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Efficacy of Doenjang, a Traditional Korean Fermented Food, against Dextran Sulfate Sodium-induced Ulcerative Colitis: Effect of Distribution of Microorganisms

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Abstract Doenjang, a traditional fermented food in Korea, has been consumed as a health food for a long time and is known worldwide. Doenjang has varying biological effects depending on the manufacturing method and fermentation or aging period. In this study, we confirmed the protective effect of Doenjang against ulcerative colitis (UC) according to distribution of microorganisms. In this experiment, a rat model of a dextran sulfate sodium (DSS)-induced UC was used. Doenjang (TSMM29 and TSMM30) and positive control (VSL#3; Desimone) were administered orally for 14 days before and after DSS induction. Our results revealed that the DSS-induced group showed decreased body weight, contraction of colon tissue, decreased colon weight, and increased inflammatory cytokine levels. On the contrary, in the TSMM-treated group, changes to body weight, colon tissue, and colon weight were recovered, and inflammatory cytokine levels were decreased. Histological results showed that the TSMM-treated group showed decreased edema and inflammatory cell infiltration, and recovery of the destroyed goblet cells In particular, the TSMM29 group showed the highest degree of recovery, thus showing that the distribution of microorganisms in Doenjang influences its biological effects in UC.

Keywords: *Doenjang, Korea traditional fermented food, microorganisms, Ulcerative colitis, Dextran sulfate sodium*

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1. Introduction

Inflammatory bowel disease (IBD) is characterized by increased inflammation [1]. It is caused by chronic recurrent inflammation of unknown cause, in addition to enteritis caused by a specific cause [2]. This disease may cause serious complications, such as colon cancer [3]. The pathogenesis of IBD has yet to be identified, but it is known that microbial infection, stress, environmental factors, and immunological abnormalities are involved [4].

IBD includes Crohn's disease and ulcerative colitis (UC), both of which have a wide range of severity [5]. UC affects the rectum and colon, and the main symptoms include abdominal pain, diarrhea, and mucous stools [6]. The lesions mainly include pathological changes in mucous membranes and submucosal tissues, as well as infiltration of inflammatory cells and ulcers [7,8]. Inflammatory cell infiltration occurs owing to overproduction of inflammatory cytokines, particularly tumor necrosis factor (TNF)-α and interleukin (IL)-6 [9,10]. This phenomenon leads to the activation of fibroblasts, endothelial cells, and other inflammatory cells, thereby promoting inflammation [11]. Therefore, the regulation of cytokines is regarded as an important factor in the alleviation of UC.

Currently, steroids and immunomodulatory drugs are used as treatments for UC [12]. However, owing to treatment failure and side effects, colon resection is often required. This requires complex surgical methods and undesired sequelae [13]. Therefore, in recent years, focused on developing effective therapeutic drugs that can minimize side effects. In particular, it focused on developing healthy functional foods through food processing. Therefore, in this study, we investigated the effect of Doenjang, a traditional Korean fermented food in UC.

Fermented foods are widely consumed because of their taste and easy storage. In particular, kimchi and paste, traditional fermented foods in Korea, are already

considered one of the best health foods in the world [14]. Doenjang, used in the present study, is a fermented soybean paste that has excellent storage properties and is an excellent source of protein [15]. Doenjang has been shown to exert various biological effects in previous studies [16]. The biological activity of soybeans is reported to be dependent on isoflavones and their derivatives [17]. However, because the fermentation degree, soaking ratio, and maturation period of Meju vary depending on the manufacturer, there is a difference in quality and biological activity between Doenjang products [18].

Therefore, in this study, to confirm the difference in biological activity on dextran sodium sulfate (DSS)-induced UC model according to the distribution of microorganisms, two Doenjang products (TSMM29 and TSMM30) were selected according to the beneficial and harmful bacteria among 31 commercially produced Doenjang (Table 1).

