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Research Article
Compound Xuejie Preparation Improved Dextran Sulfate Sodium-Induced Ulcerative Colitis in Mice by Mitigating Inflammation-Induced Damage and Downregulating TNF-α Expression

[1]M.M. Yajiao Zhao, [1]M.D. Lin Jin, [2]M.M. Xiaolong Yuan, [1]M.D. Xiaochuan Liu and [3]M.M. Guiming Zang

[1]Department of Gastroenterology, Emergency General Hospital, Beijing, China
[2]Department of Orthopedics, Daxing District Integrated Traditional Chinese and Western Medicine Hospital, Beijing, China
[3]Department of Health Medicine, Sixth Medical Center, General Hospital of the People's Liberation Army of China, Beijing, China

Abstract

Background and Objective: Ulcerative colitis (UC) is a chronic and refractory disease, which is closely related with inflammation. The current treatments for UC demonstrated efficacy, but followed with significant adverse reactions after long-term use. Compound Xuejie Preparation can enhance intestinal mucosal permeability through its effects on blood rheology. This study investigated the therapeutic potential of Compound Xuejie Preparation in a murine model of dextran sodium sulfate (DSS)-induced UC and its influence on TNF-α expression. **Materials and Methods:** Forty-five healthy male BALB/c mice were randomly assigned to three groups (15 mice per group) and subjected to specific treatments. Control group received normal drinking water and saline by gavage, DSS group had free access to 4% DSS and saline by gavage and DSS and Compound Xuejie Preparation Group (Experimental group) had free access to 4% DSS and Compound Xuejie Preparation (0.075 g/kg/day) by gavage. On the 11th day, specimens were collected for evaluation using the Disease Activity Index (DAI) score, histological assessment (colon tissue Hematoxylin and Eosin (H&E) staining, Histological Index, HI score) and TNF-α expression determined via ELISA. **Results:** Data showed that mice in DSS and experimental group exhibited worsened general conditions, increased DAI scores and elevated colon HI scores compared to the control groups ($p<0.05$). Moreover, the experimental group displayed a reduced degree of inflammation in colon tissue compared to the DSS group ($p<0.05$) and a significant decrease in TNF-α expression ($p<0.05$). **Conclusion:** Compound Xuejie Preparation mitigates inflammation-induced damage in mouse colon tissue and downregulates TNF-α expression, which might be effective in the treatment of UC.

Key words: Compound Xuejie, dextran sulfate sodium, inflammation, ulcerative colitis, tumor necrosis factor-α, traditional Chinese medicine

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Corresponding Author: M.D. Xiaochuan Liu, Department of Gastroenterology, Emergency General Hospital, Beijing, China Tel: 86 010 87935373
M.M. Guiming Zang, Department of Health Medicine, Sixth Medical Center, General Hospital of the People's Liberation Army of China, Beijing, China

Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Ulcerative colitis (UC) is a chronic and refractory disease characterized by ulceration and cyclic changes in the colonic mucosa. The exact cause and underlying mechanisms of UC remain unclear. The incidence of UC has been steadily increasing, currently affecting approximately 0.15-0.25% of the population[1]. The hallmark pathophysiological features of UC include ulcer formation and recurring damage to the endothelial barrier of microvessels[2-4]. These conditions manifest clinically as diarrhea, abdominal pain, malnutrition, weight loss and, in severe cases, intestinal bleeding. The UC can also lead to extra intestinal complications affecting the eyes, skin, joints and other organs.

Research has established a strong connection between UC and inflammation[5]. The UC triggers the production of TNF-α, which plays a critical role in regulating endothelial cell adhesion molecules, inducing the migration of white blood cells and generating harmful reactive oxygen metabolites, ultimately causing damage to the intestinal mucosa[6]. While existing treatments for UC, such as the 5-aminosalicylic acid class, glucocorticoids and immunomodulatory agents, have demonstrated efficacy, they are often associated with drug tolerance after long-term use and significant adverse reactions[7]. Therefore, there is a pressing need for the development of new therapeutic approaches.

