The effect of 6-gingerol on inflammatory response and Th17/Treg balance in DSS-induced ulcerative colitis mice

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Background: Ulcerative colitis (UC) is a non-specific chronic intestinal inflammatory disease with unclear etiology. Previous studies have suggested that the imbalance of T reg/Th17 cells may be involved in the development of UC. It was found that 6-gingerol can alleviate the intestinal inflammatory damage and improve the weight loss of colitis mice. However, whether 6-gingerol can regulate the balance of Th17/Treg cells and inhibit the intestinal inflammatory response remains to be clarified.

Methods: In this study, a dextran sulfate sodium (DSS)-induced colitis mouse model was established, and the effects of 6-gingerol on cytokines and the balance of Th17/Treg cells were observed using serial assays, including enzyme-linked immunosorbent assay (ELISA), quantitative real time-polymerase chain reaction (qPCR), and Western blotting.

Results: DSS caused the damage of bowel tissue and a 100% weight loss rate in colitis mice. The treatment of 6-gingerol can significantly relieve bowel damage and reduce incidence of weight loss to 16.7% at a low or high dose (P<0.05), which was similar to the therapeutic effect of mesalazine. It was found that DSS can up-regulate the mRNA levels of IL-6 and IL-17 in serum (by qPCR), and the serum and bowel levels of IL-6 and IL-17 (by ELISA); these levels were significantly different from those of the blank group (P<0.05). Furthermore, 6-gingerol was found to inhibit the increase of mRNA levels and serum and bowel levels of IL-6 and IL-17 induced by DSS, which is similar with mesalazine. It was also found that DSS can down-regulate the mRNA level of IL-10 in serum, along with the serum and bowel level of IL-10, with this being significantly different from that of the blank group (P<0.05). 6-gingerol could also inhibit the decrease of mRNA levels and serum and bowel levels of IL-10 induced by DSS, which is also similar to mesalazine. In addition, DSS could increase Th17 cell count and decrease Treg cell count in blood, with significant difference from that of the blank group (P<0.05). 6-gingerol could significantly (P<0.05) inhibit the increase of Th17 cells and the decrease of Treg cells induced by DSS, which is similar to the effect of mesalazine. The detection of expression levels of transcription factors RORγT for Th17 and FOXP3 for Treg at both mRNA and protein levels showed that DSS can up-regulate the mRNA and protein levels of RORγT, and down-regulate the mRNA and protein levels of FOXP3. Furthermore, 6-gingerol could significantly (P<0.05) inhibit the up-regulation of RORγT mRNA and protein, and the down-regulation of FOXP3 mRNA and protein induced by DSS, which is similar to the effect of mesalazine.

Conclusions: 6-gingerol showed efficacy in the treatment of DSS-induced UC in mice, by regulating the cell balance of Th17/Treg, and by relieving inflammatory responses both systematically and locally.

Keywords: Ulcerative colitis (UC); Th17; RORγT; Treg; FOXP3; 6-gingerol

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Introduction

Ulcerative colitis (UC) is a non-specific chronic intestinal inflammatory disease with unclear etiology (1). In the past 10 years, the incidence of UC in China has been increasing, and UC has become a common disease of the digestive system. It is characterized by recurrent diarrhea, bloody purulent stool, tenesmus, etc. The course of disease is often repeatedly prolonged, and there are many extra-intestinal manifestations.

The etiology and pathogenesis of UC have not been fully defined. It is generally recognized that the pathogenesis of UC is inflammatory damage and ulcer formation caused by abnormal activation of the immune system, which is closely related to genetic, environmental, immune, infection, psychological, or other factors (2). The immune-inflammation damage mechanism is an important factor leading to the occurrence and development of UC. Previous studies have suggested that the imbalance of helper T cell 1 (Th1) and Th2 subsets plays an important role in the pathogenesis of UC, but when researched in depth, UC cannot be explained by a single Th1/Th2 cell model in some cases (3). Researchers have found that there are 2 other cell subsets, regulatory T cells (Treg) and Th17 cells, which are different from Th1 and Th2.

