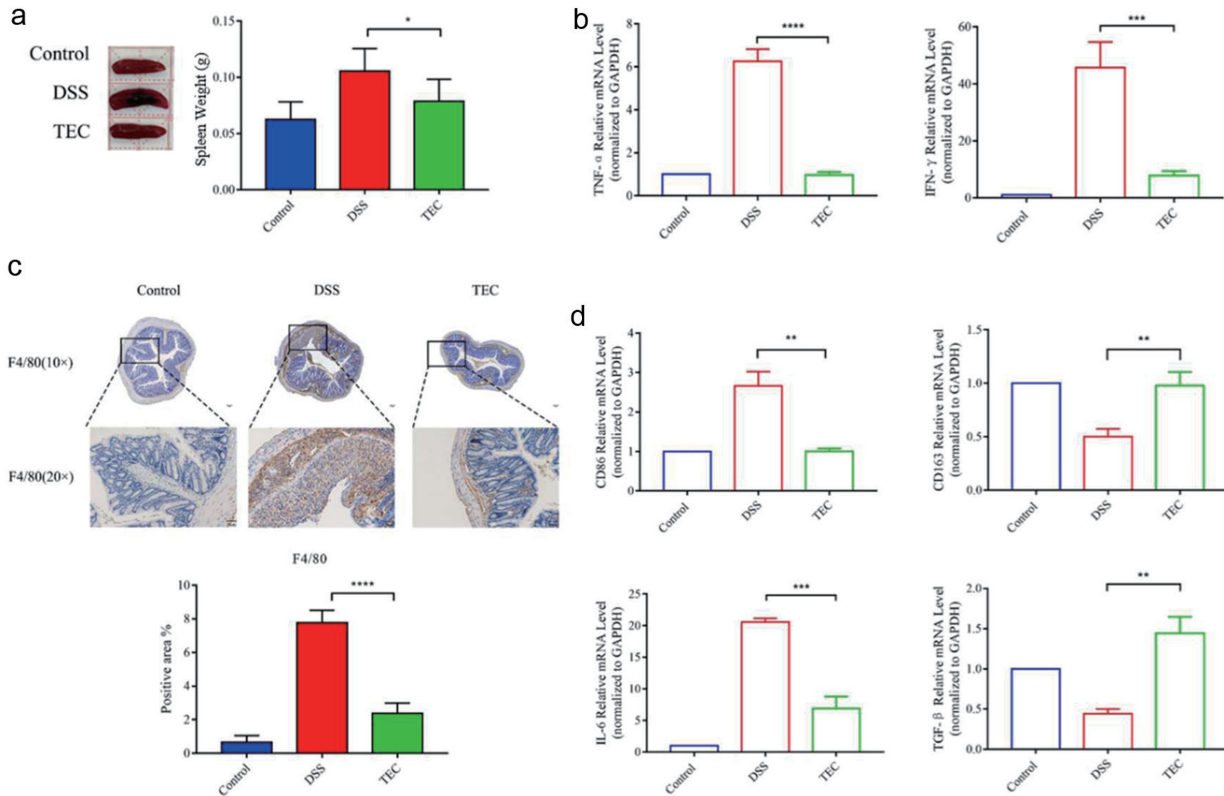

Figure 4. TEC ameliorated DSS-induced intestinal barrier dysfunction by inhibiting the activation of inflammation. (a) Appearances and weight of spleen, (b) the mRNA expression of TNF-α and IFN-γ, (c) immunohistochemical representation and positive area statistics of F4/80, (d) the mRNA expression levels of macrophage surface markers and their corresponding secreted cytokines and chemokines. The data were represented as means ± SD ($n = 3$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$ for TEC group vs DSS group).

as Type 2 Diabetes, liver and kidney injury, and cardioprotective potential (Dong et al., 2023; Wang et al., 2025; Zhang et al., 2024). These researches indicated that TEC possesses clear potential in targeting inflammation. TEC is a flavonoid frequently found in propolis and *Alpinia oxyphylla Miq*, which are well documented in regulation of intestinal barrier hemostasis (Wang et al., 2018; Wang et al., 2017; Yang et al., 2024b). However, it is hardly to find whether TEC plays a protective role in intestinal barrier hemostasis. In this study, we presented that administration of TEC effectively target DSS-induced intestinal barrier dysfunction and the mechanisms behind it involve in targeting intestinal inflammatory environments and MAPK-NF-κB-MLCK Signaling pathways.