Compound Xuejie Preparation, known for its hemostatic and blood circulation-promoting properties, holds promise as a potential treatment for UC. This preparation can enhance intestinal mucosal permeability through its effects on blood rheology, potentially improving the repair process and alleviating clinical symptoms associated with UC[8-10]. Further research and clinical studies are essential to fully understand the therapeutic potential of Compound Xuejie Preparation and its role in managing UC, offering hope for more effective and better-tolerated treatment options for this challenging condition.

In the realm of gastrointestinal research, the dextran sodium sulfate (DSS)-induced murine model of UC stands as a frequently employed experimental framework for investigating the underlying mechanisms that drive the pathogenesis of UC. This model hinges on the administration of DSS to laboratory mice via their drinking water. The DSS, a chemical agent, disrupts the integrity of the colonic epithelial barrier, precipitating mucosal damage and subsequent inflammation within the colon. Researchers can modulate the severity of UC-like symptoms in these mice-such as diarrhea, weight loss and colonic tissue inflammation-by adjusting the concentration and duration of DSS exposure[11,12].

The DSS-induced UC mouse model serves as a pivotal platform for in-depth exploration across several dimensions of UC research. Firstly, it facilitates the dissection of the intricate inflammatory mechanisms underpinning UC, encompassing the intricate dynamics of inflammatory cytokine production, immune cell infiltration and tissue damage. Secondly, this model lends itself to rigorous evaluation of prospective therapeutic agents or interventions designed to mitigate UC symptoms and attenuate inflammation, allowing for a systematic assessment of drug efficacy, dietary interventions, or alternative treatments. Additionally, it provides a conduit for investigating the genetic and molecular factors contributing to susceptibility and progression in UC. Lastly, researchers exploit this model to delve into the immunological intricacies governing UC, offering insights into the interplay between the immune system and gut mucosa during the course of inflammation[13,14].

This research employs DSS to induce a murine model of UC in BALB/c mice. Subsequently, the study assesses the impact of treatment with Compound Xuejie Preparation on the expression levels of TNF-α within the colon tissue. The determination of TNF-α expression serves as the primary research parameter, providing a fundamental experimental foundation for understanding the potential therapeutic effects of Compound Xuejie Preparation in the context of UC treatment.

MATERIALS AND METHODS

Study area: This study was proceeded at the Eighth Medical Center of the General Hospital of the People's Liberation Army of China in 2022.

Materials: The study utilized 45 healthy male BALB/c mice, approximately 8 weeks old, with a weight range of 18.70 to 22.89 g. These mice were procured from Beijing Vitong Lihua (License Number: 2012-0001). Additionally, the following materials and reagents were employed: Fecal occult blood test reagent from Zhuhai Beiso, Compound Xuejie Preparation composed of 2 g of Baiji and 10 g of Xuejie powder, both fully ground and obtained from the Pharmacy at the General Hospital of PLA Eighth Medical Center. The DSS (molecular weight: 36000-50000) used in the study was acquired from the American BD Company. Furthermore, the study employed a TNF-α ELISA kit also sourced from the American BD Company. Immunohistochemical staining was conducted using PV-6001 goat anti-rabbit and DAB kit from Zhushan Jinqiao Bio, along with anti-TNF-α/HRP rabbit anti-mouse antibodies from Boaosen Bio. Microscopic observations were made using an Olympus BX51 microscope.

Ethical consideration: The study was proceeded in compliance with the Ethics Guidelines of Animal Fairwell and Care.

Establishment of acute UC model in 4% DSS-induced mice: In accordance with the protocol outlined by He *et al.*[15], a cohort of healthy male BALB/c mice was randomly divided into three distinct groups: Control group (+saline group), DSS Group (the DSS-induced UC+saline group) and Experimental Group (the DSS-induced UC+Xuejie preparation group), with each group consisting of 15 mice. The mice were housed under controlled laboratory conditions, maintaining a standard temperature of 23±2°C and a light-dark cycle of 12 hrs each, allowing all mice to acclimatize to their environment for a period of 7 days.

