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Ginger attenuates inflammation in a mouse model of dextran sulfate sodium-induced colitis

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Abstract This study assessed the anti-inflammatory effect of ginger extract on colitis by 5% dextran sulfate sodium (DSS) in BALB/c mice. The mice were administered either distilled water or three doses of ginger extracts for 21 days. We evaluated the change in clinical and histopathological signs and cytokine and gene expression levels. Contrary to the DSS group, the ginger groups increased body weight and inhibited shortening of the colon. DAI values and colon injury in the ginger groups were lower than that in the DSS group. Ginger groups obviously inhibited the myeloperoxidase activity and cytokine and mRNA concentrations of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, but not of intestinal barrier proteins zonula occludens (ZO)-1, occludin, E-cadherin, mucin-1, and mucin-2 in colon tissues. Our results suggest the protective effect of ginger against DSS-induced colitis and that ginger could be utilized to prevent and treat irritable bowel disease.

Keywords Colitis · Dextran sulfate sodium · Ginger · Inflammation · Inflammatory bowel disease

Introduction

Inflammatory bowel disease (IBD), such as Crohn's disease (CD) or ulcerative colitis (UC), is associated with inflammation that recurs in the digestive system, without specific pathology. It is promoted by the abnormal immune reaction of the pathogens in the cell and intestinal flora, due to which inflammation occurs in the digestive system (Podolsky, 2002). Patients with IBD show frequent symptoms of melena, mucous and bloody stool, diarrhea, weight loss, abdominal pain, and anemia (Carter et al., 2004; Verhave et al., 1990). Cytokines appear to play a leading role in regulating IBD-related clinical symptoms, namely, intestinal inflammation, diarrhea, rectal bleeding, furuncle formation, and complications such as the incidence of colitis-related neoplasms (Neurath, 2014; Strober et al., 2002). Use of natural products, e.g. plant extracts or plant derivatives, has been shown to suppress IBD, and hence, is increasing worldwide. Many studies, examined in vitro and/or in vivo, have shown that plant extracts and plant derivatives, including *Prunus mume, Gardenia jasminoides, Zingiber officinale,* and *Garcinia cambogia*, adjust the level of numerous inflammatory cytokines or inflammatory agents and intercellular adhesion molecule expression to exert their anti-inflammatory effect (Awaad et al., 2013; Debnath et al., 2013). In addition, many extracts were also shown to be effective in clinical studies (Triantafyllidi et al., 2015).

Ginger is a perennial herbaceous plant belonging to *Zingiber officinale Roscoe*. It has a unique spicy and aromatic flavor, and is widely used throughout the world. Ginger has been proved to have anti-inflammatory, antioxidant, anti-gastritis, anti-ulcer, and antimicrobial activities (Ali et al., 2008; Chrubasik et al., 2005). The main ingredients of ginger are zingerones, paradols, gingerols, and shogaols, which occur in the oleoresin of ginger rhizome phenolics (Jung et al., 2018; Luettig et al., 2016). These compounds have been demonstrated to possess antioxidant, anti-inflammatory, and anti-cancer properties (Chung et al., 2009; Dugasani et al., 2010; Fan et al.,

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2015). Several studies have reported the physiological effect of ginger and its constituents in an animal model of induced colitis (Chang and Kuo, 2015; El-Abhar et al., 2008; Hsiang et al., 2013; Murakami et al., 2003). In previous studies, ginger was extracted at room temperature, using 100% ethanol and used with other colitis inducers, such as 2,4,6-trinitrobenzene sulphonic acid (TNBS) or acetic acid, in the colitis model (El-Abhar et al., 2008; Hsiang et al., 2013). However, the ginger we used in our current study was dried ginger root that was extracted using 50% ethanol at 50 °C. This condition was determined by exploring in vitro experimental results and extraction conditions using the response surface method (Kim and Kim, 2017).

In an in vivo ulcerative colitis model generated by dextran sulfate sodium (DSS), in rats, mice, and hamsters, blood loss, weight loss, small bowel enlargement, and mucosal ulcers occur early on (Kullmann et al., 2001; Sha et al., 2013). It is also characterized by injury in colon epithelial cells and absence of inflammation in the epithelial layer. This aspect is similar to that of IBD in humans, so DSS is widely used to generate experimental animal models (Dothel et al., 2013; Perse and Cerar, 2012).

In this study, we examined the inhibitory effect of ginger extracts on intestinal inflammation. Ginger extracts were administered to BALB/c mice with 5% DSS-induced colitis and their effect on colitis was examined subsequently.