Th17 cells are differentiated from naive T cells and mainly secrete IL-17 through the expression of orphan receptor related to retinoic acid receptor (RORγT). Th17 cells mediate inflammatory response (3), which is closely related to rheumatoid arthritis, allergic asthma, autoimmune encephalitis, and other autoimmune diseases. Treg cells are a sub-population of T cells with negative immune-regulation and cells are derived from naive T cells by the expression of transcription factor FOXP3, which mainly secretes inhibitory cytokines like IL-10 (3). Treg cells can control immune response and maintain immune tolerance by inhibiting the proliferation of effector T cells, weakening the activity of effector T cells, and reducing tissue damage.

Treg cells and Th17 cells restrict each other in differentiation and function, so as to maintain the immune balance. An abnormal number or function of Th17 cells and Treg cells can cause immune imbalance, and then lead to the occurrence of autoimmune diseases. It was reported (4-6) that Th17 cells in the intestinal mucosa and peripheral blood of UC patients increased significantly while Treg cells in the intestinal mucosa increased and Treg cells in the peripheral blood decreased, which suggests that the imbalance of Treg/Th17 cells may be involved in the development of UC.

At present, the main therapeutic drugs of UC are mesalazine, glucocorticoids, immunosuppressants, biological agents, etc. Although the efficacy of the above drugs in the clinical treatment of UC is significant, the long-term usage of these drugs causes common adverse reactions, and has an impact on fertility. Therefore, there is an urgent need to search for drugs with better efficacy and fewer side effects for the treatment of UC.

Gingerol is the rhizome of ginger, a perennial herb of Zingiberaceae. It has a pungent taste and a warming effect. It is used for relieving colds, vomiting, phlegm, and cough. In recent years, studies have shown that ginger has a wide range of pharmacological effects, such as anti-inflammatory, cardiotonic, anti-oxidation, anti-tumor, and immunity-enhancing effects. It can be used in the treatment of rheumatic pain, arthritis, sore throat, chronic vomiting, and other diseases. Gingerol is the main pungent substance extracted from ginger, and comprises more than 10 components including 6-gingerol, 8-gingerol, 10-gingerol, and 12-gingerol. Among them, 6-gingerol has the highest ingredient content and the strongest biological activity. One study (7) found that 6-gingerol can inhibit the primary and secondary inflammatory reactions of adjuvant arthritis mice by inhibiting the cyclooxygenase and lipooxygenase in the metabolism of arachidonic acid, and by reducing the biosynthesis of inflammatory mediators prostaglandin and leukotriene. Ajayi et al. (8) found that 6-gingerol can alleviate the intestinal inflammatory damage and improve the weight loss of colitis mice. However, whether 6-gingerol can regulate the balance of Th17/Treg cells and inhibit the intestinal inflammatory response remains to be elucidated by further research.

In this study, a dextran sulfate sodium (DSS)-induced UC mouse model was established, and the effect of 6-gingerol onTh17 and Treg was observed in colitis mice, with the aim of providing a theoretical basis for the treatment of UC with 6-gingerol.

Methods

Animal experiment

Male BALB/c mice (20–22 g BW) at 6–8 weeks of age were purchased from Sino-British SIPPR/BK Lab. Animal Ltd. (Shanghai, China) and housed in the animal facility in accordance with the approved protocol. Mice were divided into 6 groups (6 mice in each group) as follows: (I) blank group: mice were free to drink distilled water for 14 days;
(II) 6-gingerol alone group: mice were free to drink distilled water for 14 days, and 6-gingerol (Herbpurify, Chengdu, China, purity 97.8%) was given once a day by gavage at a dose of 250 mg/kg; (III) DSS group: mice were free to drink distilled water for the first 7 days, and freshly prepared 4% DSS (Yuanye, Shanghai, China) water (4 g DSS dissolved in 100 mL distilled water) for the next 7 days; (IV) 6-gingerol treatment group (low dose): mice were given 6-gingerol once a day by gavage for 14 days at a dose of 100 mg/kg, and the mice were free to drink distilled water for the first 7 days, and freshly prepared 4% DSS water for the next 7 days; (V) 6-gingerol treatment group (high dose): the mice were given 6-gingerol once a day by gavage for 14 days at a dose of 250 mg/kg, and the mice were free to drink distilled water for the first 7 days, and freshly prepared 4% DSS water for the next 7 days; (VI) mesalazine group: mice were given mesalazine once a day by gavage for 14 days at a dose of 20 mg/kg. and mice were free to drink distilled water for the first 7 days and freshly prepared 4% DSS water for the next 7 days. During the housing, weight changes of mice were monitored and recorded. All the mice were sacrificed on day 14.

