

# World Journal of *Gastroenterology*

*World J Gastroenterol* 2017 July 14; 23(26): 4661-4846



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*World Journal of Gastroenterology*  
Volume 23 Number 26 July 14, 2017

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*World Journal of Gastroenterology* (*WJG*) is now indexed in Current Contents<sup>®</sup>/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch<sup>®</sup>), Journal Citation Reports<sup>®</sup>, Index Medicus, MEDLINE, PubMed, PubMed Central and Directory of Open Access Journals. The 2017 edition of Journal Citation Reports<sup>®</sup> cites the 2016 impact factor for *WJG* as 3.365 (5-year impact factor: 3.176), ranking *WJG* as 29<sup>th</sup> among 79 journals in gastroenterology and hepatology (quartile in category Q2).

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NAME OF JOURNAL  
*World Journal of Gastroenterology*

ISSN  
ISSN 1007-9327 (print)  
ISSN 2219-2840 (online)

LAUNCH DATE  
October 1, 1995

FREQUENCY  
Weekly

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#### PUBLISHER

Baishideng Publishing Group Inc  
7901 Stoneridge Drive, Suite 501,  
Pleasanton, CA 94588, USA  
Telephone: +1-925-2238242  
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PUBLICATION DATE  
July 14, 2017

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## Basic Study

# Jianpi Qingchang decoction regulates intestinal motility of dextran sulfate sodium-induced colitis through reducing autophagy of interstitial cells of Cajal

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**Author contributions:** Dai YC performed the majority of the experiments and analyzed the data; Zhang YL and Chen X participated in the treatment of animals; Chen DL and Wang LJ performed the histological experiments; Dai YC and Tang ZP designed and coordinated the research; Dai YC and Zheng L wrote and revised the paper.

**Supported by** the National Natural Science Foundation of China, No. 81403355 and No. 81573892; and the Project of 3-Year Action Plan for Shanghai Municipal Chinese Medicine Development, No. ZY3-RCPY-2-2001.

**Institutional review board statement:** This study was reviewed and approved by the Institutional Review Board of the Institute of Digestive Disease, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

**Institutional animal care and use committee statement:** All procedures involving animals were reviewed and approved by the Institutional Animal Care and Use Committee of the Shanghai University of Traditional Chinese Medicine (No. SZY201510002).

**Conflict-of-interest statement:** The authors declare that there are no conflicts of interest related to this study.

**Data sharing statement:** No additional data are available.

**Open-Access:** This article is an open-access article which was

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**Manuscript source:** Unsolicited manuscript

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**Received:** February 20, 2017  
**Peer-review started:** February 22, 2017  
**First decision:** April 5, 2017  
**Revised:** April 30, 2017  
**Accepted:** June 18, 2017  
**Article in press:** June 19, 2017  
**Published online:** July 14, 2017

## Abstract

### AIM

To investigate the underlying effect of Jianpi Qingchang decoction (JQD) regulating intestinal motility of dextran sulfate sodium (DSS)-induced colitis in mice.

### METHODS

C57BL/6 mice were randomly divided into four groups: the control group, the DSS group, the JQD group, and the 5-aminosalicylic acid group. Except for the control group, colitis was induced in other groups by giving distilled water containing 5% DSS. Seven days after



modeling, the mice were administered corresponding drugs intragastrically. The mice were sacrificed on the 15<sup>th</sup> day. The disease activity index, macroscopic and histopathologic lesions, and ultrastructure of colon interstitial cells of Cajal (ICC) were observed. The levels of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-10 and interferon gamma (IFN- $\gamma$ ), the expression of nuclear factor-kappa B (NF- $\kappa$ B) p65, c-kit, microtubule-associated protein 1 light chain 3 (LC3-II) and Beclin-1 mRNA, and the colonic smooth muscle tension were assessed.

## RESULTS

Acute inflammation occurred in the mice administered DSS. Compared with the control group, the levels of IL-1 $\beta$ , TNF- $\alpha$ , IL-10 and IFN- $\gamma$ , the expression of LC3-II, Beclin-1 and NF- $\kappa$ B p65 mRNA, and the contractile frequency increased ( $P < 0.05$ ), the expression of c-kit mRNA and the colonic smooth muscle contractile amplitude decreased in the DSS group ( $P < 0.05$ ). Compared with the DSS group, the levels of IL-10 and IFN- $\gamma$ , the expression of c-kit mRNA, and the colonic smooth muscle contractile amplitude increased ( $P < 0.05$ ), the levels of TNF- $\alpha$  and IL-1 $\beta$ , the expression of LC3-II, Beclin-1 and NF- $\kappa$ B p65 mRNA, and the contractile frequency decreased in the JQD group ( $P < 0.05$ ).

## CONCLUSION

JQD can regulate the intestinal motility of DSS-induced colitis in mice through suppressing intestinal inflammatory cascade reaction, reducing autophagy of ICC, and regulating the network path of ICC/smooth muscle cells.

**Key words:** Intestinal motility; Interstitial cells of Cajal; Autophagy; Ulcerative colitis; Jianpi Qingchang decoction

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**Core tip:** Interstitial cells of Cajal (ICC) lead to a variety of changes in the physiological properties of the neurons in the related circuitry, which then affects gastrointestinal motility. Therefore, ICC have been accepted as a therapeutic target for gastrointestinal motility disorders. It is demonstrated in the current study that Jianpi Qingchang decoction can regulate the intestinal motility of dextran sulfate sodium-induced colitis in mice through suppressing intestinal inflammatory cascade reaction, reducing autophagy of ICC, and regulating the network path of ICC/smooth muscle cells.

Dai YC, Zheng L, Zhang YL, Chen X, Chen DL, Wang LJ, Tang ZP. Jianpi Qingchang decoction regulates intestinal motility of dextran sulfate sodium-induced colitis through reducing autophagy of interstitial cells of Cajal. *World J Gastroenterol* 2017; 23(26): 4724-4734 Available from: URL: <http://www.wjgnet.com>

## INTRODUCTION

Ulcerative colitis (UC) is a chronic intestinal disease, and its clinical manifestations are associated with the pathophysiological aspects of intestinal motility disorders, such as diarrhea and tenesmus<sup>[1,2]</sup>. Intestinal motility disorders of UC can seriously impact the quality of life (QOL) of patients due to the long disease duration. At present, improving the QOL, inducing and maintaining clinical remission and mucosal healing, and preventing complications are together regarded as the targets of UC treatments<sup>[3]</sup>.

