

Protective effects of quercetin in experimental ulcerative colitis: Potential involvement of ERK-MMP signaling

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Abstract: Background: Ulcerative colitis is a relapsing inflammatory bowel disease driven by dysregulated immunity, epithelial barrier injury and microbial imbalance. Current therapies remain limited by relapse, adverse effects and incomplete response. Quercetin has anti-inflammatory and barrier-protective activities and ERK-MMP signaling may link inflammation to mucosal tissue damage. **Objectives:** To evaluate whether the protective effects of quercetin in experimental ulcerative colitis (UC) are associated with modulation of ERK-MMP signaling, while avoiding causal overinterpretation beyond the animal and cellular evidence. **Methods:** A dextran sulfate sodium (DSS)-induced mouse model and a lipopolysaccharide (LPS)-stimulated RAW264.7 macrophage inflammatory model were used. Mice were allocated to the control, UC model and low-, medium- and high-dose quercetin groups. Disease activity index (DAI; unitless), colon length, histopathology, inflammatory cytokines and ERK/MMP-related molecules were evaluated by histological staining, ELISA, qRT-PCR and western blotting. *In-vitro*, quercetin was compared with the ERK phosphorylation inhibitor U0126 and an agonistic stimulus to explore pathway-related associations. The study was exploratory and did not include genetic rescue experiments or human validation. **Results:** In DSS-treated mice, medium- and high-dose quercetin were associated with improved colon morphology, reduced DAI scores and partial restoration of colon length. Quercetin decreased pro-inflammatory cytokine expression and increased IL-10 expression. In both mouse colon tissues and LPS-stimulated RAW264.7 cells, quercetin was associated with reduced ERK1/2 activation and lower MMP-3 and MMP-9 expression, together with partial recovery of TIMP expression. These molecular changes were directionally consistent with the effects observed after ERK inhibition *in-vitro*. **Conclusion:** Quercetin showed protective effects in experimental UC models and these effects may be associated with modulation of the ERK-MMP signaling axis. Further pathway-specific rescue experiments, pharmacokinetic studies and human-relevant models are required before this mechanism can be considered definitive or clinically translatable.

Keywords: ERK; MMPs; Quercetin; Ulcerative colitis

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease characterized by recurrent mucosal inflammation, diarrhea, rectal bleeding and abdominal pain (Higashiyama and Hokari, 2023; Kaplan and Ng, 2017). Although genetic susceptibility, dysregulated mucosal immunity, epithelial barrier injury, environmental exposure and gut microbial imbalance have all been implicated in UC pathogenesis (Gilliland *et al.*, 2024; Rubin *et al.*, 2025; Agrawal *et al.*, 2023), the molecular events that connect inflammatory signaling to tissue destruction remain incompletely defined. Current therapies, including aminosalicylates, corticosteroids, immunosuppressants and biologics, can improve symptoms but are limited by incomplete response, relapse, toxicity, cost and long-term

safety concerns (Gao *et al.*, 2019; Wu *et al.*, 2021; Dai *et al.*, 2023). Therefore, clarification of inflammation-related signaling pathways remains important for identifying adjunctive therapeutic strategies. Quercetin is a plant-derived flavonoid with antioxidant, anti-inflammatory, immunomodulatory and barrier-protective activities (Zhou *et al.*, 2023; Wang *et al.*, 2024; Dicarlo *et al.*, 2019; Wang *et al.*, 2023; Wu *et al.*, 2024; Porras *et al.*, 2019; Zhu *et al.*, 2024). Previous studies have reported that quercetin can alleviate experimental UC, reduce pro-inflammatory cytokine production, regulate oxidative stress and interact with MAPK-, NF- κ B-, NLRP3- and aryl hydrocarbon receptor-related pathways. Accordingly, the novelty of the present study lies not in the general anti-inflammatory activity of quercetin, but in the focused evaluation of whether ERK-MMP-related remodeling is associated with quercetin-mediated protection in both DSS-induced mouse colitis and LPS-induced macrophage inflammation.