On the 8th day of the experiment, the mice in the control group were provided with unrestricted access to distilled water for drinking and each mouse received a daily gavage of 1 mL of saline between 08:00 and 08:30. In DSS Group, the mice were granted free access to a 4% DSS solution as their drinking source and they also received a daily gavage of 1 mL of saline at the same time. The mice in the experimental group, following the same regimen as DSS group, had free access to a 4% DSS solution for drinking but received a daily gavage of 1 mL of Compound Xuejie Preparation at a dose of 0.075 g/kg/day concurrently.

Following the above-described procedure, the mice in each group were continuously exposed to their respective treatments for a duration of 10 days. At the end of this period, mice in the control group exhibited no signs of bloody stools and fecal occult blood tests returned negative results. In contrast, mice in DSS group displayed evident bloody stools and fecal occult blood tests were positive, confirming the successful induction of the UC model. Subsequently, on the 11th day, tissue specimens were collected for further analysis and evaluation.

Specimen collection: The procedures adhered to strict ethical guidelines for animal experimentation. Blood collection involved harvesting mouse eyeballs under controlled low-temperature conditions to obtain blood samples. Subsequently, the collected blood was left undisturbed and then subjected to low-temperature centrifugation (4°C, 3000 r/min) for 10 min, with resulting serum stored in individual EP tubes at -20°C for subsequent Enzyme-Linked Immunosorbent Assay (ELISA) analysis. To ensure human treatment, cervical dislocation was performed for euthanasia. Specimen collection involved opening the abdominal cavity along the midline to access the cecum, with the colon carefully extracted, visually examined and longitudinally incised along the mesentery. The tissue was rinsed with chilled (4°C) saline solution, dried using filter paper and a portion designated for fixation. This tissue was preserved in formalin, followed by paraffin embedding and pathological sectioning for histological analysis. These procedures were conducted in strict accordance with ethical standards to ensure the welfare of research animals and the collection of reliable study data.

Observation indicators and scoring methods: The well-being of the experimental mice was meticulously monitored on a daily basis, with a focus on three key parameters: Weight changes, stool characteristics and the presence of fecal occult blood. Each parameter was assigned a specific score to provide a comprehensive understanding of the mice's condition. A score of 0 indicated no weight loss, while higher scores reflected increasing levels of weight loss, categorized as 1-5%, 6-10%, 11-15% and 15% or more. Stool characteristics were rated on a scale of 0 for normal, 2 for loose stools and 4 for diarrhea. Fecal blood presence was scored as 0 for no occult blood, 2 for occult blood detected and 4 for visible blood in stools. The disease activity index (DAI) total score, calculated as one-third of the sum of the individual scores for weight loss, stool characteristics and fecal blood, provided a comprehensive and descriptive assessment of the overall health status of the experimental mice, with higher DAI scores indicating a greater degree of disease activity associated with UC[7].

Colon tissue HE staining picture and histopathology (histological, HI) score: Histopathological evaluation was conducted using HE staining under a pathology microscope and a HI scoring system was employed to assess various aspects of tissue pathology[16]. The scoring criteria were as follows: For the severity of inflammation, a score of 0 represented the absence of inflammation, while scores of 1, 2 and 3 indicated increasing levels of inflammation from mild to severe. In terms of the depth of inflammation, a score of 0 indicated no inflammation beyond the mucosal layer, while scores of 1, 2 and 3 signified inflammation extending into the mucosa, both mucosa and submucosa and the full tissue layer, respectively. Lastly, crypt damage was assessed with a score of 0 denoting no crypt damage, a score of 1 representing damage limited to the basal third of the crypt, a score of 2 indicating damage extending into the basal two-thirds and a score of 3 signifying the complete disappearance of the crypt structure. These scoring criteria collectively facilitated a

comprehensive evaluation of inflammation severity, depth and crypt damage in the examined colon tissue samples, yielding valuable insights into histopathological changes associated with the experimental conditions.