Materials and methods

Materials

Ginger extracts were prepared by adding 50% ethanol at 50 °C for 35 min. The extracts were subsequently filtered and lyophilized. Dextran sulfate sodium (DSS; molecular weight: 36,000–50,000) was obtained from MP Biomedicals, LLC (Santa Ana, CA, USA). Formalin (10%) solution in neutral buffer, and myeloperoxidase (MPO) activity assay kit were purchased from Sigma-Aldrich (St. Louis, MO, USA). TRIzol was obtained from Life Technologies (Rockville, MD, USA). BCA protein assay kit was purchased from Thermo Fisher Scientific Inc. (Waltham, MA, USA).

Animals

A total of 40 5-week-old female BALB/c mice were purchased from Shizuoka Laboratory Center (Shizuoka, Japan). The animals were administered a standard rodent diet with free access to water (ad libitum) and were housed in rooms sustained at 22 ± 1 °C with a 12 h light/dark cycle. The protocols were approved by the Institutional animal care and use committee (IACUC) of Ewha Womans University (Seoul, Korea) (IACUC No. 17-037).

Colitis model and administration of ginger extract

The animals were split randomly into five groups (n = 8 mice/group), namely, the control, DSS (only), DSS + ginger (100 mg/kg), DSS + ginger (300 mg/kg), and DSS + ginger (500 mg/kg). Control and DSS (only) groups were administered distilled water by oral gavage. Ginger groups were administered 100, 300, and 500 mg/kg ginger orally, once a day, maintaining the same time, from day 1 to day 21. Body weight and dietary intake were recorded once every 3 days until day 21. Colitis was induced by the intake of 5% (w/v) DSS-containing drinking water, ad libitum, for 7 consecutive days.

Disease activity index (DAI)

DAI values were calculated based on body weight loss, stool consistency, and fecal bleeding (Cooper et al., 1993), as shown in Table 1.

Histological analysis

A 1-cm distal end of colon was fixed in neutral buffered 10% formalin solution, embedded in paraffin, sliced into 4-μm sections, and stained with hematoxylin and eosin (H&E). Colonic histopathological variations were estimated from all the colon sections under light microscopy at 100× and 200× magnification. The grading system was as follows (Dieleman et al., 1998): (a) inflammation severity: 0 = none; 1 = slight; 2 = moderate; 3 = severe; (b) lesion depth: 0 = none; 1 = mucosal layer; 2 = submucosal layer; 3 = muscle layer; 4 = transmural; (c) crypt damage: 0 = none; 1 = basal 1/3 damaged; 2 = basal 2/3 damaged; 3 = only surface epithelium intact; 4 = entire crypt and epithelium lost; (d) lesion range: 1 = 1–25%; 2 = 26–50%; 3 = 51–75%; 4 = 76–100%. The number of goblet cells in

Table 1 Criteria for disease activity index

Score	Weight loss (%)	Stool consistency	Fecal bleeding
0	< 0	Normal	Normal
1	1–5	–	
2	6–10	Soft	Slightly bloody
3	11–15	Loose	Bloody
4	> 15	Diarrhea	Severely bloody

DAI [= (weight loss) + (stool consistency) + (fecal bleeding)] was used to assess the severity of colonic inflammation

crypts of three areas were counted on each H&E slide and expressed per 3 villus-crypt units.

Myeloperoxidase activity assay

Myeloperoxidase (MPO) is a prominent indicator highly expressed in neutrophils of mouse proximal colon. The proteins in the colon tissues were utilized to evaluate the MPO activity using the commercial kits. The excised colon was weighed, rapidly homogenized in MPO analysis buffer, and centrifuged at 13,000 × g for 10 min. The MPO levels were measured using the supernatant. Absorbance was measured at 412 nm. MPO concentration was expressed as units/mg tissue. One unit of MPO activity is defined as the quantity of enzyme degrading 1 μmol TNB per minute at 25 °C.

Measurement of colonic cytokines

Total frozen colon sections were homogenized in lysis buffer to get the total protein. The homogenate was centrifuged at 13,000 × g at 4 °C for 5 min. The supernatant was used to measure the levels of interleukin (IL)-1β, IL-6, and tumor necrosis factor (TNF)-α, employing commercially available ELISA kits (Abbexa Ltd, Cambridge, UK) and following the manufacturer's protocol. The total protein content in the supernatant was measured using the BCA protein assay kit.

