Oridonin attenuates dextran sulfate sodium-induced ulcerative colitis in mice via the Sirt1/NF-κB/p53 pathway

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Abstract. Ulcerative colitis (UC) is a serious chronic inflammatory bowel disease. Oridonin (Ori) has anti-inflammatory, antibacterial and antitumor activities. The current study aimed to investigate the regulatory role of Ori in UC. BALB/C mice were induced to form a model of UC using dextran sulfate sodium (DSS), after which UC mice received high-(Ori-H) and low-doses of Ori (Ori-L). Subsequently, the length of the colon was measured and hematoxylin and, eosin staining was performed to detect colonic injury. Western blot analysis was performed to detect expression level in tight junction-associated proteins in murine colon tissue. Additionally, myeloperoxidase activity and inflammatory factor concentration were detected in colon tissue using ELISA. TUNEL and western blot assays were also performed to detect cell apoptosis, and the expression level of Sirt1/NF-κB/p53 pathway-related proteins was also determined using western blot analysis. The results revealed that Ori ameliorated clinical symptoms and pathological lesions in mice with DSS-induced UC. Furthermore, Ori protected the integrity of the colonic mucosal barrier, reduced the inflammatory response and decreased oxidative stress levels in mice with DSS-induced UC. Ori treatment also inhibited intestinal mucosal cell apoptosis. These effects may have occurred via the Sirtuin-1/NF-κB/p53 pathway. In conclusion, Ori treatment inhibited DSS-induced inflammatory response, oxidative stress and intestinal mucosal apoptosis in UC mice.

Introduction

Ulcerative colitis (UC) is a serious chronic inflammatory intestinal disease with clinical manifestations that include abdominal pain, diarrhea, presence of mucous, pus and blood in the stool, and accompanied by intestinal inflammation and intestinal mucosal tissue damage (1). Patients with UC exhibit a low curative rate, high recurrence and long disease durations, and have a high risk of developing colitis-related colon cancer, which affects millions of patients worldwide (2,3). In previous years, with the improvement of population living standards and the aggravation of environmental pollution, the incidence rate of UC has been increasing yearly worldwide (4). At present, the treatment of UC includes 5-aminosalicylic acid drugs, glucocorticoids and immunosuppressants; however, the long-term use of these drugs will cause a variety of adverse reactions, reducing the quality of life of patients (5). Therefore, identifying a potential cure for UC has become a priority in recent UC research.

Traditional Chinese Medicine has the unique advantage of being a multi-system, multi-link and multi-target treatment that demonstrates good therapeutic effects in refractory diseases (6). Studies have shown that radix sophora flavescens, artemisinin and other Traditional Chinese Medicines are widely used in the treatment of UC (7,8). Oridonin (Ori) is a type of natural organic compound that is isolated from *Rabdosia rubescens*, which has anti-inflammatory, antibacterial and antitumor activities (9). Ori has been demonstrated to improve inflammation-induced bone loss in mice by inhibiting dendritic cell-specific transmembrane protein expression (10). Ori also inhibits the macrophage inflammatory response via the AKT-related pathway and alleviates ischemia/reperfusion-induced renal injury (11). This suggests that Ori plays an important role in the inflammatory response exhibited during UC. In addition, Ori has been revealed to reduce trinitrobenzene sulfonic acid (TNBS)-induced inflammatory post-irritable bowel syndrome via the pregnane X receptor (PXR)/NF-κB signaling pathway (12). Furthermore, Ori derivatives ameliorate experimental colitis by inhibiting the translocation of activated T cells and NF-Kb (13). In China, Ori is a commonly available over-the-counter herbal medicine for the treatment of inflammatory diseases (14). However, the effect of Ori on dextran sulfate sodium (DSS)-induced murine UC and the specific underlying mechanisms have not yet been reported.

Sirtuin-1 (Sirt1) plays an important role in UC, as demonstrated by the results of a previous study, in which Sirt1 reduced the endoplasmic reticulum stress-mediated apoptosis of intestinal epithelial cells in UC (15). It has also been demonstrated that the upregulation of Sirt1 inhibits NF-κB-mediated

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macrophage activation, thereby improving experimental colitis in mice (16). Moreover, Sirt1 can be used as a target of ginipinine to inhibit the NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome of macrophages, and improve the inflammatory response in colitis (17). The current study therefore aimed to determine whether Ori serves an important role in DSS-induced UC by regulating Sirt1 and examined the downstream pathways involved in this process.

