RESEARCH ARTICLE
doi: 10.2306/scienceasia1513-1874.2024.041

*ScienceAsia* 50 (2): 2024: ID 2024041: **1–8**

# Galangin modulation of the IL-23/IL-17 axis mitigates ulcerative colitis through attenuation of oxidative/nitrative stress and inflammation

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*Received 18 Jul 2023, Accepted 23 Jan 2024*
*Available online 3 May 2024*

**ABSTRACT**: The pathophysiology of Ulcerative Colitis (UC) involves the imbalance of pro-inflammatory cytokines, including interleukin (IL)-23 and IL-17, which play a crucial role in the development and progression of UC. Galangin (Gal), a natural flavonoid compound, has been shown to possess anti-inflammatory, antioxidant, and immunomodulatory properties. Therefore, this study aimed to investigate the potential therapeutic effects of Gal on a mouse model of dextran sulfate sodium (DSS)-induced UC by targeting the IL-23/IL-17 axis. Forty male C57BL/6 mice were randomly divided into four groups and assessed clinical and histopathological features. The colon tissues were collected for protein analysis using Western Blotting. Also, ELISA and colorimetric analysis were used to measure cytokines and oxidative/nitrative stress markers, respectively. The expressions of iNOS and COX-2 were measured by real-time quantitative PCR (RT-qPCR). We found that Gal treatment significantly attenuated the severity of UC, as evidenced by the improvement of clinical symptoms, histopathology, and reduced levels of pro-inflammatory cytokines, including IL-23 (fold change: 0.64; $p < 0.05$) and IL-17 (fold change: 0.56; $p < 0.05$). Moreover, Gal treatment inhibited the activation of the NF-κB pathway. Furthermore, we demonstrated that Gal treatment significantly suppressed oxidative/nitrative stress by reducing the expression levels of iNOS (fold change: 0.46; $p < 0.01$) and COX-2 (fold change: 0.52; $p < 0.01$), the two key enzymes involved in the production of reactive oxygen/nitrogen species (ROS/RNS), and increasing the activity of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase. Our findings suggested that Gal targeting the IL-23/IL-17 axis improves UC by suppressing oxidative/nitrative stress and inflammation.

**KEYWORDS**: ulcerative colitis, galangin, IL-23/IL-17 axis, NF-κB pathway, ROS/RNS

## INTRODUCTION

Ulcerative Colitis (UC) is a chronic inflammatory bowel disease (IBD) affecting millions worldwide. Although UC occurs broadly in people of all ages, it primarily affects young people, typically in their second to fourth decade of life [1–4]. UC is characterized by mucosal inflammation and oxidative stress, leading to the destruction of intestinal epithelial cells and subsequent ulceration [5, 6]. The pathogenesis of UC is believed to be multifactorial, involving genetic, environmental, and immune system factors. Numerous inflammatory markers, including myeloperoxidase (MPO), interleukin (IL)-1b, IL-6, IL-17, tumor necrosis factor-alpha (TNF-a), nuclear factor-kappa B (NF-κB), and cyclooxygenase-2 (COX-2), have been linked to elevated levels in UC [7–9]. Pro-inflammatory cytokines, such as IL-23 and IL-17, have been implicated as key mediators in the development and progression of UC [10–12].

A 10-year illness course is experienced by around one-third of UC patients. Since UC has already spread globally, finding new and powerful medications to treat UC remains a key objective [3, 13, 14]. Galangin (Gal; 3,5,7-trihydroxyflavone), a natural flavonoid compound derived from the *rhizome of Alpinia officinarum*, has gained considerable attention due to its potential therapeutic properties. Studies have demonstrated that Gal possesses anti-inflammatory, antioxidant, and immunomodulatory activities. It has been shown to inhibit the production of pro-inflammatory cytokines and chemokines, suppress the activation of nuclear factor-kappa B (NF-κB), and modulate various immune signaling pathways. Previous studies have demonstrated the protective effects of Gal in various animal models of inflammatory and oxidative stress-related diseases, including renal inflammation and disorders of gastrointestinal, cardiovascular, skin, and respiratory systems [15–18]. However, the specific mechanisms underlying the therapeutic effects of Gal in UC remain unclear. Recent studies have suggested that the IL-23/IL-17 axis plays a critical role in the pathogenesis of UC. IL-23 is a pro-inflammatory cytokine that drives T-helper 17 (Th17) differentiation, produces IL-17. IL-17, and has been shown to play a key role in inducing mucosal inflammation and oxidative stress in UC [19–21]. In addition, oxidative/nitrative stress, which is induced by the overproduction of reactive oxygen/nitrogen species (ROS/RNS), has been implicated in the development and progression