Determination of colonic mRNA expression

Total RNA from colon was isolated by soaking the latter in TRIzol. The supernatant was incubated with chloroform for 5 min and mixed with the same amount of isopropanol. cDNA was synthesized by reverse transcription using a High Capacity RNA-to-cDNA Kit and subjected to qRT-PCR using the Universal ProbeLibrary (UPL) probe method with a StepOnePlus RT-PCR system (Hoffmann-La Roche, Basel, Switzerland). The relative quantity of RNAs was calculated using the comparative ΔΔCT method upon normalization with respect to the amount of GAPDH. The sense and antisense sequences were as follows: GAPDH (sense, 5′- aagagggatgctgcccttac-3′; antisense, 5′-ccattttgtctacgggacga-3′); IL-1β (sense, 5′-agttgacggacccc-caaaag-3′; antisense, 5′-agctggatgctctcatcagg-3′); IL-6 (sense, 5′-gctaccaaactggatataatcagga-3′; antisense, 5′-ccaggtagctatggtactccagaa-3′); TNF-α (sense, 5′-tcttctcattc-ctgcttgtgg-3′; antisense, 5′-ggtctgggccatagaactga-3′); zonula occludens (ZO)-1 (sense, 5′-aaatcatccgactcctcgtc-3′; antisense, 5′-cagttggctccaacaaggtaa-3′), Occludin (sense, 5′-gtccgtgaggccttttga-3′; antisense, 5′-ggtgcataat-gattgggtttg-3′), E-cadherin (sense, 5′-atcctcgccctgctgatt-3′; antisense, 5′-accaccgttctcctccgta-3′), mucin-1 (sense, 5′-ctgttcaccaccaccatgac-3′; antisense, 5′-cttggaagggcaa-gaaaacc-3′), and mucin-2 (sense, 5′-gcagccacagatcccaaa-3′; antisense, 5′-gttggggtcccctgaagt-3′).

Statistical analysis

Results are displayed as mean ± standard deviation (SD). Data were analyzed using Statistical Analysis System version 9.4 (SAS Institute, Cary, NC). Differences between the groups were analyzed using one-way analysis of variance (ANOVA) along with a Duncan's post hoc test. Statistical significance was shown by $p < 0.05$.

Results and discussion

Ginger extracts improve the clinical symptoms of DSS-induced colitis

Female BALB/c mice were provided drinking water containing 5% DSS to induce representative symptoms of IBD, such as body weight loss, diarrhea, and rectal bleeding. Daily administration of ginger extracts was assessed in the mice with colitis. Body weight decreased sharply due to DSS intake, in contrast to control and ginger extract groups (Fig. 1A). The weight loss due to DSS treatment significantly improved in mice administered ginger extracts. Medium and high dose of ginger extracts (300 and 500 mg/kg) had the maximum effect on the weight recovery. During the 7 days of DSS administration, severe diarrhea, blood loss in feces, and body weight loss were considered as a noticeably high DAI. Ginger extract intake, at doses 100–500 mg/kg, decreased DAI sharply relative to the DSS group (Fig. 1B). Moreover, the colon length of DSS group was generally shorter than that of control group. Ginger extract intake significantly improved those symptoms (Fig. 1C, D).

Ginger (*Zingiber officinale Roscoe*) is widely used in food and beverages as spice and flavor throughout the world. Ginger and its bioactive constituents have been found to exhibit several important effects, such as anti-hyperglycemic, anti-lipidemic, anti-tumorigenic, anti-inflammatory, anti-apoptotic, and immuno-modulatory (Ali et al., 2008; Chrubasik et al., 2005). The current study rendered experimental proof of ginger extract improving the clinical symptoms in DSS-induced mice.

In this study, we provided 5% DSS-containing drinking water to the mice for 7 days to produce an acute colitis model, which exhibited severe weight loss, reduced colon length, and colonic tissue damage. Ginger extracts showed improvement of the decreased body weight and colon length and increased DAI values.