Materials and methods

Ethics statement. All the animal care and experimental procedures were performed according to the Guidelines for the Care and Use of Laboratory Animals and the ARRIVE checklist. Appropriate measures were taken to minimize pain and stress to the animals. The experiments were approved by the Experimental Animal Ethics Committee of Beihua University (approval no. BHDX2021-116; Jilin, China).

Animal experiments. Male BALB/C mice (n=20; 18±8 g), aged 6-8 weeks were randomly divided into the following four groups after 1 week of adaptive feeding: i) Control, ii) DSS, iii) Ori low-dose (Ori-L) and iv) Ori high-dose (Ori-H). A total of 5 mice were included in each group. For the DSS, Ori-L and Ori-H groups, the mice were fed with 3% DSS dissolved in drinking water for 7 days to induce acute colitis. For the Ori-L and Ori-H groups specifically, intraperitoneal injections of Ori-L (2 mg/kg) and Ori-H (10 mg/kg) commenced on day 7 and were subsequently administered once a day for 1 week (10,18). The control and DSS groups were intraperitoneally injected with the same quantity of normal saline. The body weight of the mice was recorded daily and 7 days after treatment. The duration of the experiment was 14 days. To further observe the colonic condition of the mice, the mice (n=20) were euthanized, and the colon was removed. The mice were sacrificed by cervical dislocation following anesthesia with sodium pentobarbital (40 mg/kg intraperitoneal injection). After ensuring the mice didn't have a heartbeat, tissues from the mice were collected for the subsequent experiments.

Disease activity index (DAI). Body weight, gross rectal bleeding and stool consistency were checked daily in the UC mice. A disease activity index (DAI) score was calculated based on a previously described method (19) to assess the disease severity.

Database. The STITCH database (stitch.embl.de) was used to predict the target of Ori (20,21).

H&E staining. H&E staining was performed using a H&E staining Kit (cat. no. C0105S; Beyotime Institute of Biotechnology). Murine colons were obtained, fixed in 4% buffered paraformaldehyde solution for 24 h at room temperature and embedded in paraffin. The 5-μm thick sections were subjected to H&E staining according to the manufacturer's instructions. The results were visualized and images were captured under a light microscope (magnification, x400).

Western blotting. Total protein was extracted from murine colons using RIPA lysis buffer (Beyotime Institute of Biotechnology). Cytoplasmic proteins were subsequently extracted using an extraction kit (cat. no. C500051; Sangon Biotech Co., Ltd.). Equal quantities (40 μg) protein were separated using 12% SDS-PAGE and transferred to PVDF membranes (cat. no. IPFL00010; MilliporeSigma). The membranes were blocked with 5% skimmed milk at 25°C for 1 h and incubated overnight at 4°C with the following primary antibodies (all from Abcam): Zona occludin-1 (ZO-1; 1:1,000; cat. no. ab221547), occludin (1:1,000; cat. no. ab216327), claudin-1 (1:1,000; cat. no. ab211737), Bcl-2 (1:1,000; cat. no. ab182858), Bax (1:1,000; cat. no. ab32503), cleaved caspase 3 (1:1,000; cat. no. ab214430), Sirt1 (1:1,000; cat. no. ab110304), phosphorylated (p)-NF-κB (1:1,000; cat. no. ab239882), NF-κB (1:1,000; cat. no. ab207297), acetyl-p53 (1:1,000; cat. no. ab183544) and GAPDH (1:1,000; cat. no. ab8245). A secondary antibody (1:5,000; cat. no. ab150113; Abcam) was then added and the membrane was incubated at room temperature for 1 h. Protein expression was visualized using ECL (Promega Corporation) and quantified using ImageJ software (version 146; National Institutes of Health).

Myeloperoxidase (MPO), malondialdehyde (MDA), glutathione peroxidase (GSH-Px), superoxide dismutase (SOD) and reactive oxygen species (ROS) assays in murine colon tissue. The colons of the mice were homogenized and fluidized in extraction buffer phosphate buffer solution (Beyotime Institute of Biotechnology). MPO (cat. no. A044-1-1), MDA (cat. no. A003-1-2), GSH (cat. no. A005-1-2), SOD (cat. no. A001-3-2) and ROS (cat. no. E004-1-1) activities were subsequently measured using activity kits (Nanjing Jiancheng Bioengineering Institute) along with the change in absorbance at 460 nm using a 96-well plate reader.

ELISA. Biotinylated antibodies and enzyme-linked reaction substrate were separately incubated at 37°C, following which the corresponding developer and stop solution were added. Absorbance at 450 nm was measured using a microplate luminometer (Omega Bio-Tek, Inc.). The concentrations of TNF-α (cat. no. ab208348; Abcam), IL-1β (cat. no. ab197742; Abcam) and IL-6 (cat. no. ab222503; Abcam) were subsequently calculated based on the appropriate standard curve.