of UC [6, 22].

Heretofore, the role and mechanisms of Gal-mediated protection against UC have not been studied. In this study, we aimed to investigate the potential therapeutic effects of Gal on UC by targeting the IL-23/IL-17 axis. We hypothesized that Gal treatment could attenuate UC by suppressing oxidative/nitrative stress and inflammation through Gal of the IL-23/IL-17 axis. Understanding the specific mechanisms underlying the therapeutic effects of Gal in UC could provide new insights into the development of effective treatments for this debilitating disease.

## MATERIALS AND METHODS

### Animals

The experiments were conducted on male C57BL/6 mice (8–10 weeks old) obtained from the Animal Center of Nanjing Medical University. The mice were housed in a specific pathogen-free facility with an alternate 12-h light/dark cycle and given free access to food and water. All experimental procedures were approved by the Animal Care and Use Committee of Gempharmatech Co., Ltd.

### Induction of colitis and treatment with galangin

The mice were randomly divided into four groups ($n = 10$ per group): *Control group*, mice receiving tap water ad libitum for 7 days; *Gal treated group*, mice receiving Gal dissolved in 0.5% carboxymethylcellulose and administered orally by gavage daily at a dose of 10 mg/kg/day for 7 days; *Dextran sulfate sodium (DSS) treated group*, mice receiving 2.5% (w/v) DSS (MW 36,000–50,000 Da, MP Biomedicals, LLC) in drinking water for 7 days to induce colitis; and *DSS + Gal treated group*, mice receiving DSS and orally treated by gavage with Gal (Sigma-Aldrich, St Louis, MO, USA) at a dose of 10 mg/kg body weight daily for 7 days (Gal was dissolved in 0.5% carboxymethylcellulose) [23].

### Clinical and histopathological evaluation

Body weight, stool consistency, and occult blood in feces were monitored daily. The length of the colon was measured after sacrifice. The severity of colitis was assessed by histological examination of the colon tissues. The tissues were fixed in 10% formalin, embedded in paraffin, and sectioned into 5 μm slices using a microtome. The tissue sections were stained with H&E (hematoxylin and eosin) and examined under a light microscope (Olympus BX51, Tokyo, Japan) by a blinded investigator.

### Histopathological scoring

Histopathological assessment was conducted by a blinded investigator according to the following scoring criteria of four parameters: (1) Inflammation (0–3): 0 = No inflammation; 1 = Mild inflammation, limited to the mucosa; 2 = Moderate inflammation, extending into the submucosa; 3 = Severe inflammation, transmural involvement. (2) Epithelial Damage (0–3): 0 = Intact epithelium; 1 = Focal loss of crypts; 2 = Multifocal loss of crypts; 3 = Extensive loss of crypts and surface epithelium. (3) Crypt Abscesses (0–2): 0 = Absence of crypt abscesses; 1 = Focal crypt abscesses; 2 = Multiple crypt abscesses. (4) Submucosal Changes (0–2): 0 = No submucosal changes, 1 = Mild submucosal changes, 2 = Severe submucosal changes, including fibrosis. Scores from each parameter were summed to obtain a total histopathological score for each animal.