Table 1. Microbial Distribution of Selected Doenjang

TSMM29	TSMM32
Cronobacter sakazakii	*Weissella confusa*
Tetragenococcus halophilus	*Pediococcus stilesii*
Pediococcus stilesii	*Bacillus velezensis*
Leuconostoc mesenteroides	*Leuconostoc mesenteroides*
Lactobacillus rennini	*Enterococcus hirae*
Halomonas garicola	*Halomonas garicola*
Lactobacillus sakei	*Bacillus lindianensis*
Lactobacillus paracasei	*Cronobacter sakazakii*
Staphylococcus epidermidis	*Bacillus zhangzhouensis*
Lactobacillus fermentum	*Bacillus subtilis*
Kroppenstedtia eburnea	*Enterococcus mundtii*
Chromohalobacter beijerinckii	*Pediococcus pentosaceus*
Aerosakkonema funiforme	*Tetragenococcus halophilus*
Bacillus circulans	*Lactococcus lactis*
Staphylococcus muscae	*Brevibacillus borstelensis*
Enterococcus mundtii	*Vagococcus teuberi*
Weissella diestrammenae	*Bacillus oryziterrae*
Gibbsiella greigii	*Bacillus vietnamensis*
Pantoea allii	*Vagococcus martis*
Glutamicibacter creatinolyticus	*Brevibacillus borstelensis*
Corynebacterium casei	*Vagococcus teuberi*
Bacillus nanhaiisediminis	*Pediococcus claussenii*
Virgibacillus kekensis	*Leuconostoc kimchii*
Granulicatella elegans	*Weissella diestrammenae*
Lactobacillus brevis	*Weissella koreensis*
Leuconostoc fallax	*Bacillus wiedmannii*
Streptococcus equinus	
Clostridium arbusti	
Clostridium tyrobutyricum	
Pseudomonas punonensis	

2. Materials and Methods

2.1. Next Generation Sequencing Analysis

To extract high-quality DNA from the collected samples, a Fast DNA Spin kit for food (MP Bio Laboratories, USA) was used. DNA purity was measured by measuring the absorbance (A260/280 ratio) using a NanoDrop spectrophotometer (ND-1000; Thermo Scientific, MA, USA). DNA concentration was measured using PicoGreen (Invitrogen, MA, USA) equipment and finally confirmed through 1% agarose electrophoresis. The 16s ribosomal DNA amplicon was used to extract total genomic DNA as a template. The 16s ribosomal DNA amplicon was amplified using a primer set targeting V1, V2, and V3 polymorphic regions of the 27-518 domain 27F and 518R of *Escherichia coli* 16s rRNA gene (5′-CCTATCCCCTGTGTGCCTTGGCAGTC (adapter)-TCAG (key)-AC linker-GAGTTTGATCMTGGCTCAG (27F primer)-3′, 5′-CCATCTCATCCCTGCGTGTCTC CGAC(adapter)-TCAG (key)-Barcode-AC linker)-WTTACCGCGGCTGCTGG (518R primer)-3′). The PCR products were confirmed by 2% agarose gel electrophoresis, and impurities other than the amplification product were removed using a QIAquik PCR purification kit (Qiagen, Netherlands, Germany). The same amount of PCR products was purified again using an AMPure bead kit (Agencourt Bioscience, England); then, the length and concentration of the amplified products were analyzed with Bioanalyzer 2100 (Agilent, CA, USA) using a DNA 7500 chip. The final amplification product was performed by Macrogen Co., Ltd. using the GS Junior Titanium system (Roche, Germany) sequencer, according to the manufacturer's manual.

2.2. Experimental Animal Model

Male Sprague-Dawley rats (specific-pathogen-free, 4 weeks old, 150-155 g; Samtako Co., Osan, Korea) were subjected to 1 week of acclimatization. The animals were provided sufficient diet and drinking water and maintained in a standard conditioned room (temperature, 22 ± 2°C; humidity, 55 ± 5%) under an automatic lighting schedule (12-h light/dark cycle). The animal experiments were approved by the Institutional Animal Care and Use Committee of INVIVO Co., Ltd.