TUNEL assay. TUNEL staining (Beyotime Institute of Biotechnology) was used to analyze cell apoptosis. Following fixation with 4% paraformaldehyde for 24 h at room temperature, sections of murine colons were rinsed in distilled water and incubated with 3% hydrogen peroxide in methanol for 5 min at room temperature to block endogenous peroxidase activity, following which the samples were deparaffinized using xylene and rehydrated in a descending ethanol series. The sections were incubated with 20 μg/ml proteinase K (Dako; Agilent Technologies, Inc.) for 15 min at room temperature, and TdT enzyme solution was added and incubated for 1 h at 37°C. The sections were then incubated with streptavidin-peroxidase conjugate for 30 min at 37°C. Peroxidase activity was demonstrated by the addition of 50 μl DAB for 10 min at room temperature and a light microscope was used to observe apoptosis in six randomly selected fields of view (magnification, x200).
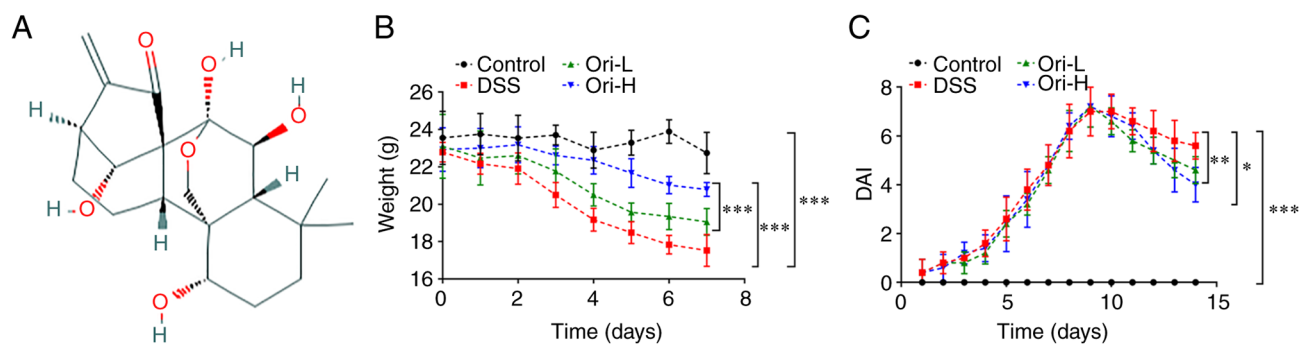
Figure 1. Ori improves the clinical symptoms in DSS-induced UC mice. (A) Chemical formula of Ori. (B) Daily body weight change in mice 7 days after the beginning of treatment. (C) DAI score of the mice. $^*P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. DSS, dextran sulfate sodium; UC, ulcerative colitis; DAI, disease activity index; Ori, oridonin; H, high-dose; L, low-dose.
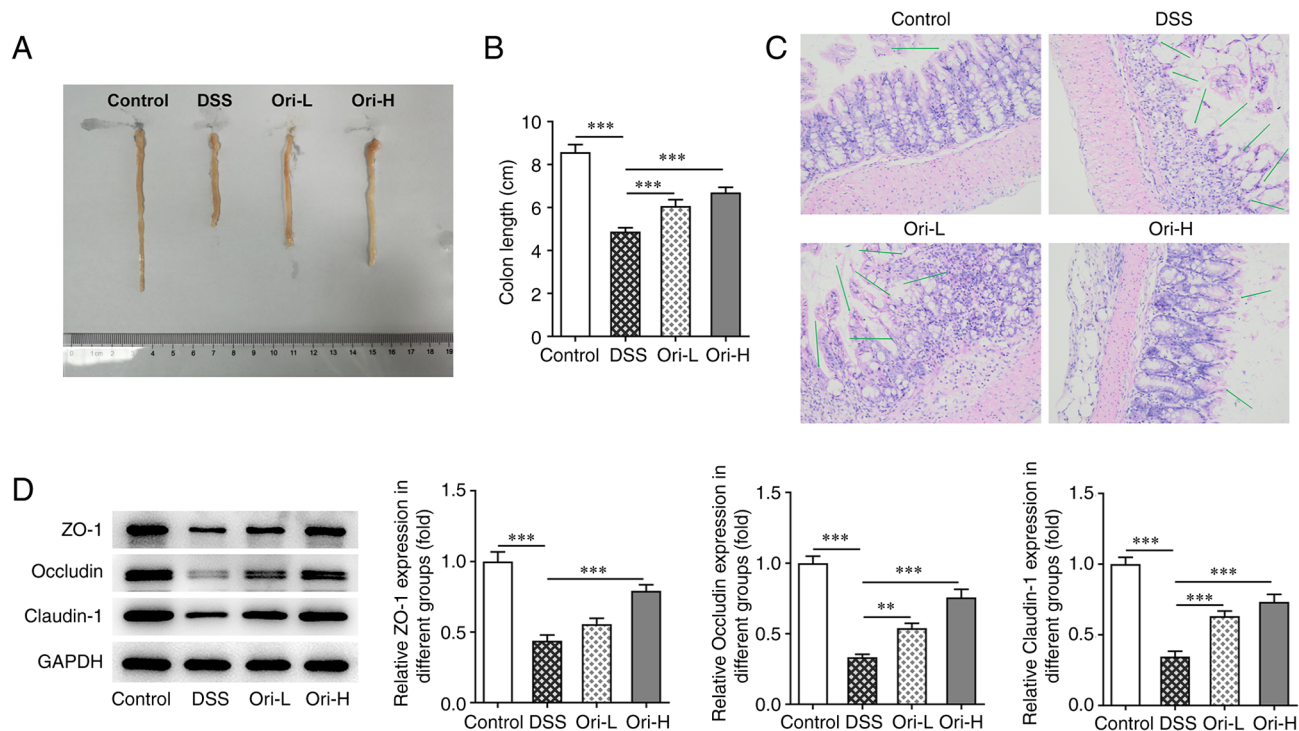