**Enzyme-linked immunosorbent assay (ELISA)**

Commercial ELISA kits were used to detect the level of IL-6, IL-10, and IL-17 in serum and bowel tissues in mice according to the manufacturer’s instructions. Briefly, serially diluted standard sample, serum, and bowel tissues samples in 100 μL of dilution buffer were added into 96-well microtiter plates in duplicate, and incubated for 1 h at room temperature. Plates were then washed 5 times with washing buffer, and 100 μL of biotinylated anti-mouse secondary antibody at 1.0 μg/mL was incubated on the plate for 1 h at room temperature. Plates were washed 5 times with washing buffer and incubated with 100 μL of a streptavidin horseradish peroxidase construct at 1.0 μg/mL. Plates were washed 5 times with washing buffer and developed for 15 min in 100 μL of a 3,3’,5,5’-tetramethylbenzidine substrate solution. The reaction was stopped with the addition of 50 μL of stopping buffer. A standard curve was made, and the level of IL-6, IL-10, and IL-17 in each sample was calculated.

**RNA extraction and quantitative real time-polymerase chain reaction (qPCR)**

Total RNA was extracted from bowel tissues by using TRIzol reagent (Takara JAPAN) according to the manufacturer’s instructions. The sequences of the used primers were as follows: IL-6, upstream 5’-TGATGGATGCTACCAACTGGA-3’, downstream 5’-TGTGACTCAGCTTATCTCTTGG-3’, IL-17, upstream 5’-AGCAGCGATCATCCCTCAA-3’, downstream 5’-CTTCATTGCGGAGAGTGCC-3’, IL-10, upstream 5’-AAGGTACTGGGTTGCCA-3’, downstream 5’-GAGAAATCGATGACAGCGCC-3’, Foxp3, upstream 5’-AGCAGTCCACTTACCAAGG-3’, downstream 5’-CTTCTTCTTCTGAGTGAGGAG-3’, RORγ, upstream 5’-AGAAGACCAACACCTCAC-3’, downstream 5’-GTGCAGGAGTAGCCACATT-3’. qRT-PCR was performed on the ABI PRISM 7500 Sequence Detection System (Biosystems, CA, USA) β-actin was used as the endogenous control to normalize mRNA. The relative expression level was quantified using the 2ΔΔCT method. Polymerase chain reaction (PCR) for each sample was performed in triplicate. All primers were produced by Realgene (Nanjing, China).

**Hematoxylin and eosin staining of tissue**

All samples were fixed in 4% formaldehyde solution and embedded in paraffin. Then, paraffin-embedded sections were de-waxed in xylene and were rehydrated in graded alcohols. The sections were incubated with hematoxylin (HE) for 30 s and washed in deionized water for 30 s. After this, 1% eosin solution was used to stain the slides. Three randomly fields were selected for examination.

**Western blotting**

The proteins were extracted from bowel tissues according to the manufacturer’s instruction. The concentration of proteins was determined by bichinchoninic acid (BCA) assay. Then, the proteins were separated by 10% SDS-PAGE and transferred onto polyvinylidene fluoride (PVDF) membranes. Following this, the membranes were blocked with 5% non-fat milk at room temperature for 2 h, and incubated with specific primary antibodies (RORγT, 1:500, Abcam, USA; FOXP3, 1:500, Abcam USA) overnight at 4 ºC, and then incubated with horseradish peroxidase (HRP)-conjugated secondary antibodies (1:5,000, Jackson, PA, USA) at room temperature for 2 h. Finally, membranes were detected by Enhanced Chemiluminescence Detection Kit after washing with Tris-buffered saline (TBST) buffer 3 times.
Flow cytometry

Peripheral blood mononuclear cells (PBMCs) were extracted from peripheral blood by using lymphocyte separation liquid (BD, USA). CD3+ (CD3+PE, 5 μL/tube, BD, USA), CD4+ (CD4+FITC, 5 μL/tube, BD, USA), and IL17A+ (IL17A+Alexa647, 5 μL/tube, BD, USA) cells were designated as Th17 cells. CD4+ (CD4+FITC, 5 μL/tube, BD, USA), CD25+ (CD25+PE, 5 μL/tube, BD, USA), and FOXP3+ (FOXP3+Alexa647, 5 μL/tube, BD, USA) cells were designated as Treg cells.