Previous clinical and experimental studies have demonstrated that Traditional Chinese Medicine (TCM) is advantageous in treating UC; its curative effect is reliable, with less side effects and low recurrence rate<sup>[4,5]</sup>. Jianpi Qingchang decoction (JQD) was made on the basis of the theory in TCM to treat UC. Previous studies found that JQD could be used to treat patients with initial or mild UC, improve their intestinal symptoms, such as diarrhea, mucous bloody stool and tenesmus, and regulate their systemic functional state, such as fatigue, consequently improving their QOL<sup>[6,7]</sup>. Furthermore, JQD could up-regulate the expression of peripheral blood mononuclear cell glucocorticoid receptor- $\alpha$  to improve hormone-dependent status to treat steroid-dependent UC<sup>[8]</sup>. Besides, JQD could suppress activation of the nuclear factor-kappa B (NF- $\kappa$ B) signaling pathway and regulate the expression of cytokines in dextran sulfate sodium (DSS)-induced colitis in mice<sup>[9]</sup>.

Recent investigations have demonstrated that inflammation influences the morphology and structure of interstitial cells of Cajal (ICC), leading to a variety of changes in the physiological properties of the neurons in the related circuitry, which then affects gastrointestinal motility<sup>[10]</sup>. Therefore, ICC have been accepted as a therapeutic target for gastrointestinal motility disorders<sup>[11]</sup>. Defective autophagy has been strongly linked to UC pathogenesis, with evidence showing that enhancing autophagy may be therapeutically beneficial by regulating inflammation and clearing intestinal pathogens<sup>[12,13]</sup>.

The regulation of autophagy might be a potential strategy for UC, which can be achieved by multi-level and multi-path interference<sup>[14]</sup>. Therefore, it was essential to study relationships between intestinal motility disorder of UC and autophagy of ICC, and to explore upstream signaling pathway regulation to strengthen or advance the beneficial autophagy response, which might be beneficial in preventing and treating intestinal dysmotility of UC<sup>[15]</sup>. JQD could improve the clinical symptoms of intestinal dysmotility, such as diarrhea and tenesmus in patients with UC,

**Table 1** Composition of Jianpi Qingchang decoction

Chinese name	Latin name	English name	Quantity in g
Zhi Huang Qi	<i>Radix astragali</i>	Milkvetch root	30
Huang Lian	<i>Coptis chinensis</i>	Coptis root	3
Dang Shen	<i>Codonopsis pilosula</i>	Pilose Asiabell root	15
Ma Chi Xian	<i>Portulaca oleracea</i> L.	herba portulacae	30
Sheng Di Yu	<i>Radix sanguisorbae</i>	Garden Burnet root	15
San Qi	<i>Panax notoginseng</i>	Notopterygium root	6
Bai Ji	<i>Bletillae rhizoma</i>	Tuber Bletillae	3
Mu Xiang	<i>Radix Aucklandiae</i>	Common Vladimiria root	6
Sheng Gan Cao	<i>Radix glycyrrhizae</i>	Licorice root	6

but the specific mechanisms remain unclear<sup>[6,7]</sup>. The aim of the present study was to investigate the effects of JQD on intestinal motility of DSS-induced colitis in mice.

## MATERIALS AND METHODS

### Materials

DSS (MW 36000-50000; MP Biomedicals, Santa Ana, CA, United States); the nine medicinal herbs of JQD raw powder, as shown in Table 1 (Pharmacy Department, Longhua Hospital affiliated to Shanghai University of TCM, Shanghai, China) dissolved in 0.5% carboxymethylcellulose sodium (CMC) solution; mesalazine [5-aminosalicylic acid (5-ASA); Sunflower Pharmaceutical Group, Jiamusi Lu Ling Pharmaceutical Co., Ltd., Liaoning, China; batch number: 111206], external coat removed, broken down, and dissolved in 0.5% CMC solution; fecal occult blood (FOB) (Huashengyuan Medical Science and Technology Co. Ltd., Beijing, China); tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin (IL)-1 $\beta$ , IL-10 and interferon gamma (IFN- $\gamma$ ) ELISA kits (eBioscience, San Diego, CA, United States); NF- $\kappa$ B antibody (Cell Signaling, Danvers, MA, United States); primer synthesis kit (Yushen Bio-Technique Co. Ltd., Shanghai, China).

### Colitis model construction and treatment

Specific pathogen-free C57BL/6 6- to 8-wk-old male mice (weight,  $25 \pm 3$  g) were purchased from Shanghai Xierpu-Bikai Bio-Technique Co. Ltd. [Certificate No. SCXK(Hu)2013-0016]. All experiments were approved by the local ethics committee for Animal Research Studies at the Shanghai University of TCM (SZY20151002). Forty-six mice were randomly divided into four groups: the control group ( $n = 10$ ), the DSS group ( $n = 12$ ), the JQD group ( $n = 12$ ), and the 5-ASA group ( $n = 12$ ). Except for the control group, colitis was induced in the other groups by giving distilled water containing 5% (w/v) DSS<sup>[16]</sup>.

Seven days after modeling, the mice were administered corresponding drugs intragastrically for 7 d. The intragastric administration dose of the mice in each group was calculated according to the conversion factor of experimental animals and clinical administration dose, which was 0.2 mL/(10 g·d) according to the body

mass of the mice<sup>[17,18]</sup>. The control group and the DSS group mice were administered 0.5% CMC solution intragastrically. The JQD group mice were administered JQD solution (17.1 g/kg per day) and the 5-ASA group mice were administered 5-ASA solution (100 mg/kg per day) intragastrically<sup>[19]</sup>.

The color, activity, feces condition, weight, and eating volume of mice were observed daily during modeling and drug administration. FOB was tested, and the severity of colitis was assessed daily using the disease activity index (DAI), which was calculated by grading on a scale of 0 to 4 using the following parameters: loss of body weight (0: normal; 1: 0%-5%; 2: 5%-10%; 3: 10%-15%; 4: > 15%), stool consistency (0: normal; 2: loose stools; 4: watery diarrhea) and FOB (0: negative; 2: positive; 4: gross bleeding)<sup>[20]</sup>.

### Tissue collection

After the drug administration for 14 d, the mice in each group were sacrificed and colon tissues (from the ileocecal junction to the anal verge) were collected. The general form of colon tissues was observed, and the length was recorded. The colon tissues were cut into three sections. One part was tiled on the filter paper, fixed at the two ends by pins, and then fixed in 4% liquor formaldehyde for hematoxylin and eosin (H and E) staining and in 2.5% glutaraldehyde for transmission electron microscopic (TEM) observation<sup>[21]</sup>. One part was cut into smooth muscle strips (2 mm wide and 10 mm long) for determining tension. The other tissues were packaged using aluminized paper, put into liquid nitrogen, and stored at -80 °C before being used for ELISA, western blotting, and mRNA analyses.