UC models were established following a previously published method [19,20]. Briefly, the experimental animals were weighed and then separated to into groups (n=10): normal control (NC), DSS (DSS+vehicle), TSMM29 (DSS+TSMM29), TSMM30 (DSS+TSMM30), and VSL#3 (DSS+VSL#3) groups. The animals were administered 4% DSS in drinking water for 7 days to induce UC. The treatments were administered orally for 14 days before and after induction: NC and DSS groups, saline; TSMM29 group, TSMM29 250 mg/kg; TSMM30 group, TSMM30 250 mg/kg; positive control group, VSL#3 (Desimone) 350 mg/kg. After induction, weight and diet were measured once a week. To quantitate diet and water consumption, the remaining amounts of feed and water were measured at a certain time the next day after feeding.

2.3. Sample Collection

The rats were anesthetized through inhalation anesthesia, and blood was collected through the abdominal vein. After blood collection, the animals were euthanized via venesection of the abdominal vein and artery. Next, colon tissue was isolated, washed with saline, and the length and weight were measured. Lesions in the colon tissue were scored [21]. After that, the lesion sites were cut and divided into two: one part was fixed in 10% neutral buffered formalin solution and the other was stored at -80°C.

2.4. Hematological Analysis

Blood samples were divided into two tubes: an EDTA tube and a 1.7 ml tube for hematological analysis and

serum separation, respectively. For hematological analysis, blood samples in EDTA tubes were rotated in a roll mixer for 30 min, and the numbers of leukocytes, lymphocytes, and granulocytes were measured using a blood analyzer.

For serum collection, blood samples in 1.7 ml tubes were coagulated at room temperature for approximately 30 min and centrifuged at 3000 rpm and 4°C for 10 min. The supernatant was recovered and stored at -80°C. Serum samples were used for ELISA. TNF-α and IL-6 levels were measured using an ELISA kit.

2.5. Histological Analysis

The tissue fixed in 10% neutral buffered formalin was embedded in a paraffin block and then cut into sections. Each section was attached to a slide and then stained with hematoxylin and eosin (H&E) staining for histological analysis.

2.6. Statistical Analysis

Statistical analysis was conducted to investigate significant differences between groups. Differences were judged to be significant when $p<0.05$. Comparisons were performed using analysis of variance (ANOVA) and Duncan's test.

3. Result

3.1. Effects of TSMM on DSS-induced UC

In previous studies, DSS-induced UC model is known to exhibit weight loss and colon contraction in the early stages of colitis [22,23]. The results of the present study showed a decrease in body weight in the DSS group compared with that in the NC group on the third week; however, this weight loss was recovered in the TSMM29 and TSMM32 groups (Table 2). Colon length (Figure 1A) was lower in the DSS group (9.7 cm) than in the NC group (12.1 cm). However, the TSMM29 and TSMM32 groups showed a colon length of 10.3 cm and 9.2 cm, respectively, showing that colon length was recovered in the TSMM29 group compared with that in the DSS group. This recovered colon length was similar to that in the positive control VSL#3 group (10.0 cm). Colon weight (Figure 1B) was 3.0 g in the normal group, 1.6 g in the DSS-induced group, 1.7 g in the TSMM29 group, and 2.0 g in the TSMM32 group, showing a significant decrease in the DSS group compared with that in the NC group as well as an increase in the TSMM29 and TSMM32 groups compared with that in the DSS group. In particular, TSMM32 showed increased colon weight similar to that in the VSL#3 group.

Table 2. Body weight change

Time variables/group	Initial	1 week	2 week	3 week
NC	160.7±1.9[a]	223.2±3.0[b]	263.0±4.0[b]	302.4±5.6[b]
DSS	157.0±2.0[a]	210.2±3.4[a]	250.8±4.6[a]	268.0±11.2[a]
TSMM29	156.1±1.5[a]	216.5±2.3[a,b]	254.6±2.2[a,b]	280.1±2.4[a]
TSMM32	156.2±1.5[a]	217.5±2.1[a,b]	261.4±3.1[b]	275.9±4.8[a]
VSL#3	157.3±1.7[a]	218.8±1.6[b]	261.5±2.3[b]	279.0±5.4[a]

"a, b" indicate significant difference at $p<0.05$. Data are expressed as mean±SEM.