Statistical analysis

All measurement data are presented as the mean ± SD of at least 3 independent experiments. Differences among groups were analyzed by analysis of variance (ANOVA), and the differences between the 2 groups were analyzed by t test. All enumeration data are presented as the percentage (%) of at least 3 independent experiments, and were analyzed by the χ2 test. All of the data were analyzed using SPSS 19.0 software (SPSS, Armonk, NY, USA) and were considered to be statistically significant when P values were <0.05.

Results

Weight loss of mice in each group

As shown in Figure 1, all the mice in DSS group lost weight during the 14 days, yielding an incidence of weight loss of 100%. The treatment with a low dose of 6-gingerol or a high dose of 6-gingerol could reduce the incidence of weight loss to 16.7%, and the difference was statistically significant (P<0.05). The incidence of weight loss in the blank group was similar to that in the 6-gingerol alone group.

Pathological changes of bowel tissues in each group

As shown in Figure 2, HE staining showed normal epithelium and gland structure and complete crypt and goblet cells in the blank group. DSS caused the destruction and disappearance of the glandular structure on the surface of mucosa, and the disappearance of crypt and goblet cells, accompanied by a large number of granulation hyperplasia and inflammatory cells infiltrating into the submucosa and muscularis. The treatment with 6-gingerol at low dose or high dose, or mesalazine, can relieve the destruction induced by DSS; HE staining showed a near-normal glandular epithelium, a small number of inflammatory cells infiltrating under the mucosa layer, a large number of repaired crypt and goblet cells, and that the muscularis mucosa, submucosa, and intrinsic muscularis were slightly thickened compared with the blank group, and accompanied by inflammatory cell infiltration. Original magnification of 200×.

mRNA levels of cytokines in the bowel tissue of each group

The mRNA levels of pro-inflammatory cytokines (IL-6 and IL-17) were assessed in the bowel tissue of each group. We found that DSS could up-regulate the mRNA levels of IL-6 and IL-17, which were significantly higher than those of the blank group (P<0.05). Although 6-gingerol alone could not significantly down-regulate the mRNA levels of IL-6 and IL-17, it could inhibit the increase of IL-6 and IL-17 mRNA induced by DSS at a low or high dose. Similarly, the therapeutic drug of mesalazine could also inhibit the increase of IL-6 and IL-17 mRNA induced by DSS, with the differences being statistically significant (P<0.05) (Figures 3,4).

In addition, the mRNA level of anti-inflammatory cytokine (IL-10) was also measured. As shown in Figure 5, DSS down-regulated the mRNA levels of IL-10, which were significantly lower than those of the blank group (P<0.05). Although 6-gingerol alone could not up-regulate the mRNA levels of IL-10, it did inhibit the decrease of IL-10 mRNA induced by DSS at a low or high dose. Similarly, mesalazine also inhibited the decrease of IL-10 mRNA induced by DSS, with the differences being statistically significant (P<0.05).
Figure 2 Pathological changes of the bowel tissues in each group (Original magnification of 200×).

Figure 3 mRNA level of IL-6 in bowel tissue (*, P<0.05).

Figure 4 mRNA level of IL-17 in bowel tissue (*, P<0.05).

Figure 5 mRNA level of IL-10 in bowel tissue (*, P<0.05).

Serum levels of cytokines in each group

The serum levels of pro-inflammatory cytokines (IL-6 and IL-17) were measured in each group. We found that DSS up-regulated the serum levels of IL-6 and IL-17, which were significantly higher than those of the blank group (P<0.05). 6-gingerol alone significantly down-regulated the serum levels of IL-6 and IL-17, which could also inhibit the increase of serum IL-6 and IL-17 induced by DSS at a low or high dose. Similarly, mesalazine also inhibited the increase of serum IL-6 and IL-17 induced by DSS, with differences being statistically significant (P<0.05) (Figures 6, 7).

In addition, the serum level of anti-inflammatory...
cytokine (IL-10) was also detected. As shown in Figure 8, DSS down-regulated the serum level of IL-10, which was significantly lower than that of the blank group (P<0.05). 6-gingerol alone up-regulated the serum level of IL-10, which could also inhibit the decrease of serum IL-10 induced by DSS at a low or high dose. Similarly, mesalazine also inhibited the decrease of serum IL-10 induced by DSS, with the differences being statistically significant (P<0.05).