### Western blot analysis

The colon tissues were collected and homogenized in ice-cold RIPA buffer with protease inhibitors (Beyotime, Shanghai, China) and centrifuged at 12,000 rpm for 10 min at 4 °C. The supernatants were collected, and the protein concentrations were determined using a BCA protein assay kit (Beyotime). Equal amounts of protein were separated by 10% SDS-PAGE and transferred onto a polyvinylidene difluoride membrane. The membranes were probed with primary antibodies against phospho-p65, p65, and β-actin (Cell Signaling Technology, Danvers, MA, USA), followed by HRP-conjugated secondary antibodies (Santa Cruz Biotechnology, Dallas, TX, USA). The protein bands were visualized using an ECL detection kit (Thermo Scientific, Washington, DC, USA).

### RNA isolation and RT-qPCR measurement

Total RNA was extracted by TRIzol (Invitrogen, Carlsbad, CA, USA) and quantified by nanodrop (Thermo Scientific, Waltham, MA, USA). After synthesizing cDNA according to the manufacturer's protocol using a cDNA synthesis kit, the expression of inducible nitric oxide synthase (iNOS) and COX-2 genes was assessed in collected tissues using a real-time PCR device (Bio-Rad, Hercules, CA, USA).

### Measurement of cytokines and oxidative/nitrative stress markers

Two separate colon tissues were homogenized in phosphate-buffered saline (PBS) containing protease and phosphatase inhibitors; and in ice-cold RIPA buffer with protease inhibitors (Beyotime). The homogenized tissues were centrifuged at 12,000 rpm for 10 min at 4 °C, the supernatants were collected, and the IL-23 and IL-17 were measured by enzyme-linked immunosorbent assay (ELISA; BioLegend, San Diego, CA, USA) according to the manufacturer's instructions. The levels of oxidative/nitrative stress markers, including reactive oxygen/nitrogen species and antioxidant enzymes, such as superoxide dismutase and glutathione peroxidase, were measured using commercially available kits.

### Measurement of IL-10 in colon tissues

IL-10 concentrations were assessed using a standard quantitative sandwich enzyme immunoassay method (Quantikine; R&D Systems, Abingdon, UK) according to the previously described procedure by Merle-Beral et al [24].

### Statistical analysis

All data were presented as mean ± SD. Statistical analysis was performed using GraphPad Prism 8.0 software (GraphPad Software, San Diego, CA, USA). The significance of differences between groups was evaluated by a one-way analysis of variance followed by the Tukey-Kramer multiple comparison test. Statistical significance was assumed at a $p$-value less than 0.05.

## RESULTS

### Galangin attenuated the severity of colitis

Compared with the DSS treated group, the Gal treated group showed a significant improvement in clinical symptoms of colitis, including reduced body weight loss, decreased diarrhea, and rectal bleeding. The colon length was significantly longer in the Gal-DSS treated group than in the DSS group, indicating a reduction in inflammation-induced colon shortening. The histopathological evaluation showed that Gal treatment significantly decreased the severity of colitis, as evidenced by decreased inflammation, edema, ulceration, and infiltration of immune cells in colon tissues ($p < 0.05$; Fig. 1).

### Galangin suppressed IL-23/IL-17 axis

The levels of pro-inflammatory cytokines IL-23 and IL-17 were significantly decreased in the colon tissues of mice with DSS-induced colitis treated with Gal compared with the DSS-treated mice ($p < 0.05$). These findings suggested that Gal suppresses the IL-23/IL-17 axis, which plays a critical role in the development and progression of UC (Fig. 2).

### Galangin enhanced the production of anti-inflammatory cytokine

To determine the effects of Gal on the production of anti-inflammatory cytokines, we measured the levels of IL-10 in the colon tissues. Treatment with DSS significantly reduced the levels IL-10, while Gal treatment significantly enhanced its production (Fig. 3).

### Galangin inhibited the activation of the NF-κB pathway

To examine the impact of Gal on the activation of the NF-κB pathway, we assessed the levels of phospho-p65 and p65 in colon tissues. Treatment with DSS significantly elevated phospho-p65 levels, without affecting p65. In contrast, Gal treatment markedly suppressed the activation of the NF-κB pathway (Fig. 4).