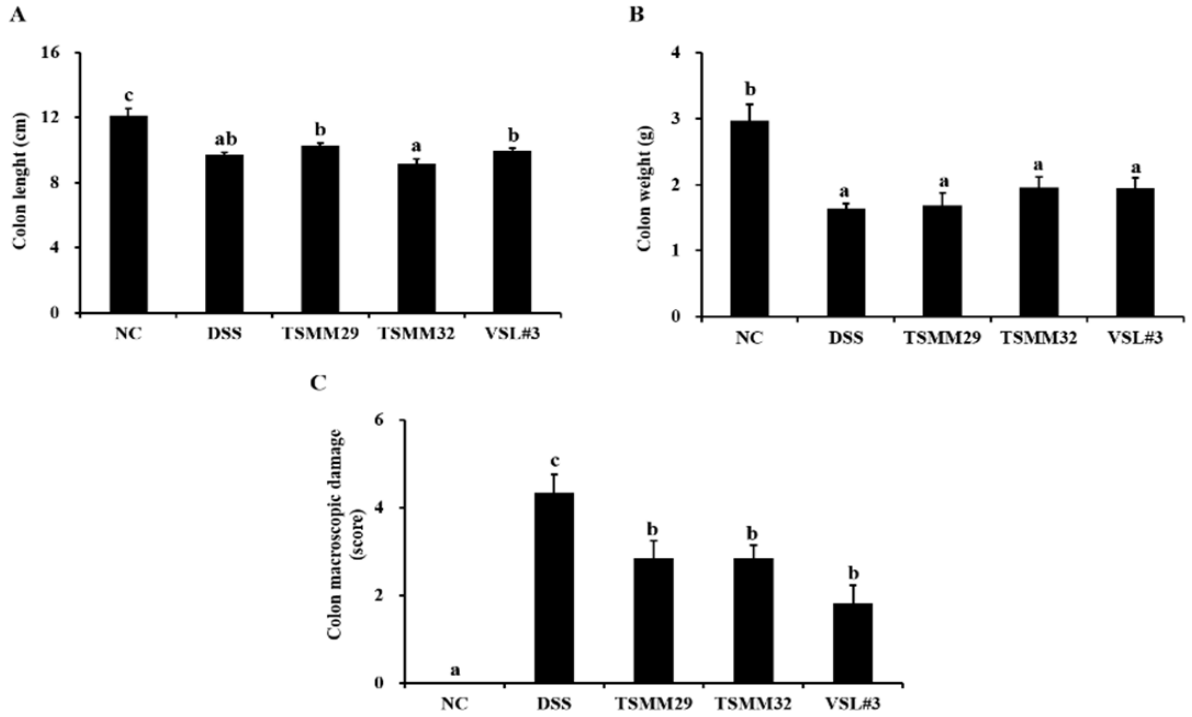

Figure 1. TSMM attenuates the common symptoms of DSS-induced UC. (A) Colon length, (B) colon weight, (C) colon macroscopic damage. NC, normal control; DSS, 4% DSS; TSMM29, TSMM29 (250 mg/kg) + 4% DSS; TSMM32 (250 mg/kg) + 4% DSS; VSL#3, Desimone (350 mg/kg) + 4% DSS. "a, b" and "c" indicate significant difference at $p<0.05$. Data are expressed as mean±SEM

UC is characterized by inflammation, ulcers, and bleeding in the colon [24]. Therefore, colon tissue was subjected to macroscopic evaluation by referring to previous studies (Table 3). Our results showed that inflammation, ulcers, and bleeding were observed in the DSS group (Figure 1C). In contrast, inflammation and ulcer bleeding were alleviated in the VSL#3 group. The TSMM29 and TSMM32 group showed significant improvement compared with the DSS group, but only slight improvement compared with the VSL#3 group. These results confirmed that TSMM could protect against the development of UC, and there was no difference in the efficacy of Doenjang according to the distribution of microorganisms.

