

Exploring the Mechanism of Chang-An-Kang on Active Ulcerative Colitis Rats Based on NF- κ B/STAT3 Signaling Pathway

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Abstract

Objectives: The objective of this study was to investigate the therapeutic effect and mechanism of Chang-An-Kang on ulcerative colitis rats.

Materials and Methods: The rat model of ulcerative colitis induced by 6% glacial acetic acid was established. The corresponding therapeutic drugs were given 24 h after the model was established. The pathological morphology of colon tissue was observed after 21 days of continuous administration. The levels of interleukin-6 (IL-6), interleukin-7 (IL-7), interleukin-10 (IL-10), and tumor necrosis factor- α (TNF- α) were measured by ELISA kit. The expression levels of NF- κ B and STAT3 proteins in colon tissue were detected by IHC.

Results: The results showed that the changes in the pathological and biochemical indexes of the rat colon tissue indicate that the model was successfully established. Chang-An-Kang could significantly reduce rat colon tissue damage, decrease the content of IL-6, IL-7, and TNF- α , and increase the content of IL-10. The NF- κ B and STAT3 protein expression levels were decreased.

Conclusion: By increasing the content of anti-inflammatory factor IL-10, decreasing the content of pro-inflammatory factors IL-6 and TNF- α , and inhibiting the expression of NF- κ B and STAT3 proteins, Chang-An-Kang can reduce inflammatory infiltration. It has an obvious therapeutic effect on acetic acid ulcerative colitis in rats.

Chang-An-Kang, ulcerative colitis, NF- κ B, STAT3, immunohistochemistry,

Keywords

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Introduction

Ulcerative colitis (UC) is a chronic inflammatory disease of the rectum and colon with unknown etiology. It is usually bloody diarrhea or purulent blood stool. It may have paroxysmal spastic colic in the left lower abdomen or lower abdomen, occasionally nausea, vomiting, epigastric discomfort, fever, and other symptoms.¹ At present, there is no effective medicine prevention and treatment for the etiology of UC. The clinical treatment of UC is still based on salicylic acid and sulfasalazine. However, the high recurrence rate limits its widespread use in UC patients.^{2,3}

Chang-An-Kang is composed of *Pulsatilla chinensis*, *Coptisine*, *Phellodendron amurense*, *Atractylodes macrocephala*, *Astragalus membranaceus*, *Poria cocos*, *Panax notoginseng*, and *Halloysitum rubrum*. It has the effect of clearing heat, promoting diuresis, and invigorating spleen.⁴ Clinical application of Chang-An-Kang has significant efficacy in the treatment of UC, mainly by eliminating intestinal inflammation, improving intestinal microcirculation, and accelerating the healing of ulcer surface.^{5,6}

but its potential mechanism is still unclear. This study explored the potential mechanism of Chang-An-Kang on UC based on the NF- κ B/STAT3 signaling pathway by establishing a UC rat model and provided an experimental basis for the clinical treatment of UC.

Materials and Methods

Experimental Animal

A total of 40 SPF male Wistar rats (200 $\pm$ 20g) were provided by the experimental animal center of *Heilongjiang Academy*

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of *Traditional Chinese Medicine Sciences* (license number: SYXK (H) 2016-008).

Experimental Drug

Drug

Chang-An-Kang is composed of *P. chinensis*, *Coptisine*, *P. amurense*, *A. macrocephala*, *A. membranaceus*, *P. cocos*, *P. notoginseng*, and *H. rubrum*. It is provided by the Heilongjiang Academy of Traditional Chinese Medicine.

Preparation of Drug

Chang-An-Kang is composed of *P. chinensis* (6 g), *Coptisine* (10 g), *P. amurense* (10 g), *A. macrocephala* (10 g), *A. membranaceus* (20 g), *P. cocos* (15 g), *P. notoginseng* (5 g), and *H. rubrum* (15 g). After soaking, the herbs were decocted and extracted twice. After filtration, the extract is combined and concentrated in a rotary evaporator solution (2 g/mL). After cooling, the extract was transferred into a sterilized glass vial and stored in a refrigerator at 4°C for later use.

Positive Control Drug

Sulfasalazine Tablets (SASP), Shanghai Sanwei Pharmaceutical Co., Ltd., Number: 22201203.

Experimental Reagents

The reagents used were hematoxylin-eosin (HE) staining kit (Biyuntian Biotechnology Co., Ltd.), IL-6, IL-7, IL-10, TNF- α ELISA kit (Nanjing Jiancheng Institute of Bioengineering), STAT3 Rabbit Monoclonal Antibody (Biyuntian Biotechnology Co., Ltd.), NF- κ B Rabbit Monoclonal Antibody (Biyuntian Biotechnology Co., Ltd.), and SABC-POD kit (Wuhan Boster Biological Technology Co., Ltd.).