ELISA method detects TNF-α expression level in serum: The ELISA assay was performed following the kit's instructions, involving coating the plate wells with the target antigen or capture antibody, adding samples, introducing an enzyme-labeled antibody, applying a substrate color-developing solution, terminating the reaction with a termination solution and finally, determining the optical density (OD) values. These steps collectively allowed for the quantitative assessment of the target antigen concentration in the samples, yielding essential data for the study or diagnostic purposes.

Statistical analysis: The statistical analysis of the data was conducted using SPSS version 20.0 software. The distribution of continuous variables is presented as Mean±Standard Deviation (SD) and was assessed by one-way ANOVA followed by a Student-Newman-Keuls *post hoc* test and $p<0.05$ were considered statistically significant.

RESULTS

General condition of mice and observation of colon specimens: In the control group, the mice exhibited a state of relative activity, characterized by a healthy fur glossiness, consistent and vigorous breathing, active foraging behavior and the presence of dark brown, well-formed granular feces devoid of mucus and pus. However, in DSS group, a notable shift in behavior was observed as early as the third day of the experiment. Mice in this group displayed signs of fatigue, curling up, reduced mobility, marked drowsiness, a significant decrease in food consumption, a gradual decline in body weight, diminished fur quality and a change in fecal consistency characterized by softer stools with visible mucus and pus adhering to the fecal surface. Their breathing patterns were irregular, alternating between breath-holding and panting. Macroscopic examination of the colon revealed distinct differences between the two groups. In the control group (Fig. 1a), colon specimens exhibited minimal edema, resembling normal colon tissue. In contrast, all colon specimens from DSS group displayed conspicuous edema and contraction, affecting the distal colon and rectum, as depicted in Fig. 1b.

Table 1 presented a comparison of the observed indicators in different mouse groups. In the control group, the average colon length measured 9.13±0.34. In contrast, the DSS group exhibited a notably shorter average colon length of 6.05±0.47, which was significantly different from the normal group ($p<0.001$). Following DSS induction, the mice treated with Compound Xuejie Preparation displayed an average colon length of 8.4±0.78, which was significantly longer than that of the DSS-induced group ($p<0.001$). These findings indicated that the DSS-induced mouse model of UC led to a significant reduction in colon length and treatment with Compound Xuejie Preparation resulted in a substantial improvement in colon length. In the control group, the average mouse body weight was 22.66±0.85, with a corresponding DAI score of 0.8±1.01. In the DSS group, there was a significant decrease in average mouse body weight to 17.30±1.93 ($p<0.001$) and a notably elevated DAI score of 7.6±1.12 ($p<0.001$). Following DSS induction and treatment with Compound Xuejie Preparation, the average mouse body weight in the experimental group improved to 19.48±1.54 ($p<0.001$) and the DAI score showed a marked decrease to 2.47±1.68 ($p<0.001$). These results demonstrate that in the DSS-induced mouse model of UC, the DSS-induced group experienced a significant reduction in body weight accompanied by a substantial increase in DAI scores. However, treatment with Compound Xuejie Preparation led to a marked improvement in body weight and a lower DAI score, indicating the therapeutic effect of Compound Xuejie Preparation.

In terms of fecal characteristics, mice in the control consistently produced dry and hard granular feces, with no observable presence of bloody stools and their fecal occult blood tests yielded negative results. However, by the third day of the experiment, some mice in DSS group began to exhibit positive or weakly positive fecal occult blood test results. By the 4th day, all mice in DSS group displayed positive fecal occult blood and their feces lost their usual consistency, adhering to the anal area. By the 6th day, noticeable redness and swelling appeared around the anus of mice in this group, accompanied by visible bloody stools, pasty feces and adherence of feces to the perianal region. The performance of the experimental group fell between that of the control group and DSS group.