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The ERK pathway was selected because ERK1/2 activation participates in inflammatory cytokine production and may influence matrix metalloproteinase (MMP) expression, extracellular matrix remodeling, epithelial injury and mucosal barrier disruption in UC (Zhang and Shi, 2020; Seyed Tabib *et al.*, 2020). MMP-3 and MMP-9 are closely associated with mucosal damage and tissue remodeling, whereas TIMPs act as endogenous regulators of MMP activity. Nevertheless, ERK-MMP signaling is only one component of the UC inflammatory network and other pathways, such as NF- κ B, JAK/STAT and NLRP3 inflammasome signaling, may also contribute. This study therefore interprets ERK-MMP modulation as a potential associated mechanism rather than as the only or definitively proven mechanism (Feuerstein *et al.*, 2020; Cao *et al.*, 2024; Sohoul *et al.*, 2023).

We hypothesized that quercetin would attenuate DSS-induced colonic injury and LPS-induced macrophage inflammatory responses and that these effects would be accompanied by reduced ERK1/2 activation and decreased MMP-3 and MMP-9 expression. To test this hypothesis, we combined an *in-vivo* DSS mouse model with an *in-vitro* LPS-stimulated RAW264.7 macrophage model and used pharmacological ERK modulation to explore, but not definitively prove, pathway dependency.

MATERIALS AND METHODS

Animals

SPF-grade male C57BL/6 mice were used for the animal experiments. Mice were housed under standard laboratory conditions with free access to standard diet and water. RAW264.7 mouse macrophage-like cells were used for the *in-vitro* inflammatory model and were cultured under recommended conditions. The animal protocol was approved by the Institutional Animal Care and Use Committee of Yishengyuan Gene Technology (Tianjin) Co., Ltd. (Approval No. YSY-DWLL-2023511).

Grouping and treatments

Animal experiment

A total of 60 SPF-grade male C57BL/6 mice were assigned to five groups (n = 12 per group): control, UC model and low-, medium- and high-dose quercetin groups (100, 200 and 300 mg/kg/day, respectively). A computer-generated randomization sequence was used and allocation information was concealed from investigators involved in outcome assessment. The control group received drinking water, whereas the model and quercetin groups received 5% DSS solution for 7 days. Model establishment was evaluated using body weight change, stool consistency, occult/gross bleeding, DAI score, colon morphology and representative histology, rather than relying solely on two mice. For final quantitative analyses, six biological replicates per group were used consistently and this sample size was based on previous DSS model practice and

experimental feasibility; the absence of a formal power calculation is acknowledged as a limitation. After model induction, control and model mice received 0.2 mL of 0.5% CMC-Na by gavage daily, while the quercetin groups received the indicated quercetin doses for 14 days. Doses were selected according to previous animal studies using quercetin in inflammatory disease models, but their direct human equivalence and translational feasibility require further pharmacokinetic assessment.

Cell experiment

LPS-stimulated RAW264.7 macrophages were used as an inflammatory cell model rather than a complete *in-vitro* UC model. Quercetin concentration was selected based on CCK-8 viability screening and preliminary response evaluation and cells were treated with 10^{-6} mol/L quercetin for 24 h. The ERK phosphorylation inhibitor U0126 was used at 10 μ mol/L for 2 h. Isoprenaline was used as an agonist to enhance ERK signaling; however, it was not considered a genetic rescue tool. Cells were assigned to six groups: control, LPS, LPS + quercetin, LPS + U0126, LPS + quercetin + agonistic stimulus and LPS + agonistic stimulus. The lack of intestinal epithelial cells, organoids and human samples is recognized as a limitation of model relevance.