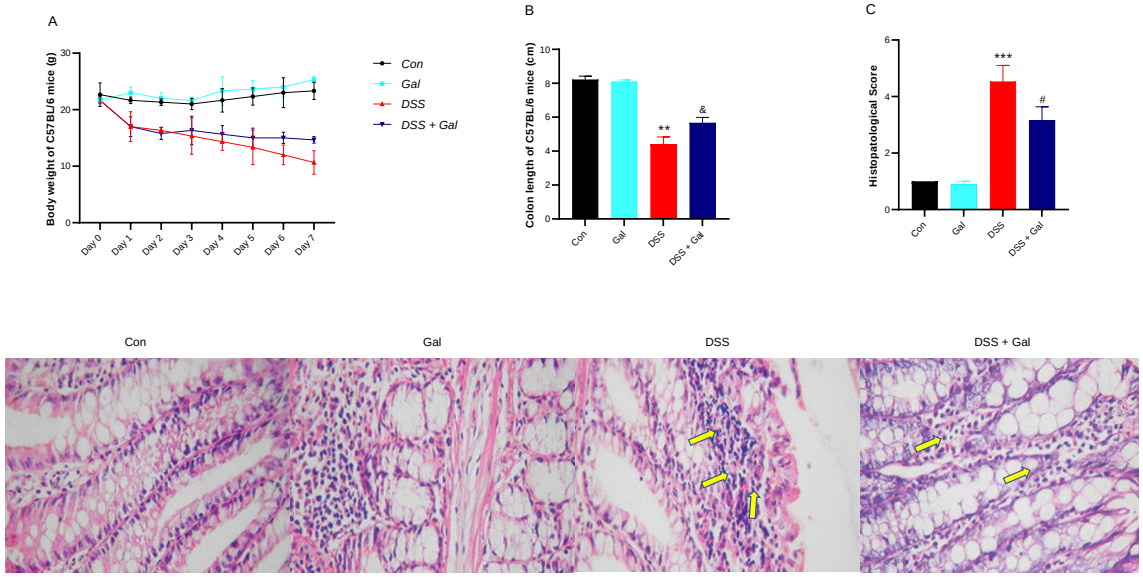


**Fig. 1** Effect of galangin on the severity of colitis in mice. (A) Body weight decreased after treatment with DSS, and when the mice were treated with Gal, body weight began to increase over time. (B) Length of the colon was decreased in mice with DSS-induced colitis, and Gal treatment inhibited the loss of colon length. (C) Histopathological evaluation of the colon showed an increase in histopathologic score. Data are presented as mean ± SD. $n = 10$/group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Con, Control Group; Gal, Gal treated Group; DSS, Dextran Sulfate Sodium treated Group; DSS + Gal, DSS + Gal treated Group.

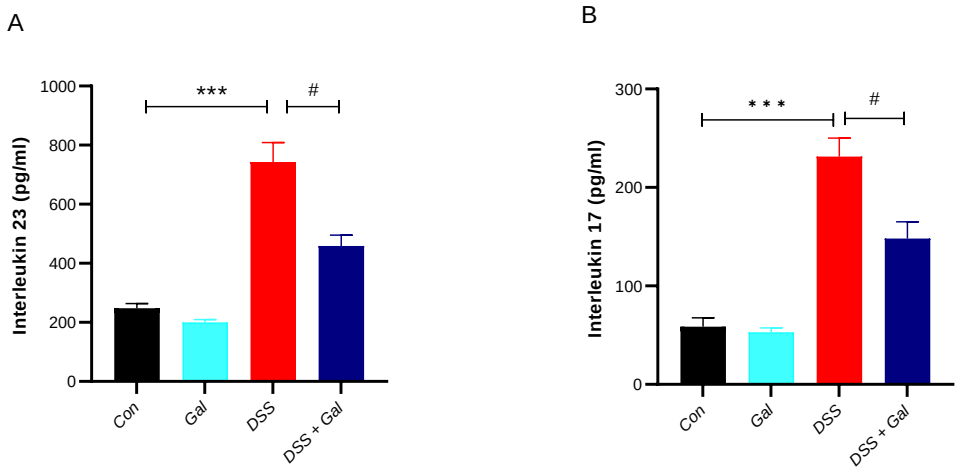


**Fig. 2** Effect of galangin on the IL-23/IL-17 axis in the colon tissues of mice. (A) Levels of IL-23 and (B) levels of IL-17, both were increased in mice with DSS induced colitis while treatment with Gal reduced the expression of IL-23/IL-17 in these mice. Data are presented as mean ± SD. $n = 10$/group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.0001$. Con, Control Group; Gal, Gal treated Group; DSS, Dextran Sulfate Sodium treated Group; DSS + Gal, DSS + Gal treated Group.