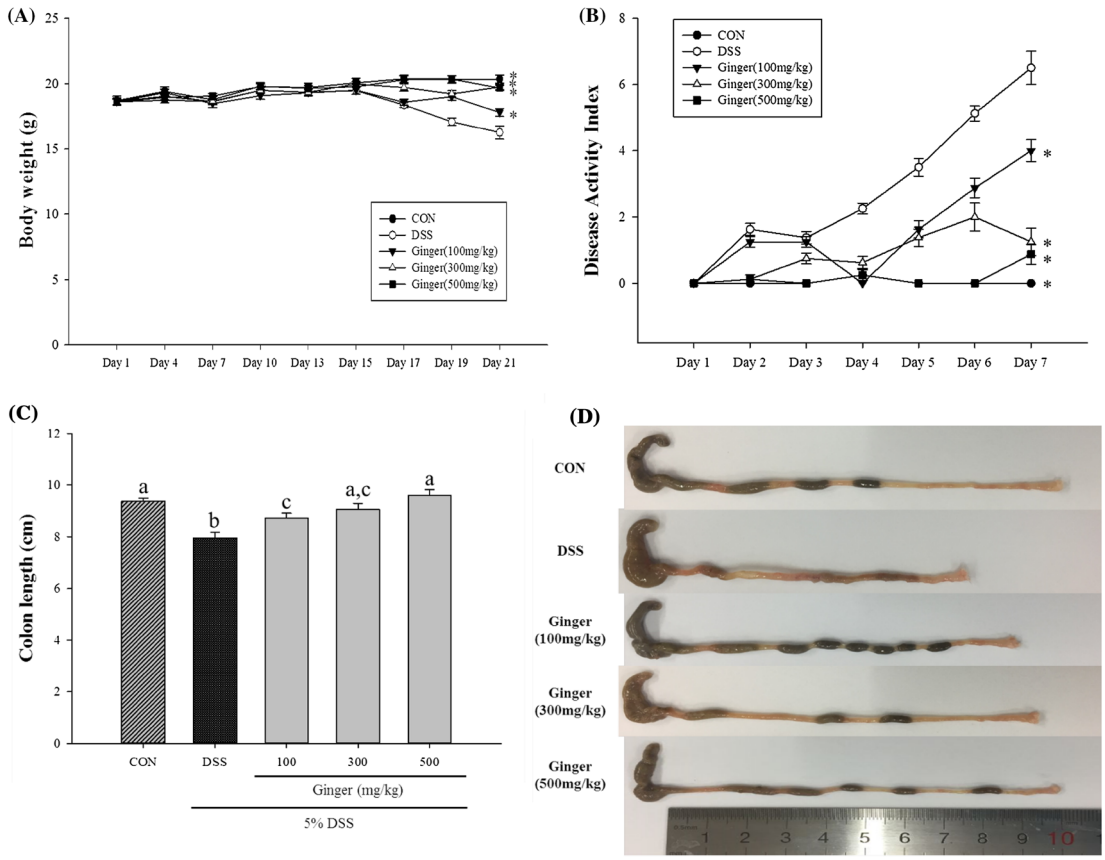

Fig. 1 Effect of ginger extracts on clinical symptoms and colon shortening in DSS-induced colitis. (**A**) Body weight was recorded simultaneously on the experimental days; (**B**) the score of disease activity index; (**C**) DSS-induced shortened colon was significantly ameliorated by ginger extracts; (**D**) representative colons of each group. (*$p < 0.05$ compared to the DSS group)

Ginger extracts attenuated the DSS-induced colonic histopathological changes

Diarrhea and fecal blood from daily DSS treatment in mice accompany colonic infection and intestinal barrier injury. In the histological sections from DSS-treated mice, critical crypt destruction and inflammatory cell invasion were checked (Fig. 2A). Ginger extracts could reduce the histopathological symptoms of colitis. The histological scores increased by approximately 1.6-fold with DSS, in contrast to the control group, but, were substantially reduced in the ginger extract group, similar to control group (Fig. 2B). Ginger extracts accompanied a dose-dependent decline in histological scores. The number of mucus-secreting goblet cells decreased in DSS group in contrast to that in control group (Fig. 2C); however, that with ginger extracts increased in a dose-dependent manner, and the highest concentration of ginger extract (500 mg/kg) was the most similar to control group.

When DSS is administered to mice, a chronic or acute colitis model with symptoms similar to UC can be generated, depending on the concentration of DSS (Baumgart and Sandborn, 2012). It is known as a good model to study pathological and immunological characteristics. Pathological features of colon in such a model include excessive formation of granules around the epidermis, severe edema of the tissue wall, hypertrophy of mucous tissue, infiltration of granulocytes including eosinophils, and reduction of goblet cells (Dieleman et al., 1998; Dothel et al., 2013; Kullmann et al., 2001). Inflammation severity, lesion depth, and crypt damage, the characteristics of patients with typical acute UC (Wang et al., 2017; Zhao et al., 2017), were observed in microscopic morphological features of the colon.

Ginger extracts reduced the MPO activity

MPO activity, which is correlated with the number of neutrophils, was investigated to check inflammatory cell infiltration in the proximal colon. In line with histological scores, MPO activity of DSS group was 1.3-times higher than of the control group. Ginger extract groups significantly restrained MPO activity induced by DSS, similar to the control group (Fig. 3).