### TEM

Colon tissues were doubly fixed with glutaraldehyde and osmic acid, dehydrated with gradients of ethyl alcohol and acetone, embedded and saturated, sliced into ultrathin sections (thickness, 50-60 nm), and doubly stained with uranyl acetate and lead citrate. The structure of ICC and autophagosomes were observed by TEM (Philips, Eindhoven, Netherlands).

### ELISA

Colons were weighed and homogenized in 1 mL of ice-

**Table 2** Polymerase chain reaction primers' gene sequences

Target gene	Primer sequence	Product length in bp
c-kit	Forward: AGGCTATCCCTGTGTGTCTG Reverse: ACATGGAGTTCACGGATGTAGA	111
LC-3II	Forward: TTATAGAGCGATACAAGGGGGAG Reverse: CGCCGTCTGATTATCTTGATGAG	109
Beclin-1	Forward: ATGGAGGGGTCTAAGGCGTC Reverse: TCCTCTCTGAGTTAGCCTCT	197
GAPDH	Forward: AGGTCGGTGTGAACGGATTG Reverse: TGTAGACCATGTAGTTGAGGTCA	123

cold RIPA lysis buffer containing 1% protease inhibitor cocktail and 1% phosphatase inhibitor cocktail. The lysate was centrifuged ( $15000 \times g$ ,  $4^{\circ}\text{C}$ ) for 15 min, and the supernatant was used for TNF- $\alpha$ , IL-1 $\beta$ , IL-10 and IFN- $\gamma$  analyses. The levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-10 and IFN- $\gamma$  in colons were measured by commercial ELISA kits following per manufacturer's instructions, respectively.

#### Western blotting analysis

The bicinchoninic acid method was utilized to quantify the protein concentrations of colon tissue extracts, which were subsequently separated by 10% sodium dodecyl sulfate-polyacrylamide gel electrophoresis. The protein spots in the gels were transferred onto polyvinylidene fluoride membranes (Amersham Pharmacia Biotech, Piscataway, NJ, United States), which were then blocked by 5% skimmed milk, Tris-buffered saline and Tween 20 at ambient temperature for 2 h. The membranes were incubated with primary antibody against NF- $\kappa$ B p65 (rabbit anti-NF- $\kappa$ B polyclonal antibody, 1:500) overnight at  $4^{\circ}\text{C}$  and then incubated with the appropriate horseradish peroxidase-conjugated secondary antibodies. Finally, the blots were visualized using an enhanced chemiluminescence detection kit (Millipore, Temecula, CA, United States), and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (Yushen Bio-Technique Co. Ltd., Shanghai, China) was used as a loading control. Three independent replicates were conducted for each experiment.

#### RNA preparation and reverse transcription-polymerase chain reaction analysis

Total RNA was isolated from mice colon tissues using TRIzol reagent (Invitrogen, Carlsbad, CA, United States) and reverse-transcribed into cDNA using a Reverse Transcription System (Promega, Madison, WI, United States). The thermal cycling conditions were as follows:  $95^{\circ}\text{C}$  for 3 s,  $95^{\circ}\text{C}$  for 5 s for 40 cycles, and  $60^{\circ}\text{C}$  for 30–34 s. The mRNA expression levels of c-kit, microtubule-associated protein 1 light chain 3 (LC3-II) and Beclin-1 were quantitatively analyzed and normalized to GAPDH levels. Three replicates were run for each assay. Table 2 shows the sequences of reverse and forward primers. The relative expression

of the target genes was analyzed by the  $\Delta\Delta\text{Ct}$  method.

#### PowerLab analysis

Colon smooth muscles from mice were perfused with Krebs (mmol/L: NaCl 8 g, KCl 0.2 g,  $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$  0.26 g,  $\text{NaH}_2\text{PO}_4 \cdot 2\text{H}_2\text{O}$  0.065 g,  $\text{NaHCO}_3$  1 g,  $\text{CaCl}_2$  0.2 g, glucose 1 g;  $37.5 \pm 0.5^{\circ}\text{C}$ , pH 7.3–7.4) bubbled with 97%  $\text{O}_2$ –3%  $\text{CO}_2$ <sup>[22,23]</sup>. One end of the smooth muscle strip was fastened to the tension converter in the bath of the perfusion system of isolated tissue, and the other end was fastened to the hook at the bottom of the bath. The load was 1.0 g, and the balance time was 30 min. After the spontaneous contraction of the smooth muscle strips became steady, electrical signals were recorded with a PowerLab 8/30 (ADInstruments, Bella Vista, Australia) and the contractile amplitude and frequency were analyzed every 5 min.

#### Statistical analysis

One-way ANOVA was used to analyze the data expressed as mean  $\pm$  SD for comparison between multiple groups and least significant difference *t*-test for internal group comparison. All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, United States). The threshold of statistical significance was set to  $P < 0.05$ . GraphPad Prism version 5.0 (GraphPad Software Inc., La Jolla, CA, United States) was used to generate histograms.

## RESULTS

#### JQD decreased DAI scores

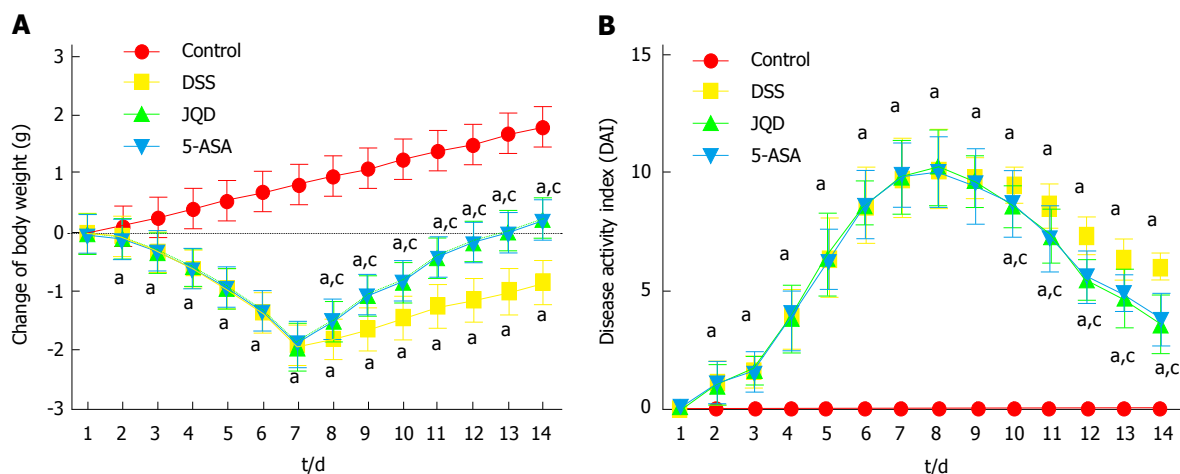
On the 2<sup>nd</sup> day of modeling, the mice in the model groups began to lose weight. Their stools became sticky, and the FOB test was positive, although the color was yellow. On the 7<sup>th</sup> day of modeling, the body weight of the model group decreased obviously, and black stool or bloody stool was visible in the anus. During modeling, the DAI scores of mice in the model groups increased gradually. Because of weight loss and bloody stool, two mice died in each of the DSS, JQD and 5-ASA groups.