Figure 2. Ori improves the pathological damage in DSS-induced UC mice. (A) Colon length in mice. (B) Statistical analysis of colon length. (C) H&E staining was used to detect the degree of colon injury. (D) Western blot analysis was used to detect the expression of tight junction-related proteins in colon tissue. $^{**}P<0.01$, $^{***}P<0.001$. Ori, oridonin; H, high-dose; L, low-dose; DSS, dextran sulfate sodium; UC, ulcerative colitis.

Statistical analysis. The data were expressed as the mean ± SD. Differences between groups were analyzed using an unpaired Student's t-test and one-way ANOVA with Tukey's post hoc test. SPSS version 21 (IBM Corp.) was used for statistical analysis and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Ori improves clinical symptoms and pathological damage in DSS-induced UC mice. The chemical structural formula of Ori is presented in Fig. 1A. At 7 days after the beginning of treatment, the daily weight of mice was measured. The results revealed that the weight of the mice in the DSS group decreased significantly over time compared with that in the

control group. Additionally, administration of Ori induced an increase in murine weight compared with that in the DSS group, as demonstrated in Fig. 1B. The DAI from the mice demonstrated that DAI was significantly higher in the DSS group compared with that in the control group. Furthermore, after day 10, when compared with that in the DSS group, the DAI decreased significantly in the Ori-L and Ori-H groups, and even more significantly in the Ori-H group (Fig. 1C).