Evaluation indices and methods

Histopathological analysis

Colon tissues were harvested, washed with PBS, fixed in 4% paraformaldehyde for 24-48 h, dehydrated, cleared, embedded in paraffin, sectioned at 4 μ m and stained with hematoxylin-eosin or Masson trichrome. DAI was calculated as a unitless composite score based on body weight loss, stool consistency and fecal bleeding. Histological injury was evaluated using a semi-quantitative scoring system considering epithelial damage, crypt destruction, inflammatory cell infiltration, edema and ulceration. Two investigators blinded to group allocation independently assessed representative sections and disagreements were resolved by consensus. Collagen deposition, inflammatory infiltration, mucosal architecture and epithelial injury were examined under a light microscope.

Quantification of inflammatory cytokines

Levels of pro-inflammatory and anti-inflammatory cytokines in mouse serum were measured using ELISA kits according to the manufacturers' instructions. Cytokine-related mRNA expression in cell lysates was analyzed by qRT-PCR. All measurements were performed using independent biological replicates and technical replicates were averaged before statistical analysis.

qRT-PCR analysis

mRNA expression of ERK1/2, MMP-3, MMP-9, TIMP and inflammatory cytokines in mouse colon tissues and/or cell lysates was determined by qRT-PCR. Total RNA was

extracted using TRIzol reagent and cDNA was synthesized according to the kit protocol. PCR conditions were 95 °C for 10 min followed by 40 cycles of 95 °C for 15 s and 62 °C for 1 min. GAPDH was used as the internal reference gene and relative expression was calculated using the $2^{-\Delta\Delta C_t}$ method. Primer specificity was confirmed by melting curve analysis and amplification efficiency was verified to be within an acceptable range before relative quantification.

Western blot analysis

Protein levels of p-ERK1/2, total ERK1/2, MMP-3, MMP-9 and TIMP in colon tissue samples and cell lysates were determined by western blotting. Total proteins were extracted, mixed with loading buffer, denatured at 95 °C for 10 min, separated by SDS-PAGE and transferred to PVDF membranes. After blocking, membranes were incubated with validated primary antibodies at 4 °C overnight, followed by incubation with corresponding secondary antibodies for 1 h at room temperature. Bands were visualized and quantified using ImageJ. p-ERK1/2 was normalized to total ERK1/2 and MMP-3, MMP-9 and TIMP were normalized to β -actin. Antibody specificity was checked according to manufacturer validation information and expected molecular weight.

Statistical analysis

All assays were independently repeated using biological replicates as indicated and results are presented as mean $\pm$ SD. Statistical analyses were performed using SPSS version 23.0. Normality and homogeneity of variance were assessed using the Shapiro-Wilk and Levene tests, respectively. For normally distributed data with equal variances, one-way ANOVA followed by post hoc multiple-comparison testing was used. For data that did not meet these assumptions, appropriate non-parametric tests were considered. Statistical significance was defined as $P \leq 0.05$. Effect direction and significance thresholds are reported in the text and figure legends; where available, exact P values were retained in the source data.

RESULTS

Quercetin reduces disease activity and restores colon length in UC mice

DSS administration significantly increased the unitless DAI score and shortened colon length (cm) compared with the control group (Fig. 1a). Quercetin treatment reduced DAI scores and partially restored colon length, with more pronounced improvement in the medium- and high-dose groups than in the low-dose group according to post hoc comparisons where indicated ($P < 0.05$). Colon length recovery was greatest in the high-dose quercetin group, whereas the low-dose group showed a smaller improvement. These data support a dose-related trend, although the study was not powered to definitively compare all quercetin doses with one another.

Overall, quercetin was associated with attenuation of clinical disease activity and colonic shortening in the DSS-induced UC mouse model.

Quercetin mitigates mucosal damage in UC mice

In the control group, the colonic mucosa showed preserved epithelial architecture, intact crypts, intact goblet cells and no obvious inflammatory infiltration or ulceration. In the UC model group, marked epithelial disruption, crypt destruction, mucosal edema and extensive inflammatory cell infiltration were observed. Medium- and high-dose quercetin treatment progressively improved mucosal architecture and reduced inflammatory infiltration and edema (Fig. 1b). A blinded semi-quantitative histological assessment was added to increase objectivity and the histological findings were consistent with the DAI and colon length results.