Following drug intervention for 7 d, two mice died in the DSS group due to obvious hematochezia. One mouse died in each of the JQD and 5-ASA groups due to severe weight loss. In the DSS group, the bloody stool gradually decreased. The stool took shape slightly with soft quality, and the FOB test was positive (6/8). The FOB test turned negative (8/9) in the JQD group and (7/9) in the 5-ASA group. During drug administration, the DAI scores decreased gradually (Figure 1).

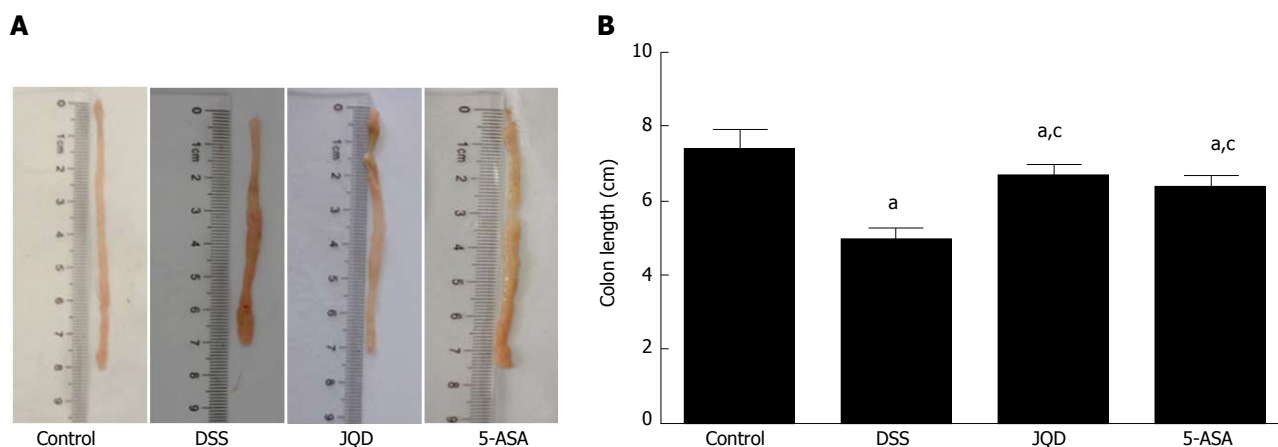
#### JQD improved colonic macroscopic appearances

In the control group, the colon had good toughness. It was not easily breakable, and the colonic mucosa was smooth. In the DSS group, the length of the colon was significantly shortened compared with the control group ( $P < 0.05$ ). The colon had poor toughness, with





**Figure 1 Body weight change and disease activity index of mice.** A: Body weight change (the change of body weight in each group of mice was compared with the body weight in the same group of mice on the 1<sup>st</sup> day); B: Disease activity index. <sup>a</sup>*P* < 0.05 vs control group, <sup>c</sup>*P* < 0.05 vs DSS group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; JQD: Jianpi Qingchang decoction.



**Figure 2 Representative image of colons.** A: Macroscopic appearance; B: Length of colon (from the appendix to the anus). <sup>a</sup>*P* < 0.05 vs control group, <sup>c</sup>*P* < 0.05 vs DSS group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; JQD: Jianpi Qingchang decoction.

congestion and edema. Partial colon had adhesion with surrounding tissue, irregular ulcer, and bleeding on the mucosa. In the JQD and 5-ASA groups, the colon had better toughness, with local congestion and edema. Partial colon had a small amount of punctate erosion (Figure 2).

#### JQD promoted repair of the colon

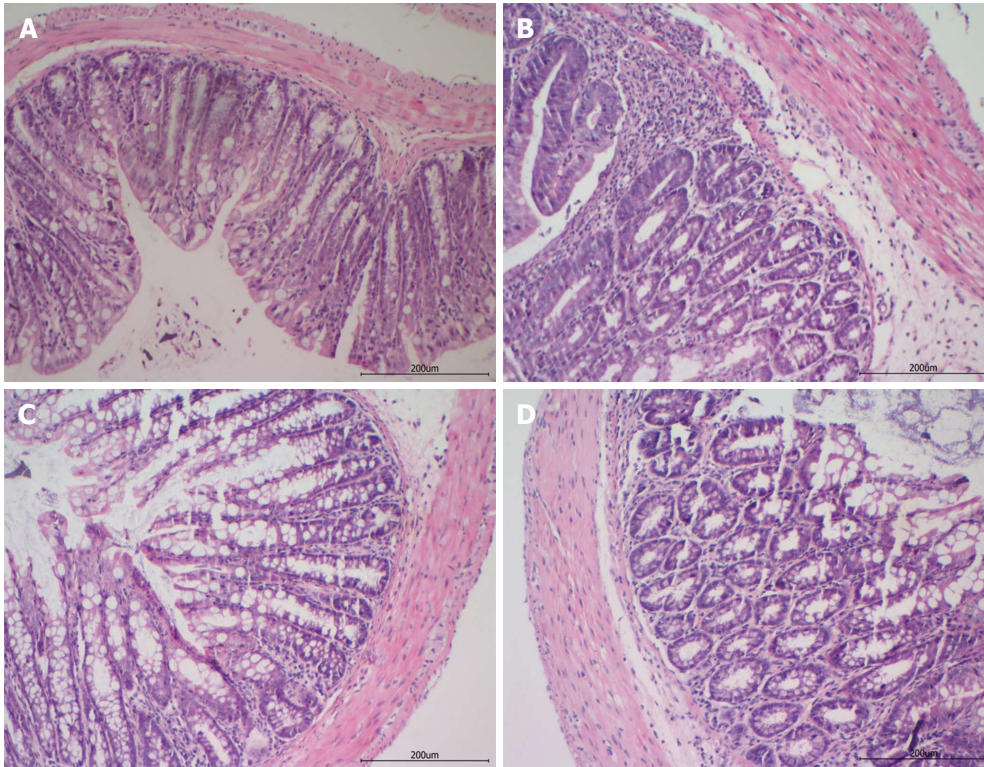
H and E staining showed that in the control group, the colons presented a normal morphology of crypts, abundant goblet cells, a small number of lamina propria mononuclear cells, no signs of mucosal thickening, and complete absence of ulcerations. However, in the DSS group, the colons presented severe epithelial damage with extensive cellular infiltration into the lamina propria and colon mucosa, mucosal thickening, glands arranged irregularly, ulcer and crypt abscess formation, and proliferating granulation tissue. In contrast, in the JQD and 5-ASA groups, the colons presented the migration and repair of epithelial cells on the erosive mucosal surface with infiltration of fewer inflammatory cells and recovery of the glandular structure (Figure 3).