Table 3. Macroscopic scoring

Score	Macroscopic morphology
0	No ulcer, no inflammation
1	No ulcer, local hyperemia
2	Ulceration without hyperemia
3	Ulceration and inflammation at one site only
4	Two or more site of ulceration and inflammation
5	Ulceration extending 2cm

3.2. Reduction of Inflammatory Factors by TSMM

In UC, the formation of ulcers occurs owing to infiltration of inflammatory cells and an increase in pro-inflammatory cytokines. Therefore, in this experiment, the effect of TSMM on changes in inflammatory factors was confirmed. First, the number of white blood cells in blood was measured to confirm changes in inflammatory cells. The measured values showed a significant increase in the DSS group compared with that in the NC group (Figure 2). However, the increased number of white blood cells was decreased in the TSMM29 and TSMM32 group. In particular, neutrophil count (granulocytes, GRA) was significantly decreased in the TSMM29 and TSMM32 group; particularly, the TSMM29 group showed neutrophil count similar to that of the VSL#3 group.

The levels of the inflammatory cytokine TNF-α significantly increased in the DSS group (16.5 pg/ml) compared with that in the NC group (6.3 pg/ml) (Figure 3A). On the contrary, TNF-α level decreased in the TSMM29 (12.5 pg/ml) and TSMM32 (12.1 pg/ml) groups, compared with that in the DSS group. IL-6 level significantly increased in the DSS group (261.0 pg/ml) compared with that in the NC group (92.9 pg/ml), but decreased in the TSMM29 (222.3 pg/ml) and TSMM32 (238.6 pg/ml) groups compared with that in the DSS group (Figure 3B). Therefore, it was confirmed that inflammatory cytokines were regulated by the administration of TSMM. Moreover, as TSMM29 showed a greater effect than TSMM32, the efficacy of Doenjang was shown to differ according to the distribution of fermentation microorganisms.

Histologically, UC causes edema of the mucosa and submucosa, infiltration of inflammatory cells, and destruction of goblet cells [25]. Based on this, in this study, colon morphology was examined through H&E staining and infiltration of inflammatory cells was assessed (Figure 4). Compared with those in the NC group, in the DSS group, edema was observed in the submucosal layer and infiltration of inflammatory cells was increased. In addition, the morphology of colon tissues changed owing to the destruction of goblet cells. However, in the TSMM group, the morphology of colon tissues was recovered, the degree of inflammatory cell infiltration was reduced, and edema of the submucosal layer was decreased, compared with those in the DSS group. In particular, the TSMM32 group showed a higher degree of recovery than the TSMM29 group. Therefore, TSMM exerts a protective effect against UC by reducing inflammatory factors, and the protective effect of Doenjang against UC varies depending on the distribution of microorganisms.