Colon length was subsequently measured in the treated mice (Fig. 2A). As presented in Fig. 2B, colon length was significantly decreased in the DSS group compared with that in the control group. Additionally, there was a significant increase in colon length following Ori treatment compared with the DSS group. H&E staining revealed that there were no notable lesions in the control group, while mice in the DSS
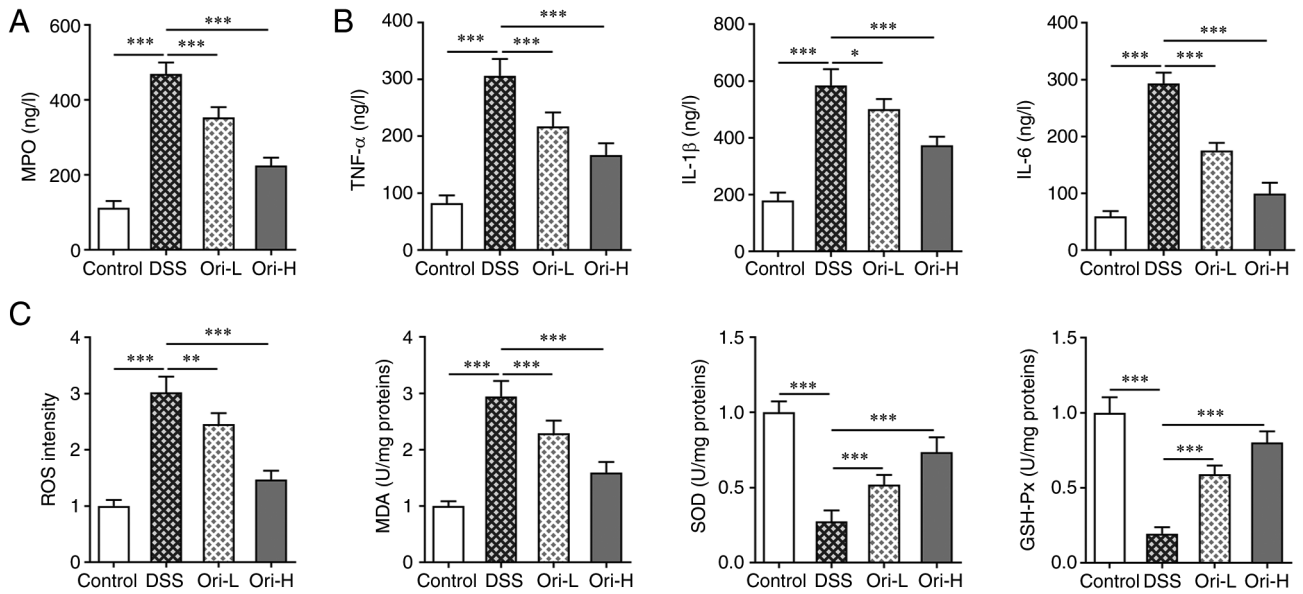
Figure 3. Ori reduces inflammatory response and oxidative stress in DSS-induced UC mice. ELISA kits were used to analyze (A) MPO concentration and (B) inflammatory factors in colon tissue. (C) Detection of proteins involved in oxidative stress were analyzed in colon tissue. *P<0.05, **P<0.01, ***P<0.001. DSS, dextran sulfate sodium; UC, ulcerative colitis; Ori, oridonin; H, high-dose; L, low-dose; MPO, myeloperoxidase; ROS, reactive oxygen species; SOD, superoxide dismutase; MDA, malondialdehyde; GSH-Px, glutathione peroxidase.
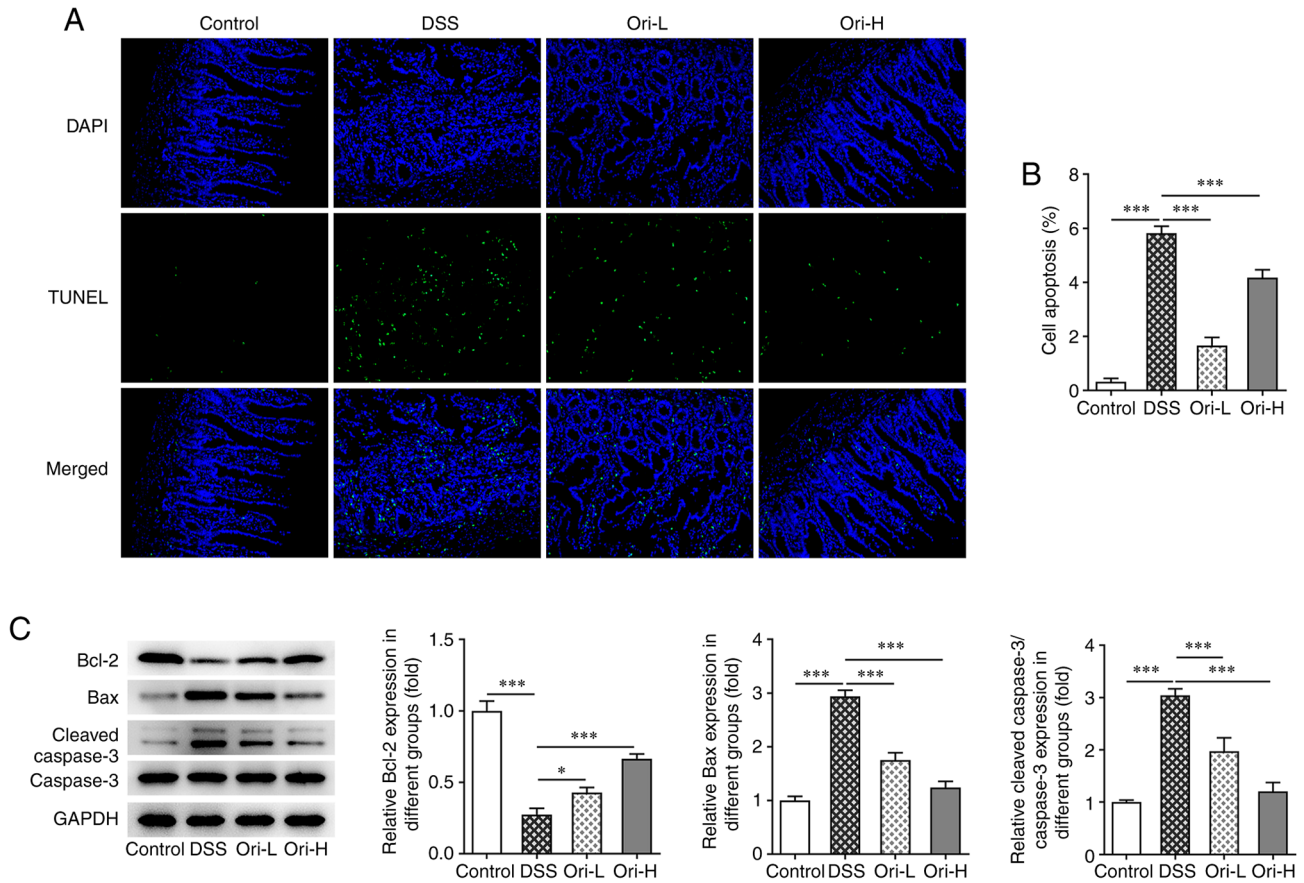