Quercetin modulates pro-inflammatory cytokines, mRNA and protein expression of key factors in DSS-induced animal models

As shown in figure 2a, DSS administration increased pro-inflammatory mediators TNF- α , IL-1 β and IL-6 and reduced the anti-inflammatory cytokine IL-10 compared with the control group. Quercetin intervention, particularly at medium and high doses, decreased TNF- α , IL-1 β and IL-6 expression and increased IL-10 expression compared with the UC model group ($P < 0.05$).

qRT-PCR results showed that the UC model group had increased mRNA expression of ERK1, ERK2, MMP-3 and MMP-9, together with decreased TIMP expression (Fig. 2b). Quercetin treatment reduced ERK1/2, MMP-3 and MMP-9 mRNA expression and partially restored TIMP expression, especially in the medium- and high-dose groups ($P < 0.05$).

Consistent with the mRNA results, western blotting showed increased p-ERK1/2, MMP-3 and MMP-9 protein levels and reduced TIMP expression in DSS-induced UC mice (Fig. 2c). Quercetin treatment was associated with lower p-ERK1/2, MMP-3 and MMP-9 levels and higher TIMP expression. These findings support an association between quercetin treatment and reduced ERK-MMP activation, but they do not by themselves prove direct pathway causality. These animal data suggest that quercetin attenuates DSS-induced intestinal inflammation and that this protection may be related to modulation of ERK-MMP-associated molecular changes.

Quercetin regulates gene and protein expression in LPS-induced cell models

In LPS-stimulated RAW264.7 macrophages, TNF- α , IL-1 β and IL-6 expression increased, whereas IL-10 expression decreased compared with the control group (Fig. 3a).