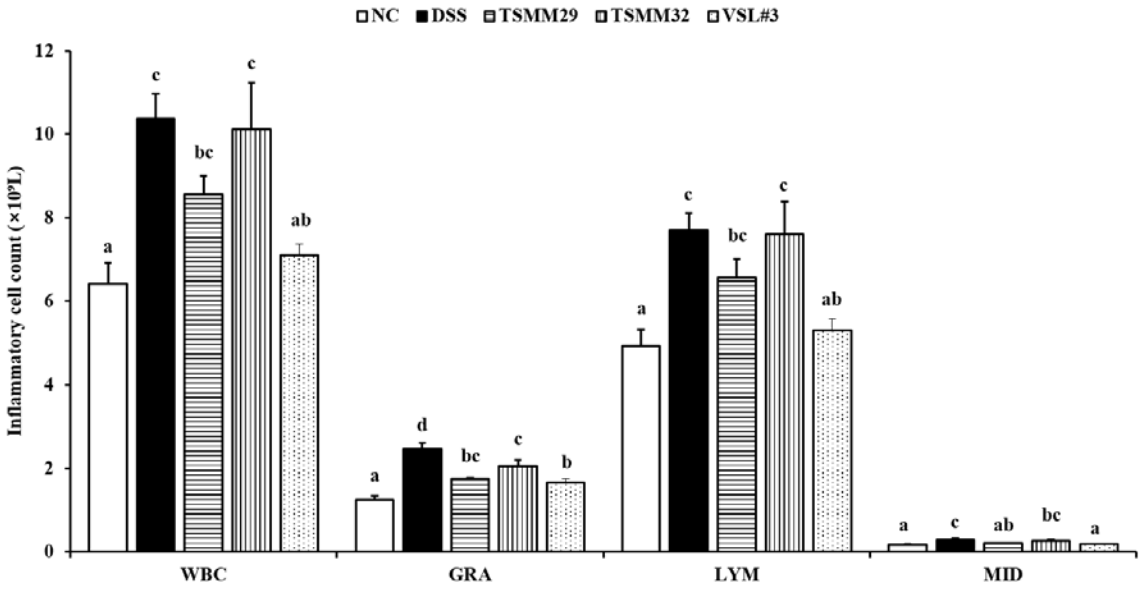

Figure 2. TSMM reduces inflammatory cells on DSS-induced UC. WBC, white blood cell; GRA, neutrophilic granulocyte; LYM, lymphocyte; MID, basophil, monocyte, and eosinophil; NC, normal control; DSS, 4% DSS; TSMM29, TSMM29 (250 mg/kg) + 4% DSS; TSMM32 (250 mg/kg) + 4% DSS; VSL#3, Desimone (350 mg/kg) + 4% DSS. "a," "b," "c," and "d" indicate significant difference at $p<0.05$. Data are expressed as mean±SEM

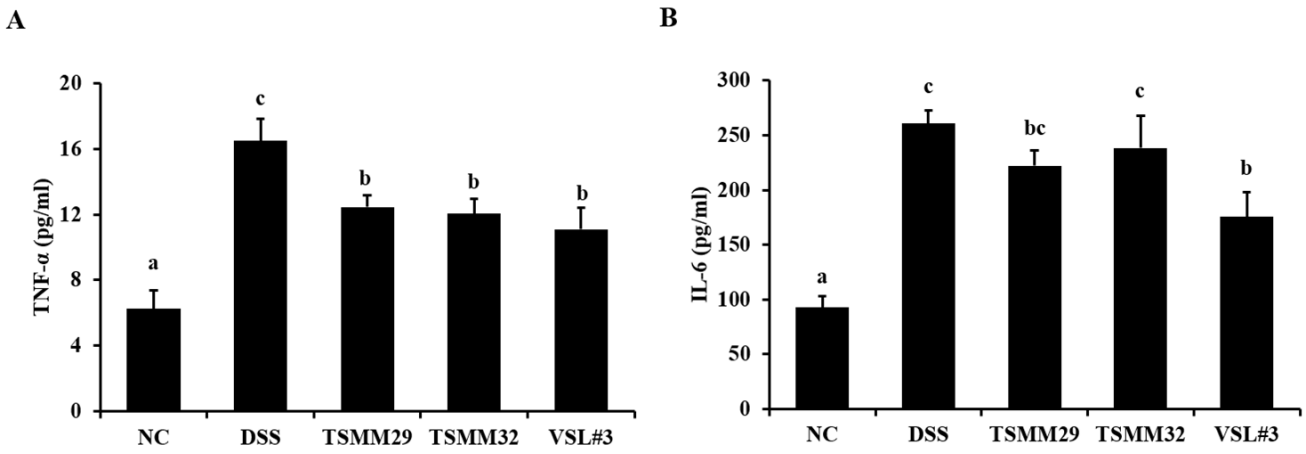

Figure 3. TSMM decrease inflammatory cytokines on DSS-induced UC. (A) TNF-α in serum, (B) IL-6 in serum. NC, normal control; DSS, 4% DSS; TSMM29, TSMM29 (250 mg/kg) + 4% DSS; TSMM32 (250 mg/kg) + 4% DSS; VSL#3, Desimone (350 mg/kg) + 4% DSS. "a, b" and "c" indicate significant difference at $p<0.05$. Data are expressed as mean±SEM