In this study, we at first observed that TEC significantly improved DSS-induced intestinal barrier dysfunction and loss of TJs. TJs play an extremely role in maintaining intestinal barrier integrity, with their dysfunction leading to increased intestinal permeability, immune system dysregulation, and exacerbation of mucosal inflammation (Katsuno et al., 2008; Phua et al., 2014). Exactly, TJs, consisting of proteins such as Claudins, Occludin, and ZO-1, are fundamental elements in sealing the adjacent intestinal epithelial cells to prevent the paracellular passage of luminal contents (Barmeyer et al., 2017). Once disrupted, harmful substances enter the body leading to diseases (Jiang et al., 2023; Wang et al., 2021b). Thus, our study of TEC in regulation of intestinal barrier integrity manifests the potential of TEC on body heath.

The local released inflammatory cytokines were investigated and the results indicated that administration of TEC effectively inhibited DSS-induced upregulation of TNFα and IFNγ. Given that macrophages are the key sources providing cytokines, we confirmed the increased infiltration of macrophages in inflamed intestine. In addition, M1-like skew of macrophage is tightly relevant to intestinal mucosal injury and M2-like macrophages are important to tissue repair (Cheng et al., 2023; Gao et al., 2024). A recent report pointed out that TEC alleviated periodontitis involving shift of M1-like Macrophages to M2-like macrophages (Yin et al., 2025). In agreement, we also observed that administration of TEC not only reduced the infiltration of macrophages, but also shifted the DSS-induced M1-like macrophages in flamed intestine skewing to M2-like phenotype. This shift of macrophage polarization manifested that administration of TEC facilitates the anti-inflammatory environment and favors tissue repair in intestine.

The inflammatory signaling pathways MAPK and NF-κB play a central role in intestinal inflammation and contribute to epithelial cell apoptosis, TJ disruption, and subsequent intestinal barrier dysfunction (Bell and Watson, 2013; Li et al., 2023b). More importantly, release of cytokines and activation of macrophages are tightly regulated by these signal pathways. The MAPK signaling pathway is implicated in the regulation of pro-inflammatory cytokine production and cellular stress responses, while NF-κB activation is a pivotal regulator of immune cell recruitment and inflammatory mediator release (Feng et al., 2024; Huang et al., 2022). Indeed, our study reflected that TEC significantly suppressed the release of inflammatory cytokines TNFα and IFNγ and blunted the activation of the main MAPK elements (ERK, p38, and JNK) and NF-κB (p65).