#### JQD suppressed ICC excessive autophagy

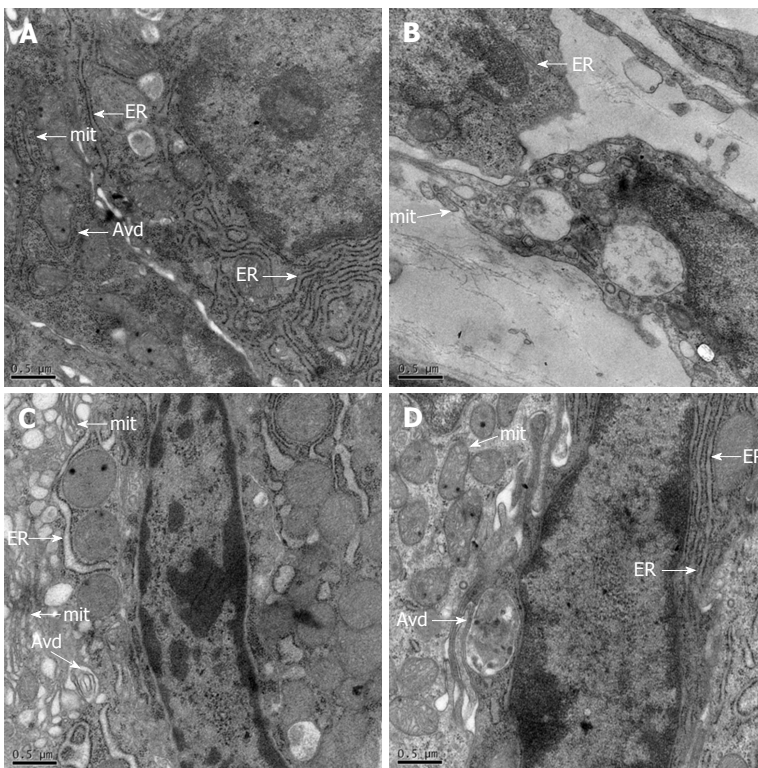
In the control group, ICC was spindle-shaped with a huge ovate nucleolus, caveolae, and numerous free ribosomes. A mass of mitochondria, and smooth and rough endoplasmic reticulum were present in the cytoplasm. ICC was located around the nerve fibers and connected with neighboring smooth muscle cells (SMCs) by intermediate junctions. A few autophagic vacuoles could be observed in ICC. In the DSS group, huge vacuoles, reducing organelles, chromatin margination, cytoplasmic liquefaction and dissolution, and almost invisible autophagic vacuoles could be observed in ICC. In the JQD and 5-ASA groups, the configuration of ICC was normal, with intact connections between cells and the ridge of mitochondria, and a few autophagic vacuoles existed (Figure 4).

#### JQD inhibited the NF- $\kappa$ B/TNF- $\alpha$ pathway, regulated the cytokine expression of IL-1 $\beta$ , IL-10 and IFN- $\gamma$ levels in colon tissue

Compared with the control group, the levels of IL-1 $\beta$ , IL-10, IFN- $\gamma$  and TNF- $\alpha$  increased in the DSS group (*P*



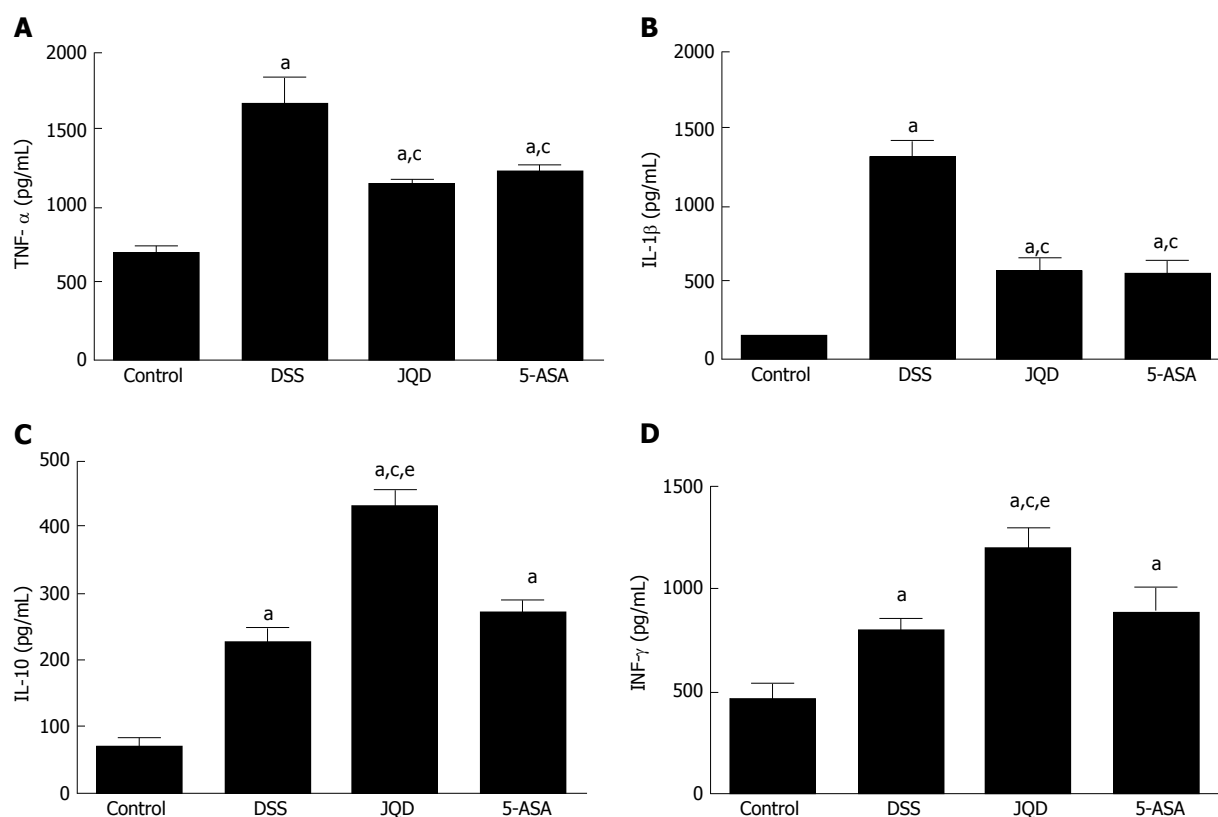
**Figure 3** Histologic images of rat colon (H and E, magnification  $\times 200$ ). A: Control group; B: DSS group; C: JQD group; D: 5-ASA group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; JQD: Jianpi Qingchang decoction.