Colon HE pathological images and HI score: In the colon HE pathology of DSS group, infiltration of neutrophils and lymphocytes can be seen and defects appear in the mucosa and submucosa layer, with ulceration and crypt abscess formation. The mice in the control group were not obvious, while those in the experimental group were lighter (Fig. 2). The histological inflammation (HI) score was performed based on the degree of pathological inflammation and depth in

Fig. 1(a-b): Macroscopic examination of the colon from the control group and DSS group, (a) In the control group, colon specimens exhibited minimal edema, resembling normal colon tissue and (b) In contrast, all colon specimens from DSS Group displayed conspicuous edema and contraction, affecting the distal colon and rectum

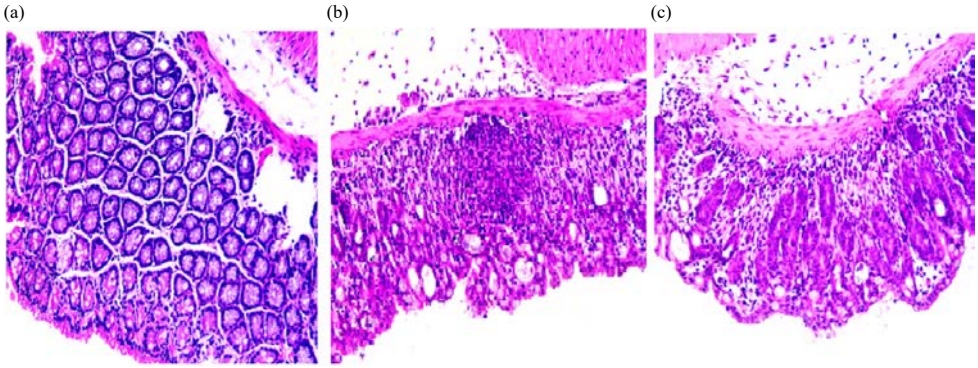

Fig. 2(a-c): Colon HE pathological images (×200), (a) Control group, showing no significant abnormal features, (b) Experimental group, displaying some abnormal features but lighter than the model group and (c) Model group, exhibiting infiltration of neutrophils and lymphocytes, defects in the mucosa and submucosa layers and ulcer formation

Table I: Comparison of mouse colon lengths

Parameters	Normal	DSS	DSS+Compound Xuejie Preparation	p-value$_1$	p-value$_2$
Colon length (cm)	9.13±0.34	6.05±0.47	8.4±0.78	<0.001*	<0.001*
Weight (g)	22.66±0.85	17.30±1.93	19.48±1.54	<0.001*	<0.001*
DAI score	0.8±1.01	7.6±1.12	2.47±1.68	<0.001*	<0.001*
HI score	0.53±0.64	7.40±0.51	4.07±0.88	<0.001*	<0.001*
TNF-α expression level (pg/mg)	3.40±0.58	118.42±6.09	30.70±3.22	<0.001*	<0.001*

p-value$_1$: DSS group vs normal group, p-value$_2$: DSS group vs DSS+Compound Xuejie Preparation group and *p<0.05

mice. The average HI score in the control group was 0.53±0.64. In the DSS group, the HI score significantly rose to 7.40±0.51 (p<0.001, Table 1). Following DSS induction and treatment with Compound Xuejie Preparation, the HI score notably decreased to 4.07±0.88 (p<0.001, Table 1) in the mice of the experimental group. These findings demonstrate that in the DSS-induced mouse model of UC, the DSS-induced group exhibited a substantial increase in HI scores, while treatment with Compound Xuejie Preparation led to a marked reduction in HI scores, indicating the therapeutic effectiveness of Compound Xuejie Preparation. This scoring system allowed for a standardized assessment of the severity of histopathological changes in the colon tissue samples from different groups.

ELISA detection of TNF-α expression: The expression levels of TNF-α in different mouse groups was measured in pg/mg using the ELISA method (Table 1): In the control group, mice displayed a TNF-α expression level of 3.40±0.58. In contrast, the DSS group exhibited a significant elevation in TNF-α expression, reaching 118.42±6.09 ($p<0.001$). However, following DSS induction and treatment with Compound Xuejie Preparation, the TNF-α expression level markedly decreased to 30.70±3.22 ($p<0.001$). These findings emphasized that in the DSS-induced mouse model of UC, the DSS-induced group experienced a substantial increase in TNF-α expression, while treatment with Compound Xuejie Preparation led to a significant reduction in TNF-α expression, highlighting the therapeutic effectiveness of Compound Xuejie Preparation.