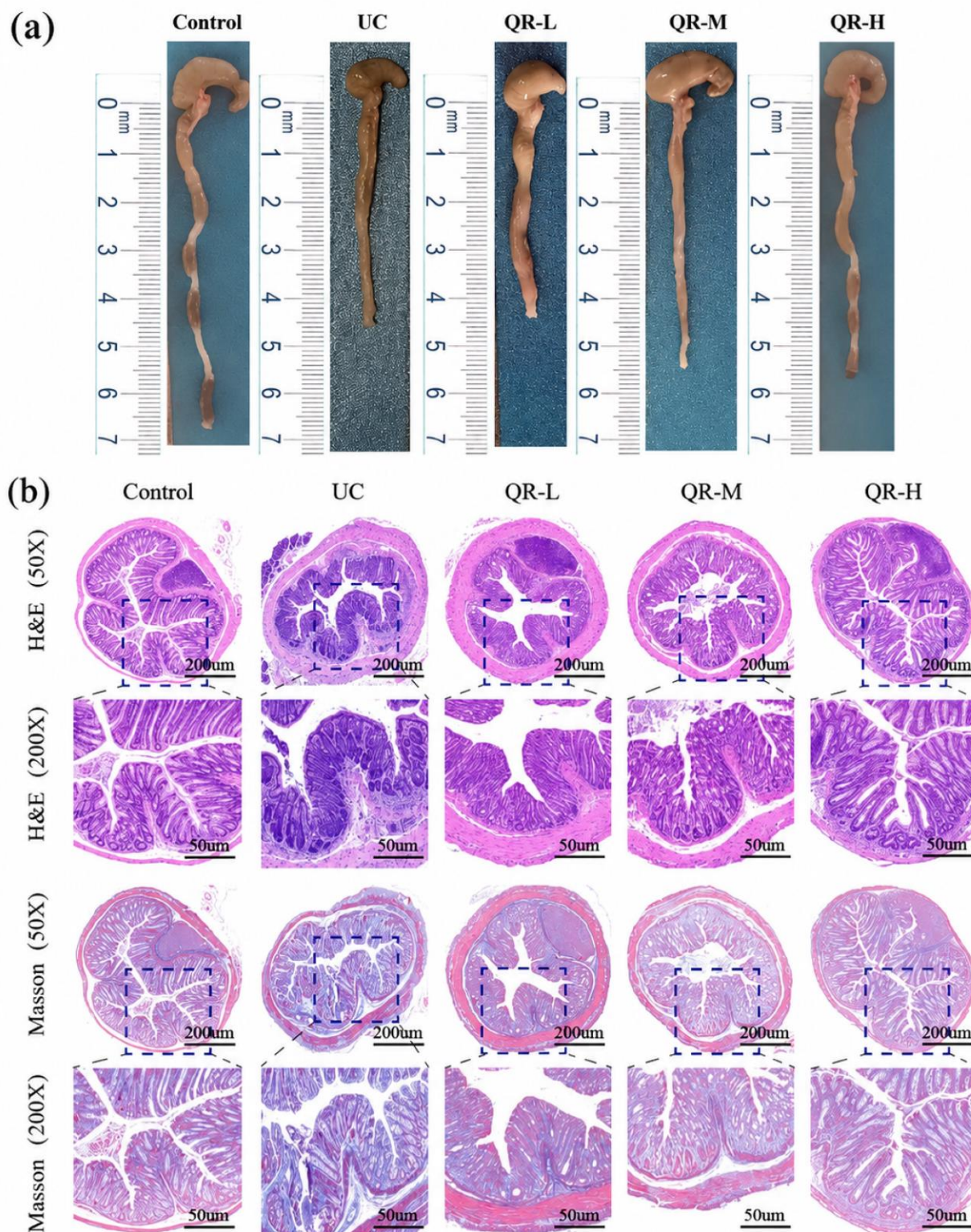


Fig. 1: Quercetin mitigates mucosal damage and inflammation in UC mice. Representative colon images from experimental mouse groups. (a) Histological images of colon tissues from experimental mouse groups at different magnifications; (b) Control: blank control group; UC: UC model group; QR-L: low-dose quercetin group; QR-M: medium-dose quercetin group; QR-H: high-dose quercetin group. DAI is reported as a unitless score, and colon length is reported in cm.