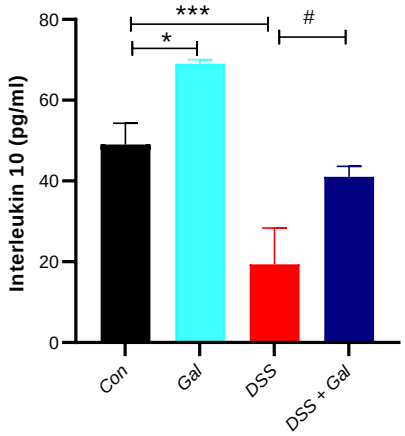


**Fig. 3** Effect of galangin on the production of the anti-inflammatory cytokine IL-10. Data are presented as mean ± SD. $n = 10$/group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Con, Control Group; Gal, Gal treated Group; DSS, Dextran Sulfate Sodium treated Group; DSS + Gal, DSS + Gal treated Group.

### Galangin suppressed oxidative/nitrative stress

Oxidative/nitrative stress markers, including iNOS and COX-2, two key enzymes involved in the production of reactive oxygen/nitrogen species (ROS/RNS), were significantly decreased in colon tissues of mice with DSS-induced colitis treated with Gal compared with mice without Gal treatment ($p < 0.01$, Fig. 5A). Gal treatment significantly increased the activity of antioxidant enzymes, including superoxide dismutase and glutathione peroxidase ($p < 0.01$; Fig. 5B).

## DISCUSSION

The present study investigated the therapeutic potential of Gal on UC by targeting the IL-23/IL-17 axis. By inhibiting the production of IL-23 and IL-17, Gal could disrupt the positive feedback loop that sustains the inflammatory response in UC. Our results demonstrated that Gal treatment attenuated the severity of colitis by reducing clinical symptoms, histopathological damage, inflammatory cytokine levels, and oxidative/nitrative stress in a mouse model of UC.

The IL-23/IL-17 axis has been demonstrated to play a pivotal role in the pathogenesis of UC. IL-23, a member of the IL-12 cytokine family, is involved in the differentiation and expansion of IL-17-producing T cells, which are key effector cells in the development and progression of UC [25]. Indeed, IL-23 is a pro-inflammatory cytokine that plays a crucial role in the development and progression of UC by promoting the differentiation and activation of Th17 cells [14, 26], which produce IL-17. IL-17 has been shown to contribute to the pathogenesis of UC by inducing inflammation and oxidative stress. According to the research by Trivedi and colleagues, melatonin treatment reduced the severity of UC by modifying a number of molecular targets, including NF-κB, IL-17, signal transducer and activator of transcription 3 (STAT-3), nuclear erythroid 2-related factor 2 (Nrf-2) [27], and matrix metalloproteinase-9 (MMP-9)-additionally, UC enhanced genotoxicity, systemic inflammation, plasma lipopolysaccharide (LPS) levels [28], and gut permeability. Treatment with melatonin promoted mucosal healing, decreased high intestinal permeability brought on by UC, and reduced plasma LPS level [29, 30]. Another study by Trivedi Coallegues was