DISCUSSION

The UC is a chronic, recurrent and refractory inflammatory disease caused by various factors such as infection, immunity, environment and genetics acting on the intestine[10]. The etiology is complex and mainly invades the mucosa and submucosa of the colon. As far as UC modeling is concerned, the acute mouse UC model induced by DSS has been recognized at home and abroad. The clinical symptoms and pathological changes are similar to human UC.

Compound Xuejie Preparation is a type of traditional Chinese medicine, mainly composed of ingredients such as dragon's blood, *Panax notoginseng* and borneol[9,10]. The preparation has the effects of promoting blood circulation to remove blood stasis and relieving pain. In some studies, Compound Xuejie Preparation has shown significant effects in promoting wound healing and tissue repair. In addition, it is also used to treat heart blood stasis syndrome, which is characterized by chest tightness and pain, fixed and immovable, worse at night, sometimes palpitations and restlessness, dark purple tongue and deep pulse[9,10].

Our previous research shows that Compound Xuejie Preparation (composed of Xuejie and Baiji) can down-regulate the ability of dendritic cells to present antigens[17], up-regulate anti-inflammatory factors, down-regulate pro-inflammatory factors, achieve good clinical efficacy while having fewer adverse reactions and no serious adverse reactions occur[18]. In this study, compared with DSS group, the clinical manifestations of mice in the experimental group were significantly reduced and the scores were lower. The main clinical manifestations of mice in DSS group were hematochezia, decrease in body mass, high DAI and HI scores, etc., but mice in the experimental group had lighter hematochezia, less obvious decrease in body mass, lower DAI and HI scores. These results indicate that Compound Xuejie Preparation plays a certain role in the treatment of UC.

Studies have confirmed that TNF-α is a pro-inflammatory cytokine with a wide range of effects. It plays an important role in the cascade reaction of UC inflammation. It can be expressed in the early stage of UC and its expression level is positively correlated with the disease[10]. Research on inflammatory cytokines can further explore the treatment methods of UC[8,19,20]. The UC can cause inflammatory cell infiltration and then produce inflammatory factors, chemokines, adhesion molecules, active oxygen components, etc., combined with inflammatory cells and immune cells to induce inflammation in intestinal tissues[21]. The TNF-α plays a core role in inflammatory cytokines. It may regulate the expression of key proteins in tight junction structures such as claudin and occludin to destroy the mucosal barrier, leading to intestinal wall rupture, disease progression, vicious cycle, leading to disease occurrence[22]. In this study, through ELISA method, it was found that the expression level of TNF-α in DSS group mouse tissue was significantly increased. Compared with the control group and the experimental group respectively, the difference was significant. This indicates that acute UC mice induced by DSS have increased expression of inflammatory factor TNF-α. After gavage treatment with Compound Xuejie Preparation, its inflammatory factor expression significantly decreased. This indicates that Compound Xuejie Preparation can improve UC inflammation.

While the DSS-induced UC mouse model is widely used and has many advantages, it also has several limitations[23-25]: Variable colonization: The model can exhibit variable colonization, which can affect the severity of colitis and the outcome of experiments. Strain background: The selection of strain background strongly affects the severity of colitis. For example, C57BL/6 mice develop more severe colitis than BALB/c in response to DSS treatment. Germ-free conditions: The germ-free conditions needed before induction are hard to control. Microbial characteristics: The microbial characteristics of DSS-triggered colitis require further clarification. These limitations should be taken into account when designing and interpreting experiments using this model.

CONCLUSION

The DSS induced acute UC model is mature and widely recognized both domestically and internationally, with clinical manifestations similar to human UC similarity. Traditional Chinese medicine and plant extracts are currently hot topics in the treatment of UC. The TNF-α plays an important role in

inflammation. The DSS group mice treated with Compound Xuejie Preparation in this study showed the mitigation of inflammation-induced damage in mouse colon tissue and the downregulation of TNF-α expression, which suggested that the Compound Xuejie Preparation plays an important role in the treatment of UC. Post treatment TNF-α content, specific therapeutic regulatory mechanisms and the effectiveness of compound blood dragon preparations. Further research is needed on the active ingredients.