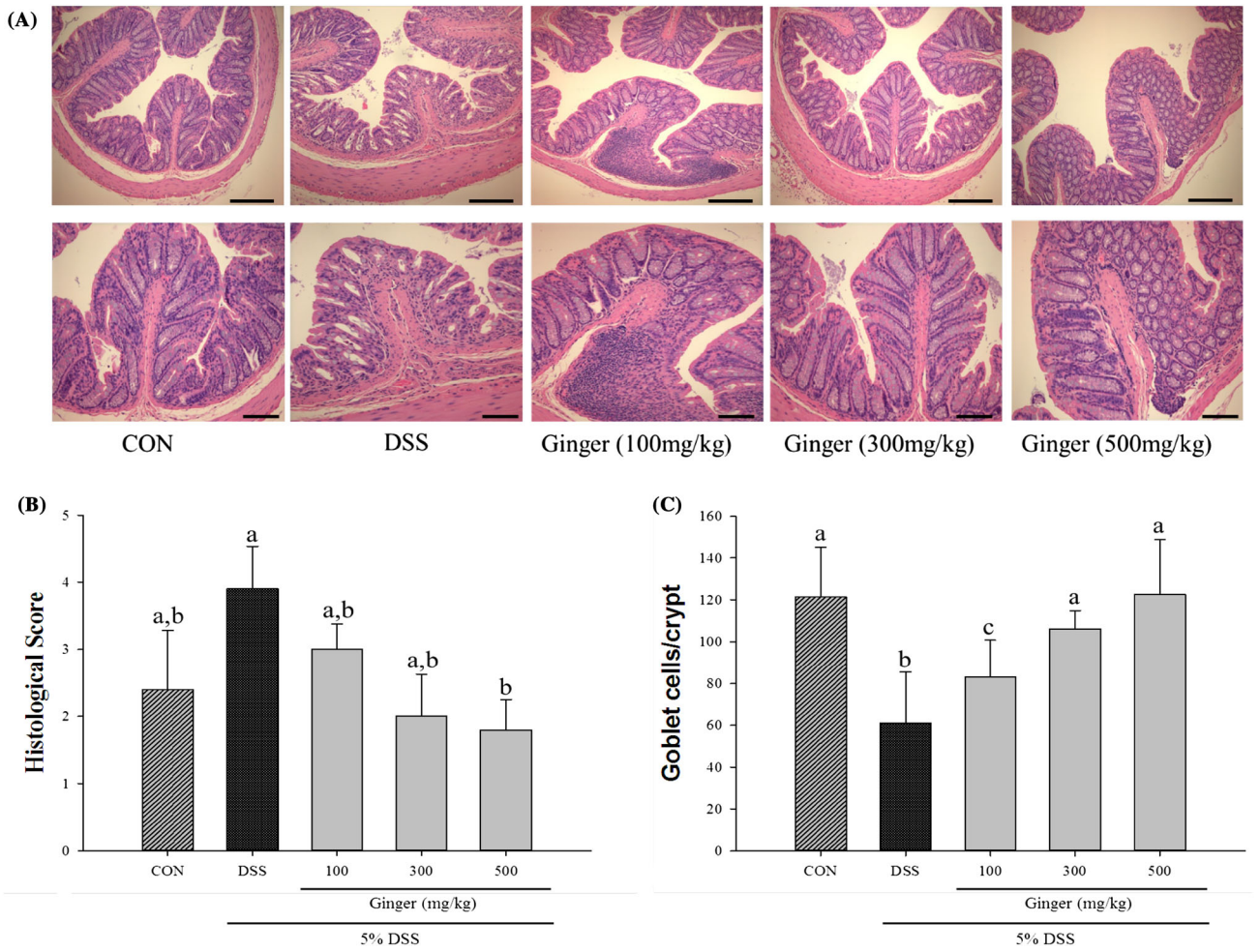

Fig. 2 (**A**) Histopathological features of colons from BALB/c mice with 5% DSS-induced colitis. Hematoxylin and Eosin staining. Magnification 100× (bar = 100 mm), 200× (bar = 200 mm). Ginger extracts effectively attenuated (**B**) histopathological changes and increased (**C**) goblet cells in the colon with 5% DSS-induced colitis

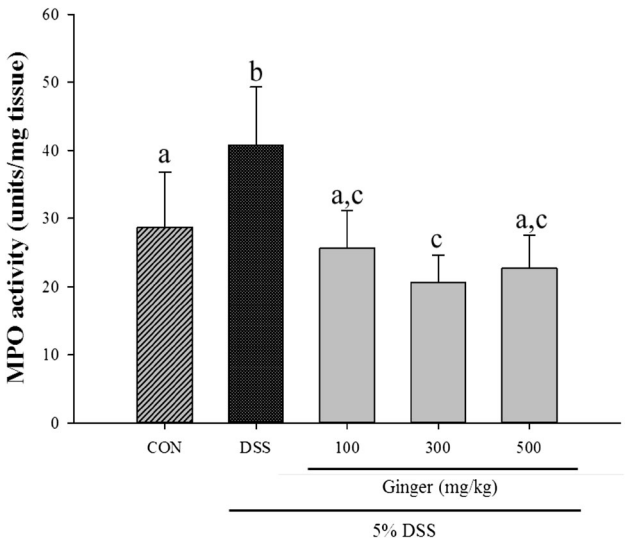

Fig. 3 Effect of ginger extracts on myeloperoxidase activity in the colon of DSS-induced BALB/c mice