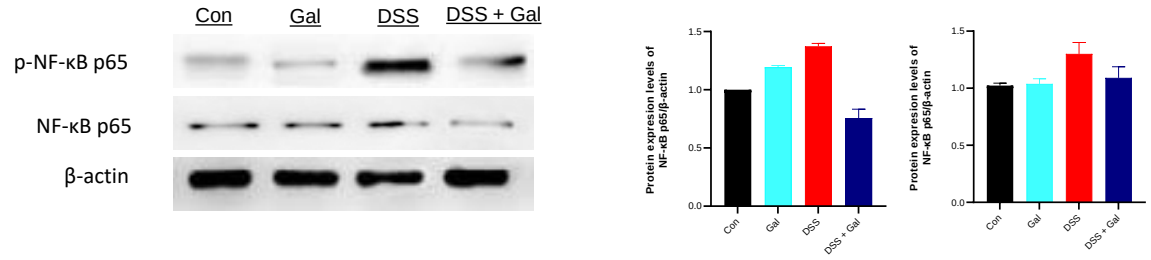


**Fig. 4** Effect of galangin on the NF-κB pathway. Western blot analysis of phospho-p65, p65, and β-actin in colon tissues. Data are presented as mean ± SD. $n = 10$/group. Con, Control Group; Gal, Gal treated Group; DSS, Dextran Sulfate Sodium treated Group; DSS + Gal, DSS + Gal treated Group.

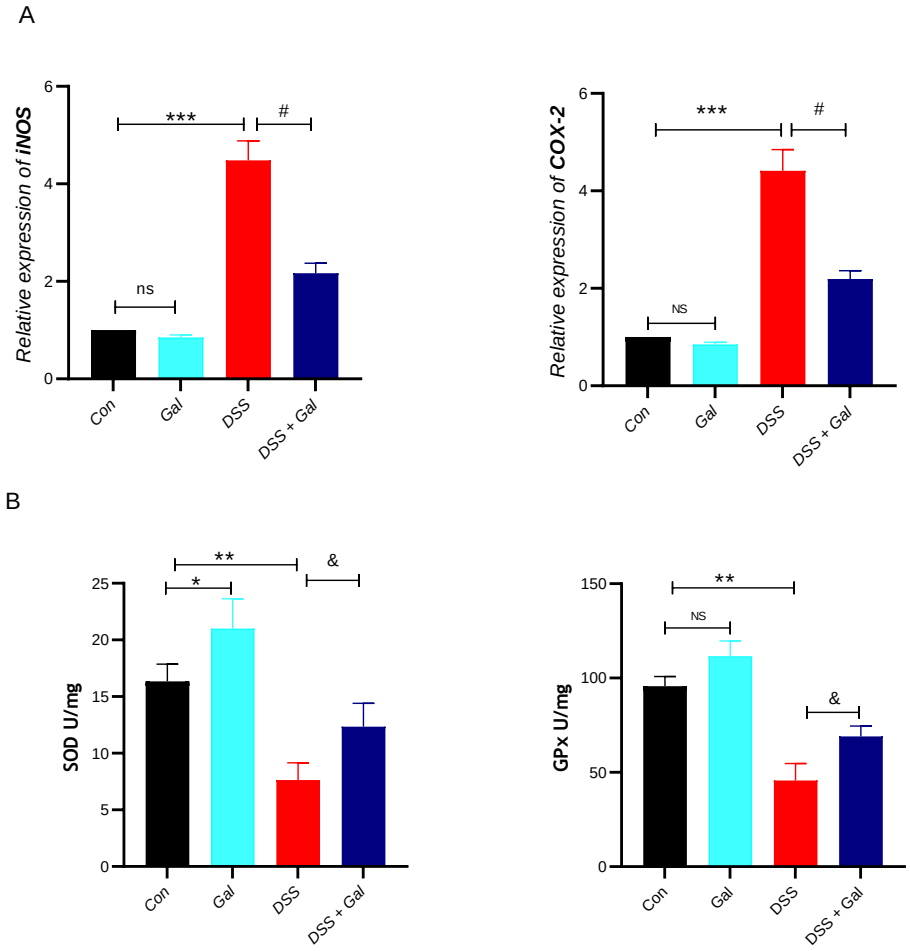


**Fig. 5** Effect of galangin on the oxidative/nitrative stress in the colon tissues of mice. (A), Levels of iNOS and COX-2, two key enzymes involved in producing ROS/RNS. The production of iNOS and COX-2 were significantly increased in the mice with DSS-induced colitis, while treatment with Gal reduced the production of these two enzymes in DSS-treated mice. (B), The activity of SOD. (C), The activity of SOD and GPx. Data are presented as mean ± SD. $n = 10$/group. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Con, Control Group; Gal, Gal treated Group; DSS, Dextran Sulfate Sodium treated Group; DSS + Gal, DSS + Gal treated Group.