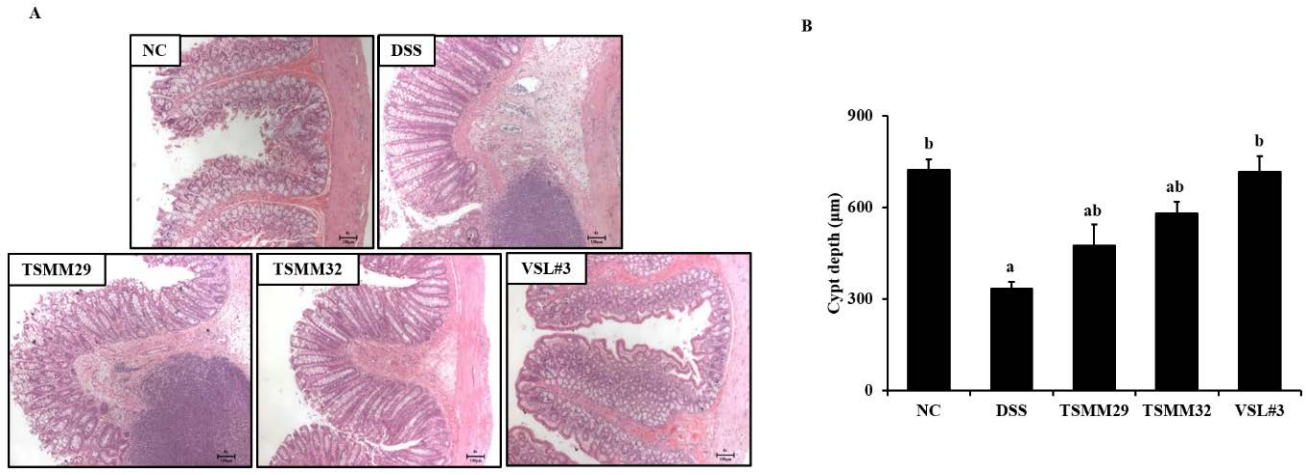

Figure 4. TSMM attenuates inflammatory response in the colon tissue of rats with DSS-induced UC. Colon tissue was stained with hematoxylin and eosin for measurement of inflammatory response. NC, normal control; DSS, 4% DSS; TSMM29, TSMM29 (250 mg/kg) + 4% DSS; TSMM32 (250 mg/kg) + 4% DSS; VSL#3, Desimone (350 mg/kg) + 4% DSS. Scale bars represent 100 μm

4. Discussion

This study was conducted to confirm the biological activity of Doenjang, a traditional Korean fermented food, according to the distribution of microorganisms to and to prove the functional excellence of Korean traditional fermented foods globally. In this study, two types of Doenjang with different distributions of microorganisms were selected, and their protective effect against UC was verified in a DSS-induced UC model. Our results confirmed that the clinical findings, inflammatory factors, and histological lesions associated with UC were recovered in the TSMM29 and TSMM32, compared with those in the DSS group. Moreover, it was suggested that Doenjang has different biological activities depending on the distribution of the microorganisms.

Previous studies have shown that Doenjang has many biological activities, such as antioxidant, anti-inflammatory, anticancer, and antidiabetic activities [26,27,28,29]. The biological activity of Doenjang is attributed to the melanoidin, isoflavones, and protein contained in soybeans, which can be increased through fermentation or aging [26,30]. In addition, the microorganisms present in Doenjang act in vivo and exhibit various biological activities [15]. Kim' study have been conducted to detect beneficial and harmful bacteria in Doenjang and to prove its biological activity [31]. These studies suggest an increase in the biological activity of Doenjang, and can prevent various diseases.