Ginger extracts reduced the pro-inflammatory cytokines

Pro-inflammatory mediators, such as IL-1β, IL-6, and TNF-α, play leading roles in the formation of colitis. In order to check whether obstructing these pro-inflammatory mediators could improve colonic inflammation in mice, we used ELISA kit to test the concentration of IL-1β, IL-6, and TNF-α in the inflamed proximal colon. In the DSS group, mucosal concentration of IL-1β, IL-6, and TNF-α increased by more than 1.6-, 5-, and 6-fold than in the control group. However, oral intake of ginger extracts significantly reduced the concentrations of IL-1β, IL-6, and TNF-α in the colonic tissue compared to that in colitis-induced mice (Fig. 4A). The highest concentration of ginger extract (500 mg/kg) was associated with IL-1β level similar to control group. All doses of ginger extract reduced the level of IL-6 and TNF-α production, similar to that in control group.

Ginger extracts reduced the pro-inflammatory mRNA expression

In order to test the anti-inflammatory effect of ginger extract on proximal colon of DSS-induced mice, qRT-PCR was conducted for all the experimental groups. The outcomes reconfigured the cases in which DSS significantly induced the levels of inflammatory mRNA expression, namely, IL-1β, IL-6 and TNF-α (Fig. 4B). In DSS group, the expression of IL-1β, IL-6, and TNF-α rose sharply by approximately 20-, 8-, and 14-fold, respectively, in comparison to that in control group. Ginger extracts highly suppressed relative mRNA expression of IL-1β, IL-6, and TNF-α. The results of IL-6 and TNF-α showed a dose-dependent decrease and were lower than that in control group at the highest concentration of ginger extract (500 mg/kg).

In IBD, IL-1β is correlated to inflammation and modulates immune cells; it is a critical cytokine in early phase of inflammation. IL-6 acts in the earlier stages of immune response and exercises pleiotropic effects. TNF-α, also, is indispensable and the earliest endogenous mediator that can intervene in the alteration of gastrointestinal barrier and permeability (Baumgart and Sandborn, 2012; Shen et al., 2018). Ginger extracts inhibited the inflammatory cytokines and mRNA expression of IL-1β, IL-6, and TNF-α induced by DSS.

Ginger extracts increased the mRNA expression of tight junction proteins

Our data showed that continuous inflammation and injury to intestinal mucosal barrier are critical to the outbreak and development of IBD. Therefore, we further explored the impact of ginger extracts on the levels of barrier function-associated proteins ZO-1, occludin, E-cadherin, mucin-1, and mucin-2 in colon. In DSS group, expression of ZO-1, occludin, E-cadherin, mucin-1, and mucin-2 decreased by approximately 5-, 1.6-, 3-, 1.2-, and 1.4-fold, respectively, in comparison to that in the control group (Fig. 5). All