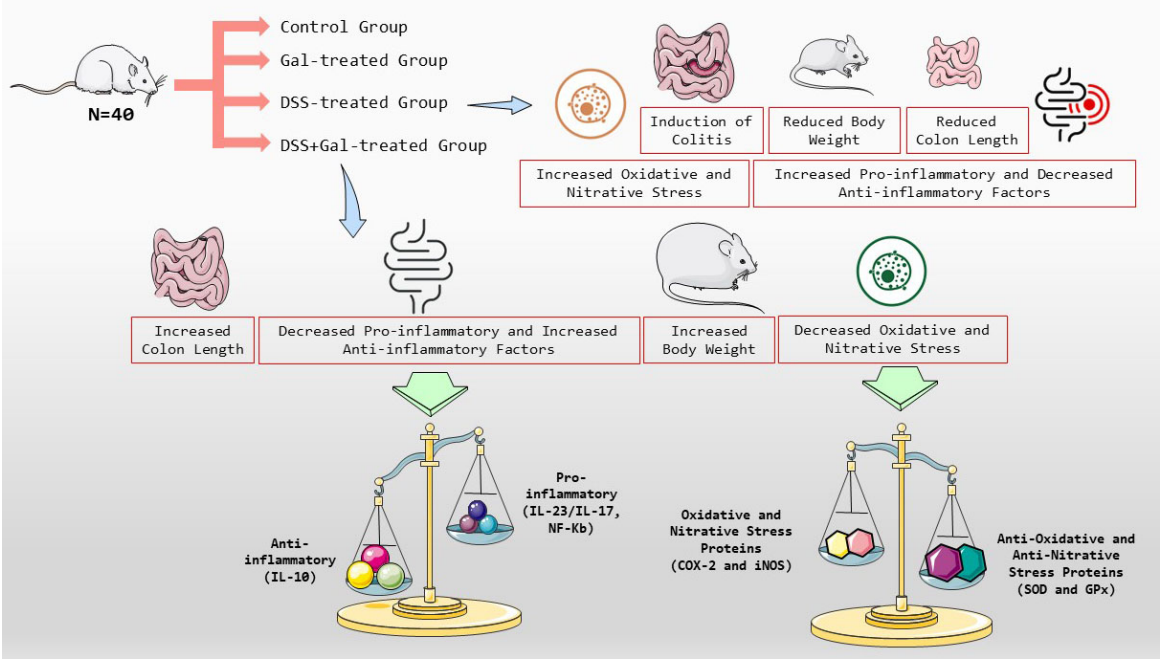


**Fig. 6** Depicting the function of Galangin on ulcerative colitis. Gal treatment could improve UC in a DSS-induced UC mouse model. Gal reduces levels of pro-inflammatory cytokines (interleukin-17 and 23; IL-23/IL-17) and suppresses oxidative/nitrative stress by reducing the expression levels of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), and increasing the activity of antioxidant enzymes (superoxide dismutase; SOD, and glutathione peroxidase; GPx). Gal: galangin; DSS: dextran sulfate sodium. UC: Ulcerative Colitis.

conducted on the role of α-lipoic acid (LA) in DSS-induced UC in mice, revealing that LA acted against UC and the associated local and systemic damage in mice. Moreover, this study has laid a foundation for developing LA as a potential agent to alleviate the severity of UC and the associated systemic damage [7]. In our study, we found significant reductions in IL-23 and IL-17 levels in the colon tissues of the DSS + Gal treated group. DSS increases the levels of IL-23 nad IL-17 in these mice but when the mice were treated with Gal, the levels of IL-23 and IL-17 were decreased. Our findings suggested that Gal ameliorates UC by suppressing the IL-23/IL-17 axis. Oxidative and nitrative stress are key mediators in UC pathogenesis [31].