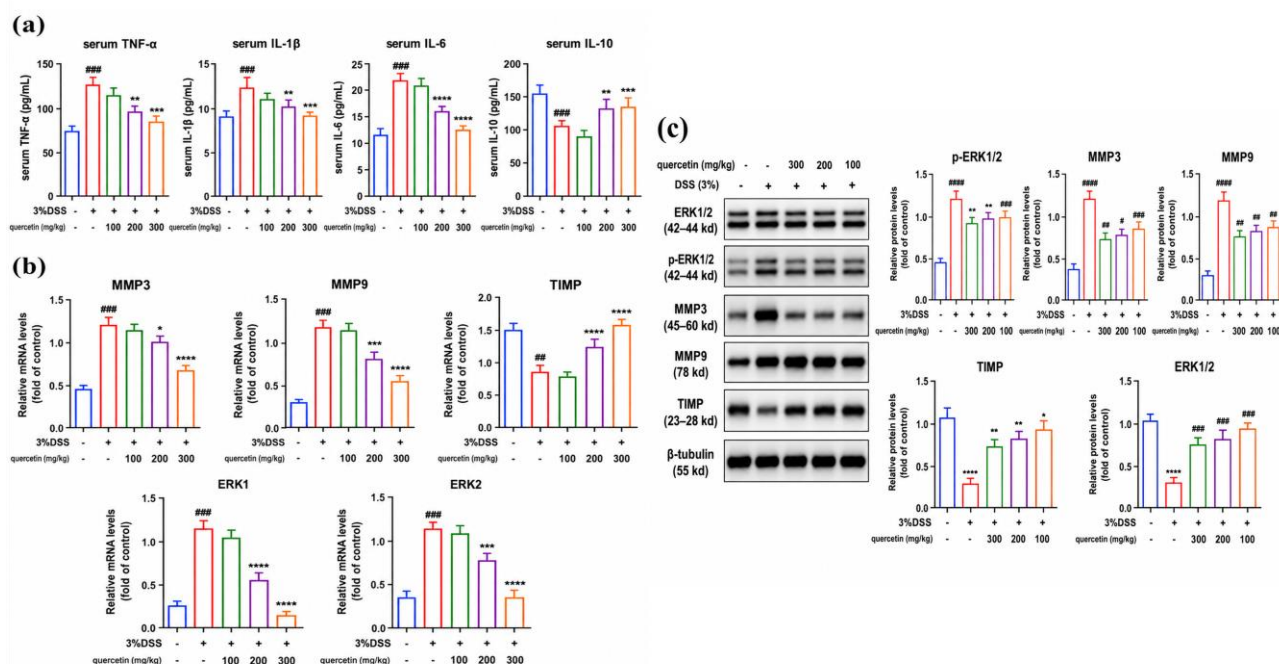


Fig. 2: Quercetin reduces pro-inflammatory cytokines and modulates ERK-MMP-related mRNA and protein expression in DSS-induced animal models. Expression levels of TNF- α , IL-1 β , IL-6 and IL-10 in animal experiments. (a) mRNA expression levels of MMP-3, MMP-9, TIMP, ERK1 and ERK2 in colonic tissues; (b) Protein expression levels of p-ERK1/2, MMP-3, MMP-9 and TIMP in animal experiments; (c) Compared with the control group: #####P < 0.0001, ###P < 0.001, ##P < 0.01, #P < 0.05; compared with the UC group: ****P < 0.0001, ***P < 0.001, **P < 0.01, *P < 0.05.

Quercetin and U0126 reduced pro-inflammatory cytokine expression and increased IL-10 expression compared with LPS stimulation alone ($P < 0.05$). The agonistic stimulus partially attenuated quercetin's anti-inflammatory effect, suggesting pathway involvement rather than definitive causality.

qRT-PCR analysis showed increased ERK1, ERK2, MMP-3 and MMP-9 mRNA expression and reduced TIMP expression in the LPS and agonistic-stimulus groups (Fig. 3b). Quercetin and U0126 downregulated ERK1/2, MMP-3 and MMP-9 expression and increased TIMP expression ($P < 0.05$).

Western blotting showed elevated p-ERK1/2, MMP-3 and MMP-9 protein levels and reduced TIMP expression after LPS stimulation (Fig. 3c). Quercetin and U0126 reduced p-ERK1/2, MMP-3 and MMP-9 protein levels and increased TIMP expression. Because rescue experiments using genetic manipulation were not performed, these results should be interpreted as pharmacological evidence supporting pathway association.

Thus, quercetin suppressed inflammatory responses in LPS-stimulated macrophages and these effects were accompanied by ERK-MMP-related changes that paralleled the *in-vivo* findings.

DISCUSSION

The present study showed that quercetin alleviated DSS-induced colonic injury in mice and reduced inflammatory activation in LPS-stimulated RAW264.7 macrophages. These effects were accompanied by decreased pro-inflammatory cytokine expression, increased IL-10 expression, lower p-ERK1/2 activation, reduced MMP-3 and MMP-9 expression and partial recovery of TIMP expression. The revised interpretation emphasizes association and pharmacological support rather than definitive causation.

The anti-inflammatory and UC-protective effects of quercetin have been reported previously; therefore, the contribution of this study is a focused analysis of ERK-MMP-associated changes across animal and cellular systems, rather than a claim that quercetin is a newly discovered anti-colitis compound. Recent studies have linked quercetin to intestinal barrier protection, regulation of oxidative stress, NLRP3-related inflammation and MAPK/NF- κ B-related signaling (Raine *et al.*, 2022; Zeng *et al.*, 2022; Zhang and Li, 2014; Cai *et al.*, 2021; Suzuki, 2020). Our findings are consistent with this literature and further suggest that changes in MMP-3/MMP-9 and TIMP may participate in quercetin-associated mucosal protection.