Figure 4. Ori inhibits cell apoptosis of intestinal mucosa in DSS-induced UC mice. (A) Apoptosis was detected using TUNEL assay. (B) Statistical analysis of apoptotic cells. (C) Western blot analysis was used to detect the expression of apoptosis-related proteins. *P<0.05, ***P<0.001. DSS, dextran sulfate sodium; UC, ulcerative colitis; Ori, oridonin; H, high dose; L, low dose.

group exhibited a number of pathological changes in their colon tissue, such as irregular and damaged surface epithelium, no branching, twisted and loosely arranged cup cells in deep crypts, and a large number of scattered lymphocytes in the
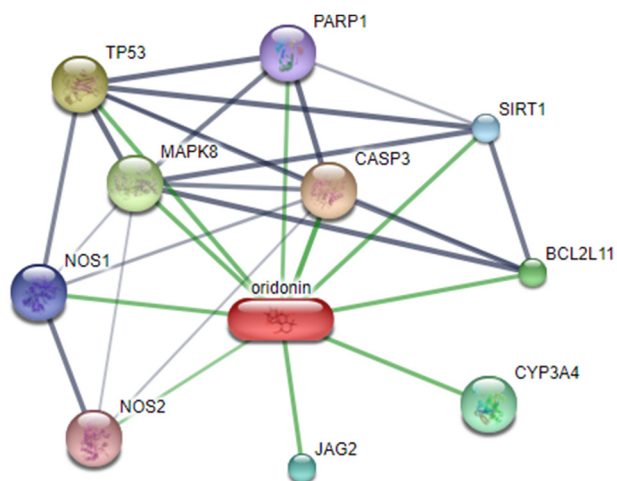
Figure 5. STITCH database prediction that SIRT1 is a potential target of oridonin.

lamina propria accompanied by epithelial cell loss. However, colon injury was reversed following Ori administration

(Fig. 2C). The expression of tight junction-related proteins was subsequently examined to measure the integrity of the colonic mucosal barrier. The results demonstrated that the protein expression level of ZO-1, occludin and claudin-1 decreased significantly in the DSS group compared with that in the control group. Furthermore, compared with that in the DSS group, the protein expression level of ZO-1, occludin and claudin-1 in the Ori-L and Ori-H groups were reversed (Fig. 2D). The results indicated that Ori protected the integrity of the colonic mucosal barrier.