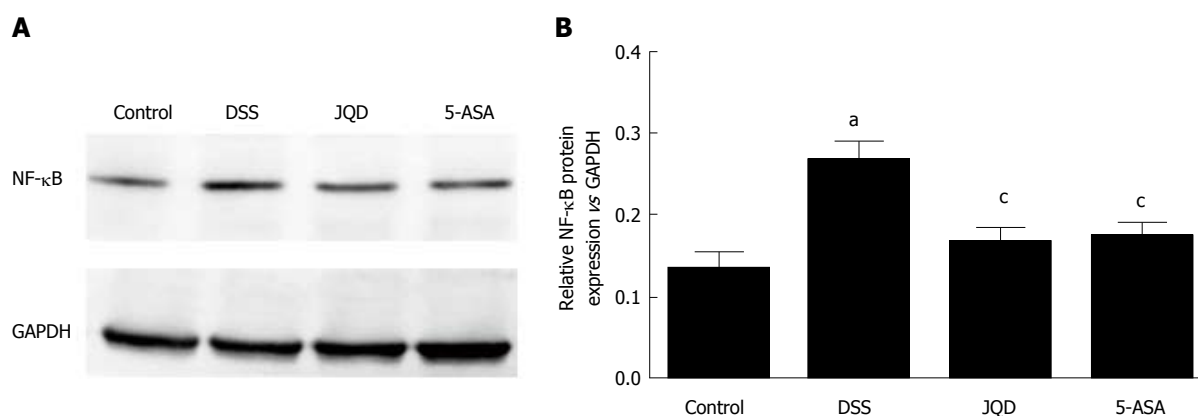
**Figure 4** Transmission electron micrographs of interstitial cells of Cajal and autophagosomes in the region of rat proximal colon (magnification  $\times 20000$ ). A: Control group; B: DSS group; C: JQD group; D: 5-ASA group. 5-ASA: 5-aminosalicylic acid; Avd: Autophagic vacuoles; DSS: Dextran sulfate sodium; ER: Endoplasmic reticulum; JQD: Jianpi Qingchang decoction; mit: Mitochondria.

$< 0.05$ ). After intervention, compared with the DSS group, the levels of IL-1 $\beta$  and TNF- $\alpha$  decreased in

the JQD and 5-ASA groups ( $P < 0.05$ ). However, no statistically significant difference was found between



**Figure 5** Enzyme linked immunosorbent assay analysis of tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , interleukin-10 and interferon- $\gamma$  expression ( $n = 6$ ). A: TNF- $\alpha$  expression in the colon; B: IL-1 $\beta$  expression in the colon; C: IL-10 expression in the colon; D: IFN- $\gamma$  expression in the colon. <sup>a</sup> $P < 0.05$  vs control group, <sup>c</sup> $P < 0.05$  vs DSS group, <sup>e</sup> $P < 0.05$  vs 5-ASA group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; IFN- $\gamma$ : Interferon- $\gamma$ ; IL: Interleukin; JQD: Jianpi Qingchang decoction; TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ .



**Figure 6** Western blot analysis of nuclear factor-kappa B p65 expression ( $n = 4$ ). A: Representative western blots of NF- $\kappa$ B p65. B: Quantitative analysis of NF- $\kappa$ B p65 protein. <sup>a</sup> $P < 0.05$  vs control group, <sup>c</sup> $P < 0.05$  vs DSS group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; JQD: Jianpi Qingchang decoction; NF- $\kappa$ B: Nuclear factor-kappa B; GAPDH: Glyceraldehyde-3-phosphate dehydrogenase.

the two groups ( $P > 0.05$ ). Compared with the DSS group, the levels of IL-10 and IFN- $\gamma$  increased in the JQD and 5-ASA groups. A statistically significant difference was found between the JQD and DSS groups ( $P < 0.05$ ), but no difference was noted between the 5-ASA and DSS groups ( $P > 0.05$ ) (Figure 5).

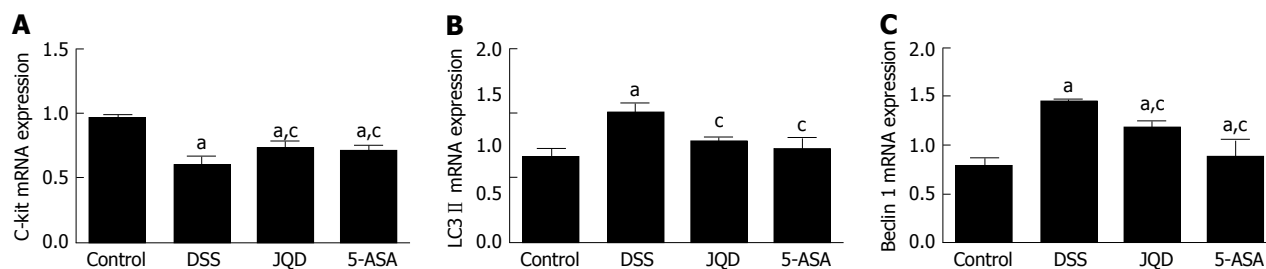
Compared with the DSS group, NF- $\kappa$ B p65 expression increased in the DSS group ( $P < 0.05$ ). After intervention, compared with the DSS group, NF- $\kappa$ B p65 expression decreased in the JQD and 5-ASA groups ( $P$

$< 0.05$ ). However, no statistically significant difference was observed between the two groups ( $P > 0.05$ ) (Figure 6).

#### **JQD regulated *c-kit*, *LC-3II* and *Beclin-1* mRNA expression in colon tissue**

Compared with the control group, *c-kit* mRNA expression decreased ( $P < 0.05$ ) and *LC-3II* mRNA and *Beclin-1* mRNA expression increased in the DSS group ( $P < 0.05$ ). After intervention, compared with the DSS group,





**Figure 7** Real-time PCR analysis of c-kit mRNA, LC-3 II mRNA and Beclin-1 mRNA expression ( $n = 3$ ). A: c-kit mRNA; B: LC-3 II mRNA; C: Beclin-1 mRNA. <sup>a</sup> $P < 0.05$  vs control group, <sup>c</sup> $P < 0.05$  vs DSS group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; JQD: Jianpi Qingchang decoction; LC-3 II: Microtubule-associated protein 1 light chain 3.

c-kit mRNA expression increased in the JQD and 5-ASA groups ( $P < 0.05$ ), LC-3II mRNA and Beclin-1 mRNA expression decreased in the JQD and 5-ASA groups ( $P < 0.05$ ). However, no statistically significant difference was found between the two groups ( $P > 0.05$ ) (Figure 7).