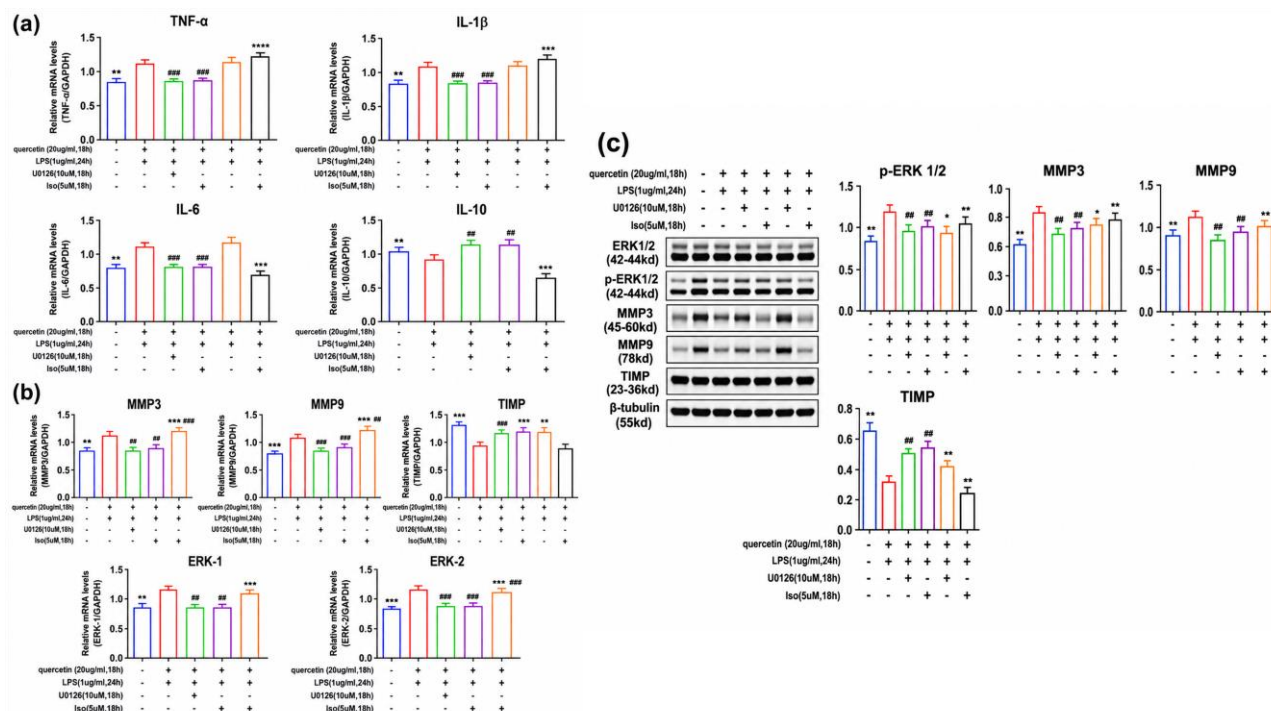


Fig. 3: Quercetin reduces pro-inflammatory cytokines and modulates ERK-MMP-related mRNA and protein expression in LPS-induced RAW264.7 macrophage experiments. Expression levels of TNF- α , IL-1 β , IL-6 and IL-10 in cell experiments (a). mRNA expression levels of MMP-3, MMP-9, TIMP, ERK1 and ERK2 in cell experiments; (b) Protein expression levels of p-ERK1/2, MMP-3, MMP-9 and TIMP in cell experiments; (c) Compared with the control group: #####P < 0.0001, ###P < 0.001, ##P < 0.01, #P < 0.05; compared with the LPS model group: ****P < 0.0001, ***P < 0.001, **P < 0.01, *P < 0.05.