IBD is a chronic inflammatory disease caused by repetitive inflammation, and UC belongs to this disease group [32]. UC causes inflammation in the mucosa and submucosa of the large intestine, resulting in bloody stool, diarrhea, and abdominal pain [33]. The DSS-induced model used in this experiment is widely used to study UC. This model is known to exhibit inflammation caused by increasing bacteria and products in the intestine, which exert harmful effects on intestinal mucosa cells and results in symptoms similar to UC [34]. The most commonly observed clinical symptoms in DSS-induced UC model are weight loss and contraction of colon tissues [35]. In this study, to confirm the establishment of DSS-induced UC model, we assessed the general clinical symptoms and body weight. Our results revealed that compared with the NC group, the DSS group showed body weight loss, colon tissue weight loss and contraction were confirmed through autopsy. However, the TSMM29 and TSMM30 groups recovered a decrease in body weight reduced colon tissue contraction, and colon tissue weight. But, the protective effects of TSMM29 and TSMM30 against UC did not

differ, showing no variation according to the microorganism distribution. Therefore, these results indicated that Doenjang had a protective effect against UC, irrespective of the distribution of microorganisms.

Large intestine tissues are divided into four layers: mucosa, submucosa, muscularis propria, and serosa [36]. UC is caused by inflammation in the mucosa and submucosa [30]. With inflammation, inflammatory cell infiltration occurs and inflammatory cytokine levels increase [37]. In particular, IL-6 and TNF-α levels were significantly increased in patients with UC [38]. The secretion of TNF-α causes tissue damage and inflammatory diseases [39]. Previous studies have reported that the reduction of TNF-α relieves UC, and in fact, TNF-α inhibitors are used in the treatment of UC [40]. Therefore, the regulation of inflammatory cytokines is an important factor in UC. In this experiment, hematologic analysis was performed to confirm whether Doenjang administration regulates the inflammatory factors associated with UC. The results showed that the number of leukocytes increased in the DSS group, but decreased in the TSMM29 and TSMM30 groups. IL-6 and TNF-α levels also significantly increased in the DSS group compared with those in the NC group. Moreover, the secretion of inflammatory cytokines was reduced in the VSL#3 group. Similar to the VSL#3 group, both the TSMM29 and TSMM32 groups showed a significant decrease in TNF-α level compared with the DSS group. However, the decrease in IL-6 level in the TSMM groups was not significant compared with that in the DSS group.

Next, to confirm the effect of UC on histology, H&E staining was performed. The DSS-induced group showed edema and inflammatory cell infiltration in the mucosa and submucosa, as well as colon tissue injury due to destruction of goblet cells. Compared with the DSS group, the TSMM group showed recovery of the destroyed tissue as well as decreased edema and inflammatory cell infiltration. In particular, the TSMM32 group showed the highest degree of recovery. Therefore, Doenjang intake can reduce the incidence of UC by controlling the inflammatory factors that are increased in UC. Moreover, the biological efficacy of Doenjang in reducing inflammatory factors differs according to the distribution of microorganisms.

5. Conclusion

Doenjang exhibits many biological activities, but they vary owing to the different periods of manufacturing, fermentation, and maturation. In this study, we investigated the effect of Doenjang with different microorganism distributions in UC. In the DSS-induced UC model, TSMM29 or TSMM30 administration reduced the common symptoms and inflammatory factors associated with UC. Moreover, the distribution of microorganisms was proven to affect the biological activity of Doenjang. This is expected to contribute to the future development of Korean traditional fermented foods with higher biological activity, and it supports the functional excellence of Korean traditional fermented foods.

Conflict of Interests

There is no conflict of interest.

Acknowledgements

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Availability of Data and Materials

The data that support the findings of this study are included in this published article or are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The present study was approved and supervised by the the Institutional Animal Care and Use Committee of INVIVO Co., Ltd. All animal experiments carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals. Significant efforts were made in order to minimize both the number of animals used and their suffering.

Contributions of Authors

Conceived and designed the experiments: DYJ, HJY, SJJ. Performed the experiment: NRS. Analyzed the data: HYL, YMP, DYS and NRS. Contributed reagents/ materials/ analysis tool: DYJ, HYL. Wrote the paper: NRS.

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