**Bowel levels of cytokines in each group**

The bowel levels of pro-inflammatory cytokines (IL-6 and IL-17) were measured in each group. We found that DSS up-regulated the bowel levels of IL-6 and IL-17, which were significantly higher than those of the blank group (P<0.05). Although 6-gingerol alone did not significantly down-regulate the bowel level of IL-6, it did inhibit the increase of IL-6 induced by DSS at a high dose, but not at a low dose (Figure 9). We also found that 6-gingerol alone could significantly down-regulate the bowel level of IL-17, which can also inhibit the increase of IL-17 induced by DSS at a low or high dose (Figure 10). Similarly, mesalazine also inhibited the increase of bowel IL-6 and IL-17 induced by DSS, with the differences being statistically significant (P<0.05) (Figures 9,10).

In addition, the bowel level of anti-inflammatory cytokine (IL-10) was also measured. As shown in Figure 11,
DSS down-regulated the bowel level of IL-10, which was significantly lower than that of the blank group (P<0.05). Although 6-gingerol alone did not significantly up-regulate the bowel level of IL-10, it did inhibit the decrease of bowel IL-10 induced by DSS at a high dose, but not at a low dose. Similarly, mesalazine also inhibited the decrease of bowel IL-10 induced by DSS, with the differences being statistically significant (P<0.05).

**Th17 and Treg cells in the peripheral blood of each group**

As shown in Figure 12, DSS increased the cell count of Th17 in the peripheral blood, which was significantly higher than that of the blank group (P<0.05). Although 6-gingerol did not significantly decrease the cell count of Th17, it did significantly inhibit the increase of Th17 cell induced by DSS at a high dose, but not at a low dose. Similarly, mesalazine also inhibited the increase of Th17 cell induced by DSS, with the differences were statistically significant (P<0.05).

As shown in Figure 13, DSS decreased the cell count of Treg in peripheral blood, which was significantly lower than that of the blank group (P<0.05). Although 6-gingerol did not significantly increase the cell count of Treg, it did significantly inhibit the decrease of Treg cell induced by DSS at a high dose, but not at a low dose. Similarly, mesalazine also inhibited the decrease of Treg cell induced by DSS, with the differences being statistically significant.
Figure 13 Treg cells in the peripheral blood of each group (*, P<0.05).

Figure 14 mRNA level of RORγT in the bowel tissue of each group (*, P<0.05).

Expression levels of RORγT and FOXP3 in the bowel tissue of each group

The expression levels of transcription factors RORγT for Th17 and FOXP3 for Treg were measured. As shown in Figure 14, DSS up-regulated the mRNA level of RORγT, which was significantly higher than that of the blank group (P<0.05). Although 6-gingerol alone did not significantly down-regulate the mRNA level of RORγT,
it did significantly inhibit the up-regulation of RORγT mRNA induced by DSS at a low and high dose. Similarly, mesalazine also inhibited the up-regulation of RORγT mRNA induced by DSS, with the differences being statistically significant (P<0.05). As shown in Figure 15, DSS significantly down-regulated the mRNA level of FOXP3, which was significantly lower than that of the blank group (P<0.05). 6-gingerol alone did not significantly up-regulate the mRNA level of FOXP3, which also significantly inhibited the down-regulation of FOXP3 mRNA induced by DSS at a low or high dose. Similarly, mesalazine also inhibited the down-regulation of FOXP3 mRNA induced by DSS, with the differences being statistically significant (P<0.05).

We also measured the protein expression of RORγT and FOXP3. As shown in Figure 16, DSS up-regulated the protein level of RORγT and down-regulated the protein level of FOXP3. We also found 6-gingerol alone did not down-regulate the protein level of RORγT or up-regulate the protein level of FOXP3, but it did significantly inhibit the up-regulation of RORγT protein and the down-regulation of FOXP3 protein induced by DSS at a low or high dose. Similarly, mesalazine also inhibited the up-regulation of RORγT protein and the down-regulation of FOXP3 protein induced by DSS.

**Discussion**

Although the efficacy of the current drugs for the clinical treatment of UC, including mesalazine, glucocorticoids and immunosuppressants, is significant, the adverse reactions and the impact on fertility have limited their wider application in the clinical setting. Therefore, there is an urgent need to screen novel and potential drugs in the treatment of UC. 6-gingerol has been reported to participate in alleviating the intestinal inflammatory damage of colitis mice (8) although its exact role remains elusive. In this study, we examined the role of 6-gingerol on Th17 and Treg cells in DSS-induced colitis mice, with the aim of providing a theoretical basis for the treatment of UC.