ERK signaling was selected because it is involved in inflammatory signal transduction and may regulate MMP expression, while MMP-3 and MMP-9 contribute to extracellular matrix degradation and mucosal remodeling (Le Berre *et al.*, 2023; Rosenberg *et al.*, 2013; Gros *et al.*, 2024; Plastira *et al.*, 2020). However, UC involves multiple interacting pathways, including NF- κ B, JAK/STAT, NLRP3 inflammasome signaling, oxidative stress and epithelial barrier dysfunction. Thus, ERK-MMP modulation should be regarded as one potential component of quercetin action rather than the sole mechanism (Wang *et al.*, 2024; Wu *et al.*, 2021; Yang *et al.*, 2024). The use of U0126 and an agonistic stimulus provided pharmacological support for pathway involvement, but the lack of genetic knockdown, overexpression, or rescue experiments prevents a definitive causal conclusion. The *in vivo* and *in vitro* findings were directionally consistent: quercetin reduced inflammatory cytokine production and was associated with reduced ERK-MMP activation in both models. Nevertheless, RAW264.7 macrophages stimulated with LPS do not fully reproduce the intestinal epithelial, stromal, microbial and immune-cell interactions that occur in human UC. Therefore, future studies should include intestinal epithelial cells, co-culture systems, organoids, human tissues, MMP activity assays, epithelial barrier integrity assays and pathway-specific rescue experiments.

Limitations

Several limitations should be noted. First, this was an exploratory animal and cellular study without formal a priori sample size calculation. Second, the final quantitative animal analyses used $n = 6$ biological replicates per group and larger studies are needed to confirm effect sizes. Third, although randomization, allocation concealment and blinded histological assessment were clarified, residual experimental bias cannot be completely excluded. Fourth, inflammatory markers were measured at limited time points. Fifth, DSS-induced colitis and LPS-stimulated macrophages cannot fully replicate human UC. Sixth, quercetin bioavailability, metabolism, tissue distribution and the feasibility of a human-equivalent dose were not directly assessed. Seventh, no human tissue, organoid, genetic rescue, MMP enzymatic activity, or intestinal barrier integrity assay was performed. These limitations restrict causal and translational interpretation.

CONCLUSION

Quercetin attenuated experimental UC-related injury and inflammatory responses in DSS-induced mice and LPS-stimulated macrophages. The protective effects were accompanied by reduced ERK1/2 activation, decreased MMP-3 and MMP-9 expression and partial recovery of

TIMP expression, suggesting that ERK-MMP signaling may be involved. However, this pathway should be considered a potential associated mechanism rather than a definitively proven causal pathway. Further pathway-specific, pharmacokinetic and human-relevant studies are required.

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None.

Author's contributions

Qiuzan Zhang and Qiliang Zhang: Conceived and designed experiments; Min Guo, Yongheng Wen, Na Shen and Zhiqian Zhou: Carried out experiments and analyzed the data; Qiliang Zhang and Min Guo: Wrote the manuscript; Qiuzan Zhang and Yanrong Wang: Revised the manuscript. All authors read and approved the final manuscript.

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Data availability statement

The data generated and analyzed during the present study are available from the corresponding author upon reasonable request. Original image files, qRT-PCR Ct values, western blot densitometry data and replicate-level datasets can be provided for verification where permitted by institutional policy.

Ethical approval

All animal experiments complied with the guidelines of Tianjin Medical Experimental Animal Care and the Tianjin Regulations for the Administration of Laboratory Animals. The protocol was approved by the Institutional Animal Care and Use Committee of Yishengyuan Gene Technology (Tianjin) Co., Ltd. (Approval No. YSY-DWLL-2023511). Animals were monitored daily for body weight, stool consistency, bleeding, activity and general condition. Humane endpoints were predefined for severe weight loss, persistent bleeding, lethargy, or distress and efforts were made to minimize animal suffering. This study was performed in adherence with the ARRIVE guidelines. See supplementary file for the ARRIVE checklist.

Conflicts of interest

The authors declare no conflicts of interest.

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