### JQD regulated intestinal motility

Compared with the control group, the colonic smooth muscle contractile amplitude decreased, while the contractile frequency increased in the DSS group ( $P < 0.05$ ). After intervention, compared with the DSS group, the colonic smooth muscle contractile amplitude increased, while the contractile frequency decreased in the JQD and 5-ASA groups ( $P < 0.05$ ). There was statistically significant difference between the two groups ( $P < 0.05$ ) (Figure 8).

## DISCUSSION

The main clinical manifestations of UC include the intestinal motility disorder symptoms<sup>[24]</sup>. The abnormal expression of NF- $\kappa$ B/TNF- $\alpha$  pathway and cytokine expression is related to not only the intestinal mucosal inflammation of UC but also the intestinal motility. Research has revealed that the secretion of inflammatory factors increases in UC. TNF- $\alpha$  and IL-1 $\beta$  can inhibit L-type Ca<sup>2+</sup> channels in the circular smooth muscle of colon and activate NF- $\kappa$ B. Then, NF- $\kappa$ B enter into the cell nucleus, which inhibits subunit description of L-type Ca<sup>2+</sup> channel  $\alpha$ 1C. Subsequently, the number of Ca<sup>2+</sup> channels in the cytomembrane of smooth muscle and Ca<sup>2+</sup> entering into cells decrease. This inhibits the recovery of SMC contraction<sup>[25]</sup>. IL-1 $\beta$  can increase the levels of cytokine IL-6, IL-8 and TNF- $\alpha$  produced by macrophagocytes. Therefore, the neutrophils aggregate near the inflammatory site, which causes a series of pathological changes such as intestinal epithelial cell damage, crypt abscess and small-vessel vasculitis, leading to the abnormal proliferation of SMCs. The proliferation of abnormal SMCs makes them become thin in UC, resulting in motility disorder<sup>[26]</sup>.

This study found that JQD could repair colonic tissues of DSS-induced colitis in mice, and that this

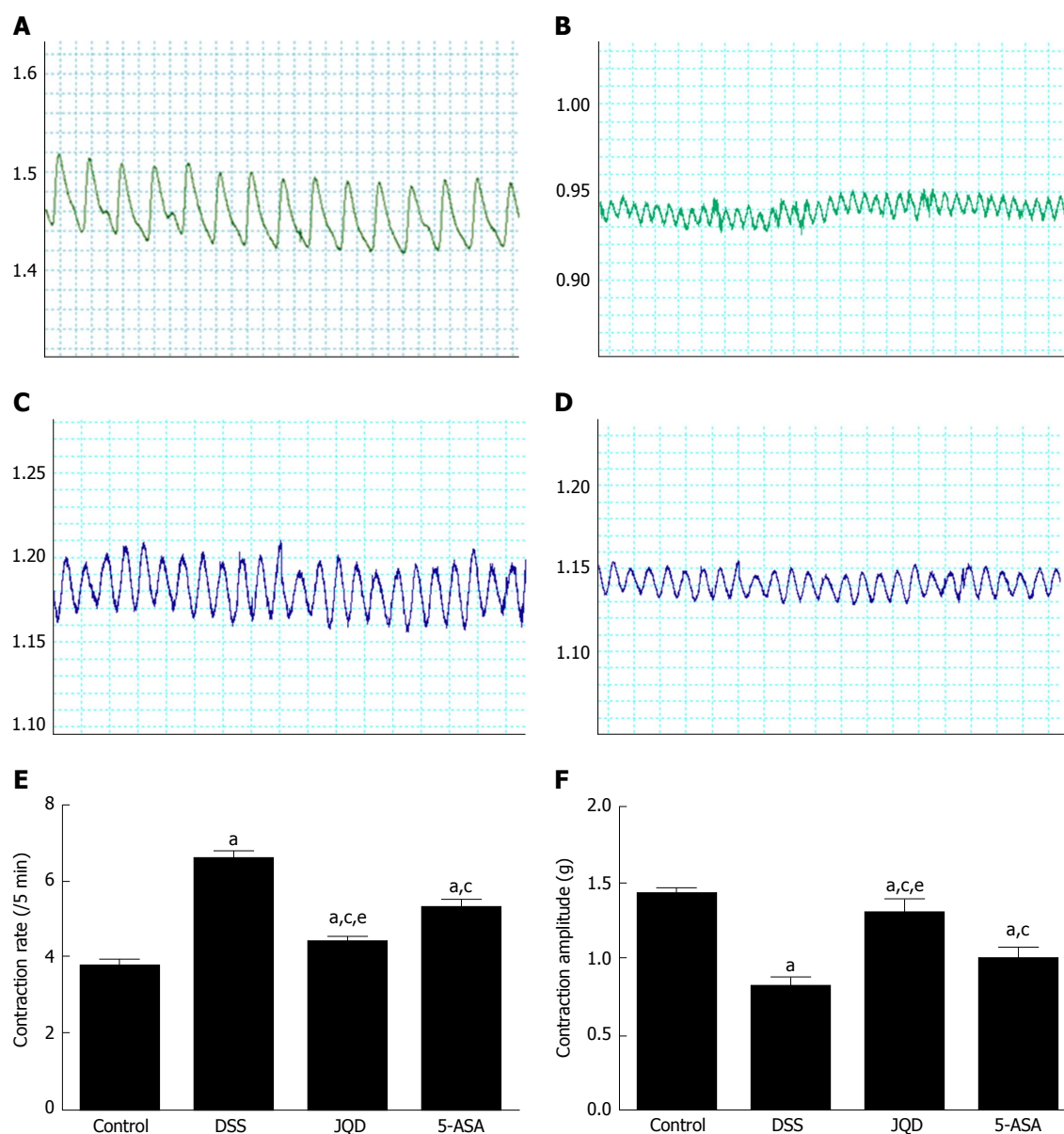
effect involved inhibiting the NF- $\kappa$ B/TNF- $\alpha$  pathway, reducing the level of proinflammatory factor IL-1 $\beta$ , increasing the level of anti-inflammatory factor IL-10 and immunomodulatory factor IFN- $\gamma$ , and suppressing the intestinal inflammatory cascade reaction. The aggravation of inflammatory reaction led to the filtration of a large number of immune cells, which damaged the colonic mucosa. The repair of colonic mucosa might be due to the decrease in immune inflammatory response after JQD treatment.

This study also found that compared with the control group, the levels of IL-10 and IFN- $\gamma$  increased in the DSS group, which was in accordance with some previous studies<sup>[27,28]</sup>. This finding reflected that the bodies of mice had self-regulation and self-recovery effects on colitis induced by DSS, but the weak effect was not enough to cope with intestinal inflammation so that the lesions in intestinal mucosa still existed. However, the self-regulation and self-recovery effects were enhanced under the intervention of JQD, and the increasing levels of IL-10 and IFN- $\gamma$  blocked the secretion of proinflammatory cytokines. Therefore, JQD promoted the recovery of intestinal mucosa.