The current study showed that 6-gingerol can significantly alleviate bowel damage, relieve pathological inflammatory cell infiltration, and reduce the incidence of weight loss in UC mice at low dose or high dose, indicating 6-gingerol to be effective in the treatment of UC in a UC mice model.

UC is an immune-mediated intestinal inflammatory disease, which has a variety of pathogeneses (9). Immunological factors are most closely related to the occurrence of UC, and CD4+ T cell subsets are particularly important in immune regulation (10). In the past, it was thought that UC was a kind of intestinal inflammation mainly mediated by humoral immunity, which was itself mediated by Th2 cells. In recent years, the nature of Th17 cells and Treg cells has been gradually uncovered, and they are considered to be closely linked to the process of differentiation. They can transform each other and perform corresponding functions through different transcription pathways and characteristic cytokines (11). Th17/Treg balance is the key factor to maintain intestinal immune homeostasis (12). Therefore, we examined the effect of 6-gingerol on the number and function of Th17 and Treg cells. The results showed that 6-gingerol could significantly inhibit the increase of Th17 cell count and the decrease of Treg cell count induced by DSS. Functionally, 6-gingerol could significantly inhibit the up-regulation of Th17 transcription factor-RORγT and the down-regulation of Treg transcription factor-FOXP3 induced by DSS at both the mRNA and protein levels. All the results above suggest that 6-gingerol can effectively relieve the damage of bowel tissue in UC mice by regulating Th17/Treg balance.
IL-6 plays an important role in many immune system responses, including the activation of B cell growth and final differentiation, stimulation of T cell proliferation, and differentiation of cytotoxic T cells. IL-6 is a powerful cytokine involved in the regulation of inflammation in UC, and plays a key role in Th17 response and Treg inhibition (13-15). Th17 secretes IL-17 to promote inflammatory response, and Treg can secrete IL-10 to maintain immune tolerance to autoantigens and prevent the occurrence of autoimmune diseases (16). Treg cell abnormalities are involved in a variety of autoimmune and inflammatory diseases, such as type 1 diabetes, multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, and inflammatory bowel disease. Therefore, we further examined the effect of 6-gingerol on the levels of IL-6, IL-17, and IL-10. We found that 6-gingerol significantly reduced the levels of IL-6 and IL-17 in serum and bowel tissue, which were significantly lower than those in UC mice. We also found that 6-gingerol increased IL-10 level in serum and bowel tissue, which was significantly higher than that in UC mice. The changes of the cytokines above indicate that 6-gingerol can effectively relieve the damage of bowel tissue in UC mice by relieving inflammatory responses both systematically and locally.

The destruction of the UC intestinal epithelial barrier and the continuous stimulation of intestinal cavity antigen make macrophages and dendritic cells secrete a large number of pro-inflammatory factor IL-6, thus promoting the differentiation of Th1 and Th17 cell lines and inhibiting the function of Treg. Treg cells, when deficient in function, are not capable of resisting the pro-inflammatory effect of the hyperactive Th17 cells, resulting in the increase of many inflammatory factors and the amplification of inflammatory response (17) thus causing the damage of colon tissue (18,19). Therefore, when IL-6 is over expressed, the differentiation and function of Treg cells and Th17 cells are out of balance. One study (20) showed that blocking IL-6 may control Th17-mediated immune response. Therefore, we speculated that 6-gingerol can inhibit the expression and secretion of IL-6, maintain the balance of Th17/Treg, and thus inhibit Th17-mediated inflammatory response.

There were some limitations in this study. Firstly, the animal number in each group was small, which might have caused some statistical bias. Secondly, the underlying mechanisms were not explored, and thus in-depth study is needed in further research. To conclude, 6-gingerol was effective in the treatment of DSS-induced UC in mice by regulating the balance of Th17/Treg and relieving inflammatory responses both systematically and locally.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/atm.2020.03.141). The authors report grants from Wuxi City Health and Family Planning Commission, during the conduct of the study.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Animal experiments were approved by The Third People’s Hospital of Wuxi Medical Ethics Committee (No. 2018121201).

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