Moreover, IL-10, a widely investigated anti-inflammatory cytokine, paradoxically plays a role in the advancement of colitis. The anti-inflammatory response mediated by IL-10 through the JAK1/STAT3 pathway serves as a crucial negative regulator, modulating the extent and duration of inflammation. Patients with IL-10 and IL-10R deficiencies are more susceptible to experience severe Inflammatory Bowel Diseases (IBDs), exhibiting a reduced responsiveness to medical medications [32]. In the present study, the results demonstrated that Gal treatment increases the expression of IL-10 and modulates the inflammatory response in the colon of mice with DSS-induced colitis.

Furthermore, the NF-κB pathway is a major signaling pathway in activating inflammatory responses. NF-κB is a transcription factor that regulates the expression of various genes involved in inflammation, immunity, and cell survival. The activation of NF-κB is controlled by the IκB kinase (IKK) complex, which phosphorylates IκB, leading to its ubiquitination and degradation, thereby releasing NF-κB for translocation into the nucleus and subsequent transcriptional activation of target genes [33]. Increased levels of NF-κB and the accompanying inflammatory mediators are well-known biological indicators of inflammatory reactions, and their levels have a strong relationship with the pathophysiology of UC [34]. Therefore, inhibiting NF-κB-dependent inflammatory responses might be thought of as a successful treatment approach for stopping the development and progression of UC. According to Huang et al [35], Gal treatment reduced IκBα phosphorylation, NF-κB phosphorylation, and nuclear translocation in this regard. It also suppressed the release of pro-inflammatory TNF-α, IL-1β, and IL-6 that was caused by cisplatin. Gal treatment also prevented the ERK and p38 phosphorylations caused by cisplatin. Moreover, TLR-2 induced the production of IL-17 and IL-23 leading to the stimulation of the IL-6, STAT3, and NF-κB pathway [36]. Gal treatment decreased the production of IL-17 and IL-23, thus

alleviated the activation of NF-κB pathway. In our study, we showed that Gal treatment inhibited the activation of the NF-κB pathway, which suggested that Gal might exert anti-inflammatory effects by inhibiting NF-κB-mediated transcriptional activation.

Furthermore, in response to inflammation, an increase in ROS/RNS causes oxidative/nitrative stress, which leads to damage of DNA, proteins, and lipids in colon tissues. Gal, a potent antioxidant, has been shown to scavenge ROS/RNS and enhance the activity of antioxidant enzymes. In line with previous studies, our findings indicated that Gal treatment suppressed oxidative/nitrative stress and enhanced the activity of antioxidant enzymes in the colon tissues of UC mice.

In general, previous studies have shown that Gal improves UC by regulating intestinal motility, promoting proliferation and repair of intestinal epithelial cells, and modulating immune response [37]. Our study provided evidence that, in addition to these mechanisms, Gal modulated the IL-23/IL-17 axis, suppressed oxidative/nitrative stress, and improved inflammation in UC (Fig. 6).

As a promising therapeutic agent, Gal showed an acceptable anti-inflammatory potential for the treatment of UC. However, there has been very few findings for the judgment of clinical outcome of Gal as a medication for UC. It is important to note that the clinical implications would depend on the outcomes of well-designed clinical trials. A more comprehensive examination of signaling pathways underlying the action of Gal on UC might be beneficial for developing Gal into a pharmaceutical for clinical trials.

## CONCLUSION

The present study proved that Gal treatment targeting the IL-23/IL-17 axis improved UC by suppressing oxidative/nitrative stress and inflammation in mouse model. Gal might represent a novel therapeutic approach for UC that required further investigation to determine its safety and efficacy in humans. Our results suggested that modulating the IL-23/IL-17 axis and reducing oxidative/nitrative stress might be promising approaches in developing new treatments for UC.

*Acknowledgements*: We thank Hamed Afshari "Department of Mechanical and Bio-Mechanical Engineering, Urmia Branch, Islamic Azad University, Urmia, Iran" for reviewing and editing the manuscript.

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