SIGNIFICANCE STATEMENT

The UC is a chronic disease closely related with inflammation. The TNF-α plays an important role in inflammation. This study aimed to assess the impact of Compound Xuejie Preparation on the expression levels of TNF-α within the colon tissue in DSS-induced rat model. The mitigation of inflammation-induced damage in mouse colon tissue was observed and the downregulation of TNF-α expression was recorded. This study provided a fundamental experimental foundation for understanding the potential therapeutic effects of Compound Xuejie Preparation in the context of UC treatment. Further study can focus on the *in vivo* study and clinical trials of Compound Xuejie Preparation in humans with UC to further validate the therapeutic efficacy of Compound Xuejie Preparation.

REFERENCES

1. Halpin, S.J. and A.C. Ford, 2012. Prevalence of symptoms meeting criteria for irritable bowel syndrome in inflammatory bowel disease: Systematic review and meta-analysis. Am. J. Gastroenterol., 107: 1474-1482.
2. Chidlow, J.H., J.J.M. Greer, C. Anthoni, P. Bernatchez and C. Fernadez-Hernando *et al*., 2009. Endothelial caveolin-1 regulates pathologic angiogenesis in a mouse model of colitis. Gastroenterology, 136: 575-584.E2.
3. Liu, Y., X.Y. Wang, X. Yang, S. Jing, L. Zhu and S.H. Gao, 2013. Lung and intestine: A specific link in an ulcerative colitis rat model. Gastroenterol. Res. Pract., Vol. 2013. 10.1155/2013/124530.
4. Lukin, D., D. Faleck, R. Xu, Y. Zhang and A. Weiss *et al*., 2022. Comparative safety and effectiveness of vedolizumab to tumor necrosis factor antagonist therapy for ulcerative colitis. Clin. Gastroenterol. Hepatol., 20: 126-135.
5. Saltzman, K., L.J. Rossoff, H. Gouda and S. Tongia, 2001. Mesalamine-induced unilateral eosinophilic pneumonia. Am. J. Roentgenol., 177: 257-257.
6. Slavchev, G., A. Dacheva, Y. Vutova, S. Djambazov and T. Vekov, 2020. PGI25 pharmacoeconomic evaluation of drug therapies for treatment of ulcerative colitis (UC). Value Health, Vol. 23. 10.1016/j.jval.2020.08.791.
7. Naito, Y., T. Takagi, K. Katada, K. Uchiyama and M. Kuroda *et al*., 2006. Partially hydrolyzed guar gum down-regulates colonic inflammatory response in dextran sulfate sodium-induced colitis in mice. J. Nutr. Biochem., 17: 402-409.
8. Gupta, R.A., M.N. Motiwala, U.N. Mahajan and S.G. Sabre, 2018. Protective effect of *Sesbania grandiflora* on acetic acid induced ulcerative colitis in mice by inhibition of TNF-α and IL-6. J. Ethnopharmacol., 219: 222-232.
9. Yu-Ling, S., L. Na, J. Yu-Qing, L. Chun-Jing and L. Ying, 2008. Observation on clinical efficacy and nursing of liquid compound dracorhodin enema in the treatment of pateints with ulcerative colitis. Mod. Nurs., 4: 2976-2978.
10. Xue-Ming, W., L. Nan and X. Li-Min, 2013. Meta-analysis of compound Xuejie in the treatment of ulcerative colitis [In Chinese]. Clin. J. Med. Officer, 41: 347-349.
11. Li, R., X. Huang, L. Yang, X. Liang, W. Huang, K.P. Lai and L. Zhou, 2022. Integrated analysis reveals the targets and mechanisms in immunosuppressive effect of mesalazine on ulcerative colitis. Front. Nutr., Vol. 9. 10.3389/fnut.2022.867692.
12. Park, J.I., S.M. Seo, J.H. Park, H.Y. Jeon, J.Y. Kim, S.H. Ryu and Y.K. Choi, 2018. A murine colitis model developed using a combination of dextran sulfate sodium and *Citrobacter rodentium*. J. Microbiol., 56: 272-279.
13. Jakubczyk, D., K. Leszczyńska and S. Górska, 2020. The effectiveness of probiotics in the treatment of inflammatory bowel disease (IBD)-A critical review. Nutrients, Vol. 12. 10.3390/nu12071973.
14. Perše, M. and A. Cerar, 2012. Dextran sodium sulphate colitis mouse model: Traps and tricks. J. Biomed. Biotechnol., Vol. 2012. 10.1155/2012/718617.
15. He, D., H. Wu, Y. Song, C. Wang, D. Wang and G. Wei, 2024. Se/GSH-enriched *Candida utilis* ameliorates DSS-induced colitis in mice by preventing oxidative stress and improving immune responses. Food Biosci., Vol. 58. 10.1016/j.fbio.2024.103656.
16. Park, M.Y., G.E. Ji and M.K. Sung, 2012. Dietary kaempferol suppresses inflammation of dextran sulfate sodium-induced colitis in mice. Dig. Dis. Sci., 57: 355-363.
17. Shurin, M.R., 1996. Dendritic cells presenting tumor antigen. Cancer Immunol. Immunother., 43: 158-164.
18. Nan, L., W. Xue-Ming, J. Yang, S. Yu-ling and W. Xin *et al*., 2015. Effects of resina draconis on toll-like receptor-4/nuclear factor-kappaB and dendritic cell phenotypes in colitis. Chin. J. Tissue Eng. Res., 19: 752-758.
19. Malham, M., J. James, C. Jakobsen, E. Høgdall and K. Holmstroem *et al*., 2021. The mucosal microRNA profile relates to age and severity of disease in patients with ulcerative colitis. Gastroenterology, Vol. 160. 10.1053/j.gastro.2021.01.065.