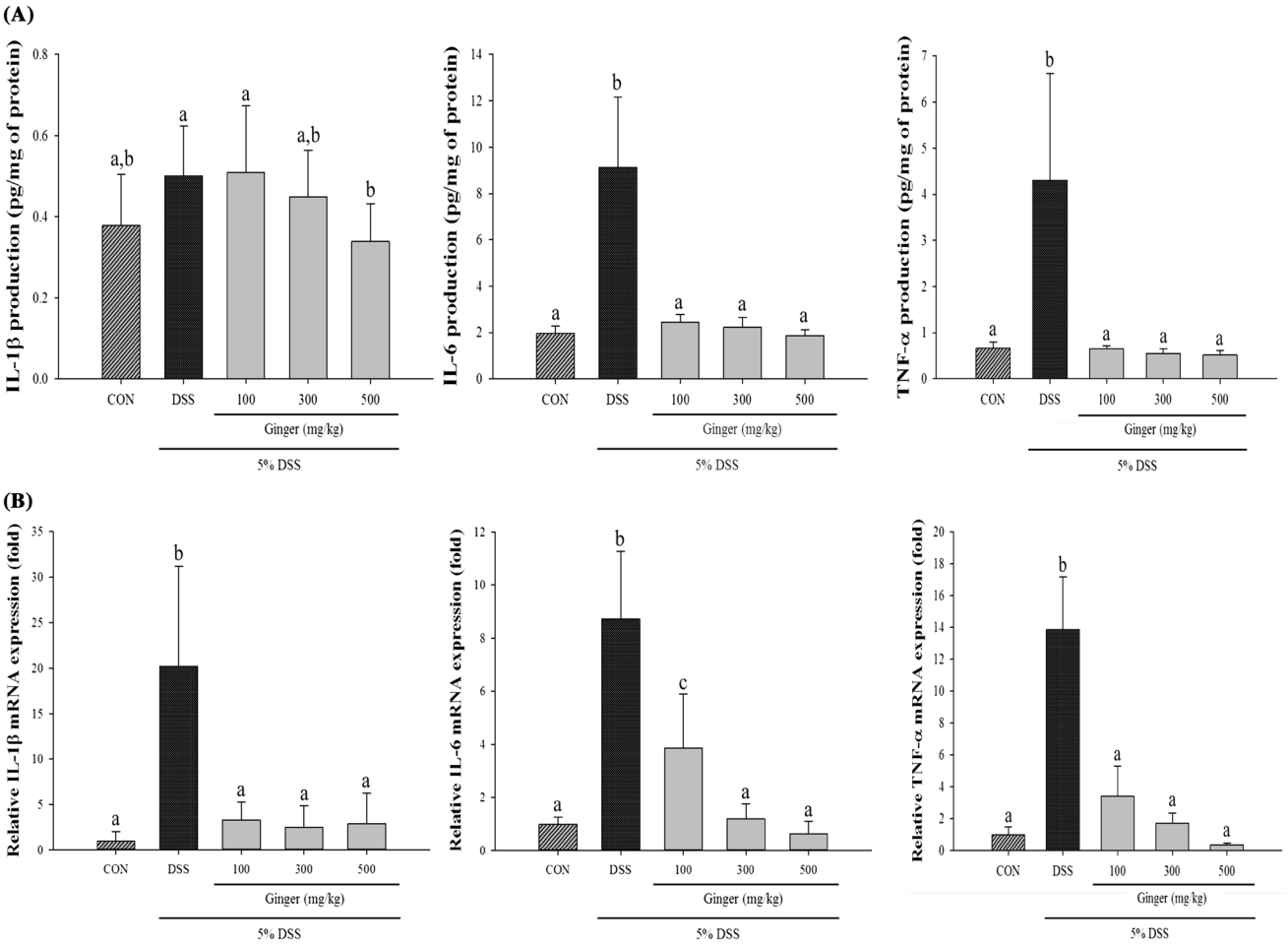

Fig. 4 Effect of ginger extracts on inflammatory cytokines and mRNA levels in the colon. (**A**) Concentration profile of IL-1β, IL-6, and TNF-α; (**B**) Relative mRNA expression profiles of IL-1β, IL-6, and TNF-α