Ori reduces the inflammatory response and oxidative stress in DSS-induced UC mice. To detect colon tissue infiltration in UC-induced mice, MPO concentration in colon tissue was detected. Compared with that in the control group, MPO concentration in the DSS group was significantly increased. Furthermore, MPO concentration was inhibited in the Ori-L and Ori-H groups compared with that in the DSS group (Fig. 3A). ELISA was performed to detect inflammatory factor concentration in murine colon tissue. The results revealed that, when compared with that in the control group, TNF-α, IL-1β and IL-6 concentration was significantly increased after DSS
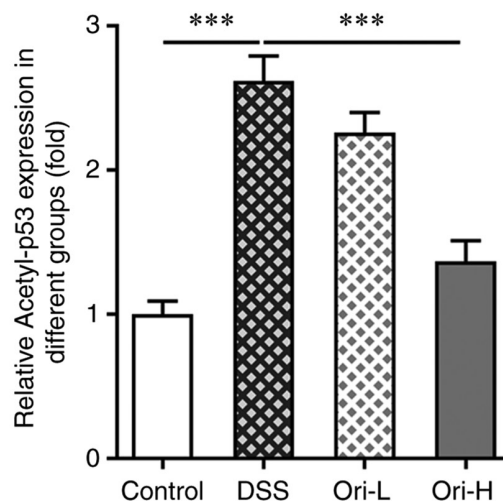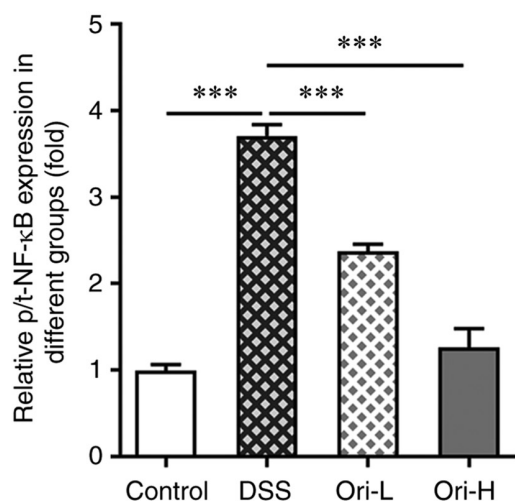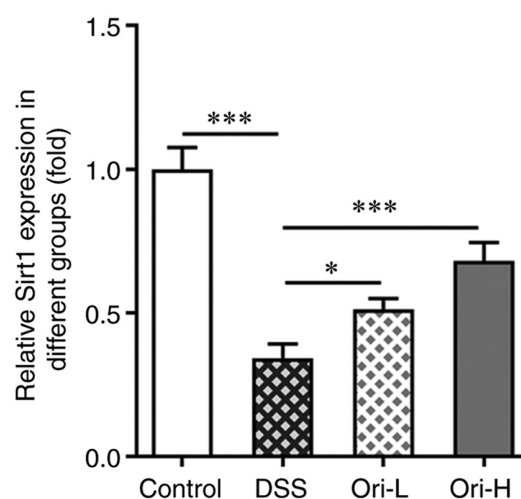
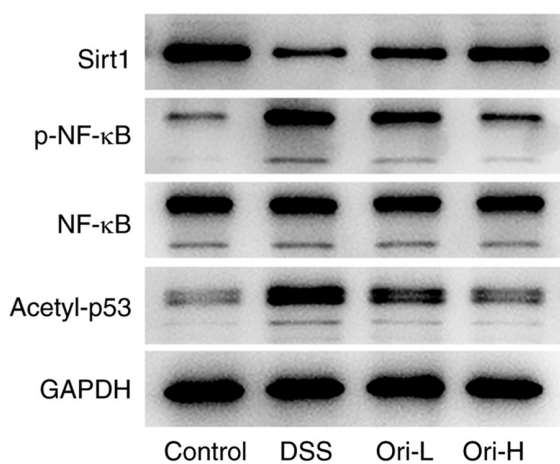

Figure 6. Ori activated the Sirt1/NF-κB/p53 signaling pathway. Western blot was used to detect the expression of Sirt1/NF-κB/p53 signaling pathway-related proteins. *P<0.05, ***P<0.001. Ori, oridonin; H, high-dose; L, low-dose; DSS, dextran sulfate sodium; p, phosphorylated.

induction. In addition, TNF-α, IL-1β and IL-6 concentrations were all significantly decreased after Ori administration compared with that in the DSS group (Fig. 3B). The concentrations of oxidative stress-related indices, including ROS, MDA, GSH-Px and SOD were subsequently detected. The data revealed comparable concentration trends between ROS and MDA, and TNF-α, IL-1β and IL-6. However, the concentration trend of GSH-Px and SOD were the reverse of TNF-α, IL-1β and IL-6 (Fig. 3C). The results indicated that Ori treatment reduced the inflammatory response and oxidative stress in DSS-induced UC mice.

Ori inhibits intestinal mucosa cell apoptosis in DSS-induced UC mice. A TUNEL assay was performed to detect cell apoptosis. The results revealed that, compared with that in the control group, apoptosis was significantly increased in the DSS group (Fig. 4A and B). Furthermore, decreased Bcl-2 and increased Bax and cleaved caspase 3 (Fig. 4C) protein expression levels were observed. After Ori administration, apoptosis was reversed, Bcl-2 protein expression levels were increased and Bax, and cleaved caspase 3 protein expression levels were decreased.