Accordingly, we observed that the downstream target of

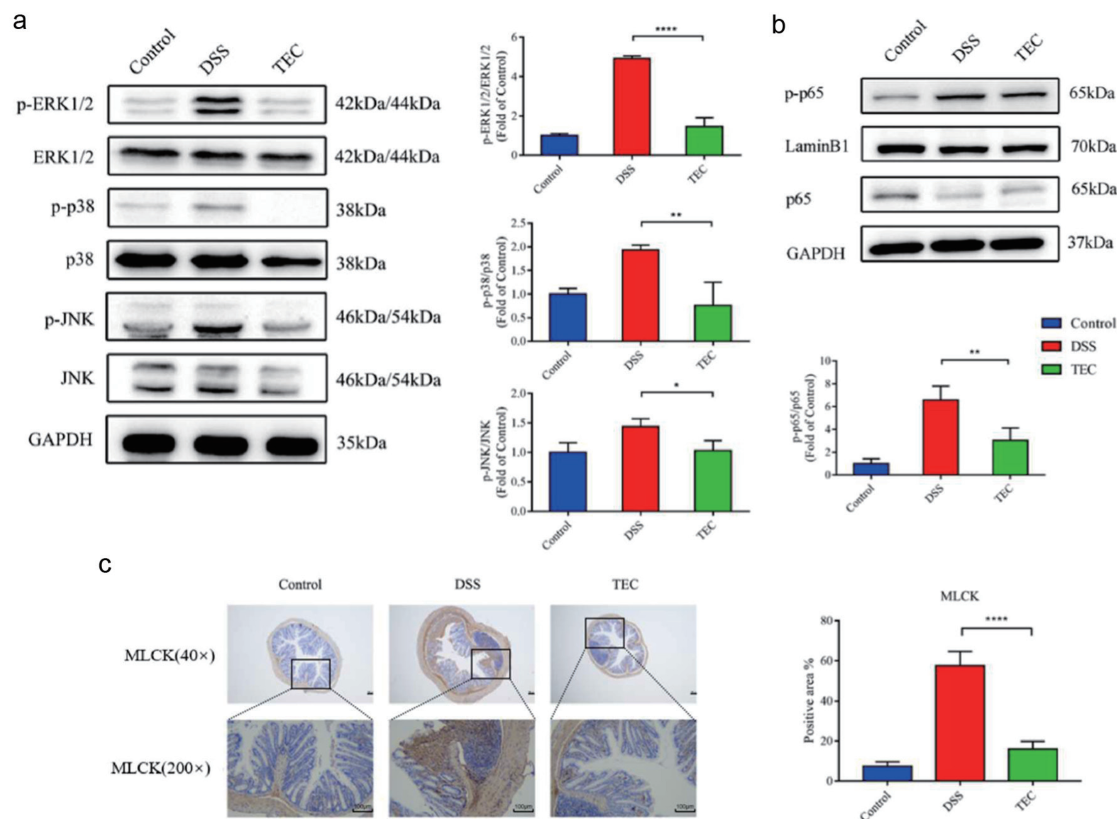

Figure 5. TEC ameliorated DSS-induced UC by inhibiting the activation of MAPK-NF-κB-MLCK pathway. (a) Representative western blot images and the expressions of ERK1/2, p-ERK1/2, p38, p-p38, JNK, and p-JNK, (b) representative western blot images and the expressions of p65 and p-p65, (c) representative MLCK immunohistochemical map of mouse colon tissue and positive area statistics. The grayscale values of each band were analyzed by Image J software. The data were represented as means ± SD (n = 3, *P < 0.05, **P < 0.01, ****P < 0.0001 for TEC group vs DSS group).

MAPK/NF-κB MLCK was suppressed when TEC was added. Upon inflammation stimuli, MLCK activates actomyosin contraction leading to distribution and loss of TJs so as to contribute to intestinal permeability (Lv et al., 2024; Peng et al., 2025; Wang et al., 2021a). These findings, together with our observation that administration of TEC alleviated DSS-induced loss of TJs, suggested that the mechanism of TEC on intestinal barrier homeostasis is closely related to the MAPK-NF-κB -MLCK Signaling Cascade.

In summary, our results identified that the dietary flavonoid TEC prevents against DSS-induced intestinal barrier injury. As to the mechanisms, administration of TEC effectively protects the intestinal barrier integrity involving in targeting MAPK-NF-κB-MLCK signal cascade to alleviate DSS-induced loss of TJs, infiltration of macrophages, and M1-like macrophages. The study recommended that TEC might be a potential nutraceutical for intestinal barrier homeostasis.

Data availability

Data will be made available on request.

Conflict of interest

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

Author contributions

Zihan Yang and Ying Zhou: Writing-original draft, Methodology. Jia Song, Yuxin Wang, Dan Yang: Investigation, Methodology, Data curation. Hui Zhao and Qi Tang: Supervision, Investigation, Methodology.

Supplementary material

Table S1. Information of Antibodies.

Table S2. Primer sequence.

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