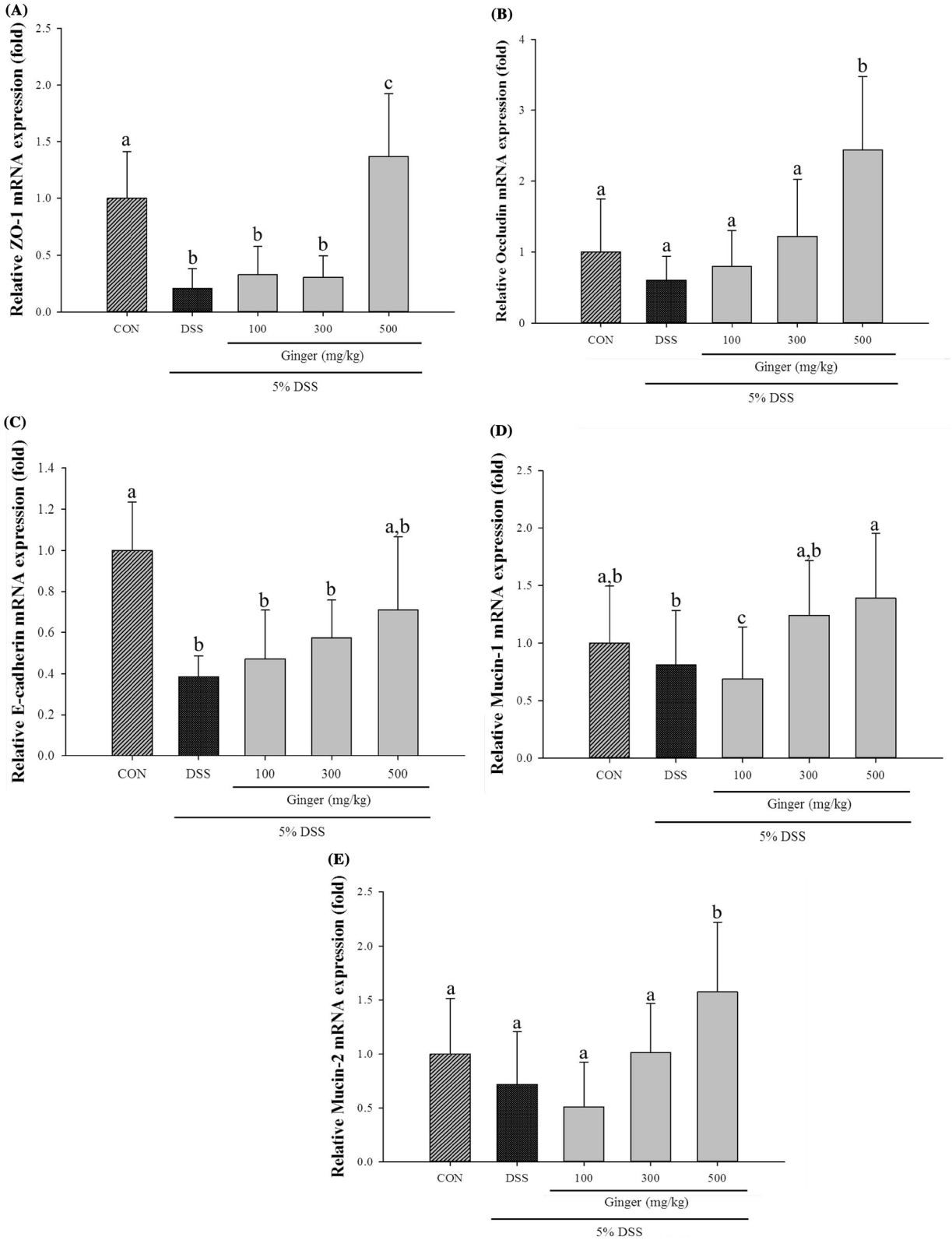

Fig. 5 Effect of ginger extracts on relative mRNA expression of tight junction proteins in the colon. Relative mRNA expression profiles of (**A**) ZO-1; (**B**) Occludin; (**C**) E-cadherin; (**D**) mucin-1; (**E**) mucin-2

doses of ginger extract enhanced the mRNA expression levels of tight junction (TJ) proteins in colonic mucosa. At the highest concentration of ginger extract (500 mg/kg), ZO-1, occludin, mucin-1, and mucin-2 had 1.4-, 2.4-, 1.4-, and 1.6-fold higher mRNA expression levels than in the control group. E-cadherin, at ginger extract concentration of 500 mg/kg, was approximately twice as high as in DSS group.

The intestinal mucosa performs an immunological function by acting as a barrier for the inflow of microorganisms, by-products thereof, antigens, toxins, etc. into the bloodstream in the intestinal tract (DeMeo et al., 2002). The intestinal mucosal cells maintain a gap between themselves in a single layer. When a stimulation or damage occurs, the tight junction among the cells weakens and permeability is increased. Various inflammatory and immune responses as well as many diseases result therefrom. E-cadherin is a notable protein of adherens junctions (AJ) and is a mediator of cell–cell adhesion between epithelial cells (Zbar et al., 2004). E-cadherin-containing junction molecules become unstable when inflammatory cytokines activate the mediator of signaling pathway (Schnoor, 2015). Mucin-1 and -2, which are mainly secreted and expressed in the epithelial goblet cells of intestine, form protective layers against physiological, biological, and chemical stress in the colonic mucosa (Hayashi et al., 2001; Yu et al., 2018). In IBD, mucins are decreased, as a result of which the mucosal layer is thinner than normal and weaker in barrier function in the colon. Moreover, altered intestinal barrier and permeability have shown structural irregularities in TJ proteins containing ZO-1 and occludin (Yu et al., 2018). Such stress promotes pathogenic invasion in the intestines, leading to irritation, which makes cell contacts unstable (Schnoor, 2015). Thus, maintenance of intestinal mucosal barrier integrity is very important to intestinal health by regulating TJ and AJ proteins. In our study, the levels of barrier function-related proteins, namely, ZO-1, occludin, E-cadherin, mucin-1, and mucin-2, were reduced in DSS group, whereas ginger extracts improved barrier integrity by reducing the severity of colitis.

This study, however, has certain limitations. First, we could not verify the barrier function directly, including localization and mechanism of action of TJ and AJ-related proteins. Second, we could not recognize the main active component in ginger extract and the anti-inflammatory activities and mechanism of main components. The components of ginger, such as gingerol, shogaol, and zingerone, have been reported to possess anti-inflammatory activities in in vitro *and* in vivo (Chrubasik et al., 2005). 6-Gingerol has been studied to protect the intestinal mucosa and demonstrated beneficial effect with physiological and pathological signs (Chang and Kuo, 2015). Therefore, this study should be further verified in vitro and ultimately validated for clinical trial.

In conclusion, in order to examine the effect of ginger on colitis, ginger extracts were orally administered to mice with DSS-induced colitis. Tissue pathology, inflammatory cytokines, and TJ proteins were studied for validating the beneficial effect of ginger on colitis and ginger extracts effectively showed improvement of colitis.

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