Ori affects the Sirt1/NF-κB/p53 signaling pathway. The STITCH database predicted that Sirt1 was a potential target of Ori (Fig. 5). The current study also revealed that the protein expression levels of Sirt1, p-NF-κB and acetyl-p53 were significantly increased in the DSS group compared with that in the control group, indicating that the Sirt1/NF-κB/p53 pathway was activated in DSS-induced UC mice. The protein expressions levels of Sirt1, p-NF-κB and acetyl-p53 were reversed after Ori-L and Ori-H administration (Fig. 6). These results suggested that the activated Sirt1/NF-κB/p53 signaling pathway in DSS-induced UC mice was blocked by Ori.

Discussion

UC is a major type of inflammatory bowel disease. In recent years, the incidence rate of UC has been increasing yearly and its pathogenesis and, treatment have become a focus of research (5). At present, a variety of modeling methods have been used to induce UC animals, among which the DSS chemical method has been widely used, as it produces similar effects to that of human UC (22). In the current study, DSS was used in the present study to induce UC in mice and then related indicators of UC were detected in mice after DSS induction. The results revealed that the DAI in mice significantly increased, while colon length decreased, and colon lesions became apparent. In addition, inflammatory response and oxidative stress levels in the colon tissues of DSS-induced mice were significantly increased. The results indicated that UC occurred in DSS-induced mice.

A previous study has demonstrated that Ori alleviates TNBS-induced inflammatory post-irritable bowel syndrome via the PXR/NF-κB signaling pathway (12). In addition, Ori protects against experimental murine brain injury by inhibiting the NLRP3 inflammasome (18). Ori has also exerted protective effects against lipopolysaccharide-induced acute lung injury by modulating nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated oxidative stress and

Nrf2-independent NLRP3, and NF-κB pathways (23). It has therefore been suggested that Ori plays a role in inflammatory bowel disease. The current study demonstrated that Ori significantly increased the length of the colon in DSS-induced UC mice and improved pathological colon injury. In addition, Ori reduced the levels of the inflammatory response and oxidative stress, while inhibiting apoptosis in DSS-induced UC mice.

Under normal conditions, the intestinal tract functions as a complete barrier to prevent pathogenic antigens from invading the body and maintaining normal bodily function. However, when intestinal epithelial tight junction proteins are damaged, various pathogenic microorganisms, within the lumen, invade into the body, causing mucosal inflammation and triggering the immune response (24). The present study detected the distribution and expression of specific tight junction-related proteins, including ZO-1, occludin and claudin-1, in murine colons to determine the integrity of the colonic intestinal barrier. The results revealed that Ori treatment significantly increased the protein expression level of ZO-1, occludin and claudin-1 in the colon tissue of DSS-induced UC mice. The results suggested that Ori protected the integrity of the colonic mucosal barrier.

The STITCH database predicted that Sirt1 was a potential target of Ori. The present study also determined that the expression level of Sirt1 in the colon tissues of mice increased after Ori was administered to the DSS-treated group. The protein expression levels of p-NF-κB and acetyl-p53 were also increased, which are downstream proteins of Sirt1. It has been previously demonstrated that the inhibition of NF-κB-mediated macrophage activation by Sirt1 upregulation can improve experimental colitis in mice (16). These results suggest that Sirt1 plays an important role in UC. The results of the present study preliminarily concluded that Ori may ameliorate UC in mice by targeting the Sirt1/NF-κB/p53 pathway. However, these results should be further verified using pathway inhibitors in future experiments. Ori can improve irritable bowel syndrome induced by TNBS; however, there is a lack of research into Ori in DSS-induced UC and the targeting of Ori on Sirt1 in UC; therefore, to the best of our knowledge, for the first time, the present study provided preliminary results.

There are also limitations in the present study. The experiments into the mechanism of Ori on UC are deficient. The mechanism involved will be further investigated in future studies using Sirt1/NF-κB/p53 pathway inhibitors. In addition, we have discussed the effect of Ori in UC animal models but have not verified it in UC cell experiments. We will further verify it in UC cell experiments in the following experiments.

In conclusion, the present study demonstrated that Ori alleviated DSS-induced inflammatory response, oxidative stress and intestinal mucosal apoptosis in UC mice possibly via the Sirt1/NF-κB/p53 pathway. The results may provide a strong research basis for the clinical treatment of UC with Ori.

Availability of data and materials

The analyzed datasets used and/or generated during the present study are available from the corresponding author on reasonable request.

Authors' contributions

DW contributed to the conception and design of this study. MW performed the experiments, collected the data and performed statistical analysis with the help of BX and LL. MW drafted the manuscript, which was corrected and revised by DW. DW and MW confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

All animal procedures were performed according to the NIH Guide for the Care and Use of Laboratory Animals approved by the Experimental Animal Ethics Committee of Beihua University (approval no. BHDX2021-116; Jilin, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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