The ICC/SMC network pathway is the basic functional unit of gastrointestinal motility. It causes effective transmission of nerve impulse to the surrounding smooth muscle, leading to gastrointestinal motility<sup>[29]</sup>. The abnormal ICC/SMC network pathway has a certain relationship with intestinal motility disorder of UC<sup>[30]</sup>. ICC often shows multiple secondary lysosomes, large confluent lipid bodies, and disrupted aggregates of vacuolated glycogen clusters. Intermediate filaments show margination and clumping in patients with UC<sup>[31]</sup>.

The intestinal motility disorder in DSS-induced colitis is caused by the decreased expression of sarco-plasmic endoplasmic reticular calcium ATPase 2 and phospholamban in SMCs, and the increased activity of calmodulin kinase II and the level of histone deacetylases 4 in the cytoplasm. In addition, the increased expression of the contractile proteins associated with the actin filaments of SMCs, which inhibits the interaction between the myosin filaments, is also an important factor<sup>[32]</sup>.

This study found that under physiological conditions, moderate autophagy maintained the growth,



**Figure 8** PowerLab analysis on the contraction of colonic smooth muscle in mice ( $n = 6$ ). A: Control group; B: DSS group; C: JQD group; D: 5-ASA group; E: Contraction rate (1/5 min); F: Contraction amplitude (g). <sup>a</sup> $P < 0.05$  vs control group, <sup>e</sup> $P < 0.05$  vs DSS group, <sup>c</sup> $P < 0.05$  vs 5-ASA group. 5-ASA: 5-aminosalicylic acid; DSS: Dextran sulfate sodium; JQD: Jianpi Qingchang decoction.

differentiation, survival and homeostasis of colonic ICC. Under pathological conditions, in a model of DSS-induced colitis, excessive autophagy occurred in ICC, leading to programmed cell death. Pathological microstructure revealed reduced organelles, chromatin margination, cytoplasmic dissolution, changes in mitochondria and vacuoles, and reduced or absent autophagic vacuoles. Findings at the molecular level were reduced c-kit protein expression and increased LC3-II and Beclin-1 protein expression. The colonic smooth muscle contractile amplitude decreased while contractile frequency increased in the model of DSS-induced colitis. The main abnormal manifestations of intestinal motility were reducing muscle tension and increasing unordered propulsion motility. This was similar to the intestinal dysmotility in patients with UC,

finally causing diarrhea and tenesmus. JQD can inhibit excessive autophagy in ICC, regulate the ICC/SMC network pathway, increase the contractive amplitude, and decrease the contractive frequency of smooth muscle. Hence, the colonic smooth muscle tends to be normal and regulates intestinal tract dynamics.

JQD reflects the features of TCM treatment for UC on the basis of syndrome differentiation<sup>[33]</sup>. As a complete decoction, *Codonopsis pilosula* and *Radix astragali* could nourish qi, *Portulaca oleracea* L and *Radix sanguisorbae* could clear heat and dampness, *Panax notoginseng* and *Bletillae rhizoma* could promote blood circulation by removing blood stasis. Modern studies have found that *R. astragali* containing *Astragalus polysaccharide* can effectively ameliorate 2, 4, 6-trinitrobenzene sulfonic acid-induced experimental



colitis in rats, probably through restoring the number of regulatory T cells, inhibiting IL-17 levels in Peyer's patches, and regulating the expression of TNF- $\alpha$  and IL-1 $\beta$ <sup>[34]</sup>. *Berberine*, the main component of *Coptis chinensis*, can down-regulate the level of IFN- $\gamma$  and IL-12, up-regulate the levels of IL-4 and IL-10 in DSS-induced colitis, and relieve inflammatory reaction in intestinal epithelial cells<sup>[35,36]</sup>. *Ginsenoside-Rg1*, the main component of *P. notoginseng*, can prolong the bleeding and clotting time, down-regulate the thromboxane B2 level, and up-regulate the 6-keto-prostaglandin F1a level to improve the hypercoagulable state in DSS-induced colitis in mice<sup>[37]</sup>.

This study found that the NF- $\kappa$ B/TNF- $\alpha$  pathway was activated in DSS-induced colitis in mice. Abnormal expression of cytokines, excessive autophagy of ICC finally resulted in abnormal motility in UC. JQD can repair the colonic tissues in DSS-induced colitis in mice and regulate the intestinal motility through suppressing intestinal inflammatory cascade reaction, reducing excessive autophagy of ICC, and regulating the network path of ICC/SMCs.

## ACKNOWLEDGMENTS

We would like to thank our colleagues in the Institute of Digestive Disease affiliated to Shanghai University of Traditional Chinese Medicine for their help and support in this research.

## COMMENTS

### Background

The main clinical manifestations of ulcerative colitis (UC) include the intestinal motility disorder symptoms of abdominal pain, diarrhea and tenesmus, besides bloody stool with mucus and pus. Intestinal motility disorder of UC can seriously impact the quality of life (QOL) of patients.

### Research frontiers

Interstitial cells of Cajal (ICC) have been accepted as a therapeutic target for gastrointestinal motility disorders. The regulation of autophagy might be a potential strategy for UC, which can be achieved by multi-level and multi-path interference. Therefore, it was essential to study relationships between intestinal motility disorder of UC and autophagy of ICC, and to explore upstream signaling pathway regulation to strengthen or advance the beneficial autophagy response, which might be beneficial in preventing and treating intestinal dysmotility of UC.

### Innovations and breakthroughs

Previous studies found that Jianpi Qingchang decoction (JQD) could be used to treat patients with initial or mild UC, improve their intestinal symptoms, such as diarrhea, mucous bloody stool and tenesmus, regulate their systemic functional state, such as fatigue, and consequently improve their QOL. This study provided evidence that JQD can repair colonic tissues of dextran sulfate sodium-induced colitis in mice and regulate the intestinal motility through suppressing intestinal inflammatory cascade reaction, reducing excessive autophagy of ICC, and regulating the network path of ICC/smooth muscle cells.

### Applications

The present study provides evidence that JQD, a traditional Chinese medicine recipe, regulates intestinal motility in UC.

## Terminology

ICCs serve as electrical pacemakers, active propagation pathways for slow waves, and mediators of enteric motor neurotransmission and are involved in abnormality of intestinal motility. Recent investigations have demonstrated that inflammation influences the morphology and structure of ICC, leads to a variety of changes in the physiological properties of the neurons in this circuitry, and then affects the gastrointestinal motility.

## Peer-review

This work focuses on the application of an herbal remedy in an animal model of inflammation.

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