20. Sandborn, W.J., L. Peyrin-Biroulet, A.I. Sharara, C. Su and I. Modesto *et al*., 2022. Efficacy and safety of tofacitinib in ulcerative colitis based on prior tumor necrosis factor inhibitor failure status. Clin. Gastroenterol. Hepatol., 20: 591-601.E8.
21. Lichtenstein, G.R., E.V. Loftus Jr, S.C. Wei, A.O. Damião and D. Judd *et al*., 2020. DOP61 tofacitinib, an oral, small-molecule janus kinase inhibitor, in the treatment of ulcerative colitis: Analysis of an open-label, long-term extension study with up to 5.9 years of treatment. J. Crohn's Colitis, 14: S100-S101.
22. Rubin, D.T., M.C. Dubinsky, S. Danese, R. Saad-Hossne and D.P. de Leon *et al*., 2020. P653 efficacy and safety of an additional 8 weeks of tofacitinib induction therapy: Updated results of the OCTAVE open study for tofacitinib 8-week induction non-responders. J. Crohn's Colitis, 14: S537-S539.
23. Baydi, Z., Y. Limami, L. Khalki, N. Zaid and A. Naya *et al*., 2021. An update of research animal models of inflammatory bowel disease. Sci. World J., Vol. 2021. 10.1155/2021/7479540.
24. Huang, C., J. Wang, H. Liu, R. Huang and X. Yan *et al*., 2022. Ketone body β-hydroxybutyrate ameliorates colitis by promoting M2 macrophage polarization through the STAT6-dependent signaling pathway. BMC Med., Vol. 2022. 10.1186/s12916-022-02352-x.
25. Xu, H.M., H.L. Huang, Y.D. Liu, J.Q. Zhu and Y.L. Zhou *et al*., 2021. Selection strategy of dextran sulfate sodium-induced acute or chronic colitis mouse models based on gut microbial profile. BMC Microbiol., Vol. 21. 10.1186/s12866-021-02342-8.