Method

Establish UC Model

The rats were raised under conventional conditions in the laboratory. Rats were randomly divided into blank control group (BC), model control group (MC), SASP group, and Chang-An-Kang group according to body weight. Except for the rats in the BC group, the rats in each group were given 10% MgSO₄ solution by gavage, 3 mL/kg, twice/day for 3 days, and then fasted for 24 h without water deprivation. The rats were anesthetized with 2% sodium pentobarbital intraperitoneally and then fixed. The stomach needle was inserted about 8 cm from the anus (colon), and 2 mL of 6% glacial acetic acid was slowly injected into the stomach with a syringe. The rats in the BC group were injected with the

same volume of normal saline. Then 0.3 mL air was injected into the anus of rats for 1.5 h.^{7,8} After natural wakefulness, the rats in the BC and MC groups were given normal saline by gavage (10 mL/kg, once/day). The rats in the SASP group were given sulfasalazine tablets (0.5 g/kg, once/day).⁹ The rats in the Chang-An-Kang group were given experimental drugs (5.98 mL/kg, twice/day).¹⁰ After continuous administration for 21 days, during the trial, rats in each group were free to feed and drink during the experiment.

Index Detection

Colonic Histomorphology

Preparation of colon tissue paraffin sections: Rats were fasted for 24 h after the last administration. After the rats were anesthetized and killed, the whole colon (2–10 cm away from the anus) was quickly cut off. The intestinal contents were removed with normal saline. After washing with PBS solution twice, the colon was fixed in 10% formaldehyde solution. After 24 h, the colon was dehydrated in an ethanol gradient and embedded in paraffin. The thickness of the paraffin section was 5 μ m. After drying, the colon was stored in the section box for use.

Dewaxing process of dry paraffin sections: It was soaked in xylene I for 15 min, xylene II for 15 min, 100% ethanol I for 15 min, 100% ethanol II for 15 min, 95% ethanol I for 5 min, 95% ethanol II for 5 min, 80% ethanol for 5 min, 30% ethanol for 5 min, and deionized water for 10 min, then stained in hematoxylin for 4 min, washed with 1% hydrochloric acid alcohol for 5 s, washed with weak ammonia water twice, and washed with water for 10 min. After staining, the effect was observed under a microscope. Eosin staining was performed for 12 min, and then it was soaked in 80% ethanol for 5 s, 95% ethanol for 5 s, 100% ethanol I for 5 min, 100% ethanol II for 10 min, xylene I for 10 min, and xylene II for 10 min. The slides were mounted with neutral gum and observed under a microscope.

Contents of IL-6, IL-7, IL-10, and TNF- α in Colonic Tissue

Notably, 10 mg of rat colon tissue was taken, the tissue was homogenized and centrifuged at 4°C for 15 min, and the supernatant at 3000 rpm/min was taken. The contents of IL-6, IL-7, IL-10, and TNF- α in rat colon tissue were detected according to the kit steps.

Detection of NF- κ B and STAT3 Protein Expression in Colon Tissue by IHC

The pathological colon tissues (0.5 $\times$ 0.5 cm²) were taken, fixed in 10% formaldehyde solution, and prepared into paraffin sections. Three view fields were randomly selected under a 20 $\times$ microscope. The positive cell area (Area) and integrated optical density (IOD) of NF- κ B and STAT3

proteins staining in colonic tissue were analyzed by the Image-pro plus image softening method. The expression of NF- κ B and STAT3 proteins in colonic tissue was semi-quantitatively analyzed.

The expression process of NF- κ B protein in colon tissue was detected by IHC: The dried paraffin sections were dewaxed with xylene I for 15 min, xylene II for 15 min, 100% ethanol I for 15 min, 100% ethanol II for 15 min, 95% ethanol I for 5 min, 95% ethanol II for 5 min, 80% ethanol for 5 min, 30% ethanol for 5 min, and deionized water for 10 min. The deparaffinized sections were washed with PBS solution for 3 min for three times, the residual PBS was removed by suction, non-immune serum solution was added, and they were incubated for 10 min (room temperature). The blocking solution was sucked. Sufficient antibody was added with a concentration of 1:500 to the sections, and they were incubated overnight at 4°C in a wet box. They were washed with PBS for 3 min for three times, the residual PBS was removed by suction, enough biotin-labeled goat anti-rabbit was added with a concentration of 1:1000, and they were incubated for 10 min (room temperature). They were washed with PBS for 3 min for three times, residual PBS was removed by suction, streptavidin-peroxidase was added, and they were incubated for 10 min (room temperature). They were washed with PBS for 3 min for three times, the residual PBS was absorbed, DAB chromogenic solution was added in the dark, they were rinsed with deionized water, the staining degree was observed under the microscope, and the nucleus was stained with hematoxylin for 2 min, washed with weak ammonia blue and deionized water, dehydrated with gradient ethanol and xylene according to the reverse order of dewaxing, and mounted in neutral resin after drying under the microscope observation photos.

The IHC method was used to detect the expression of STAT3 protein in colon tissue, which was the same as that of NF- κ B protein.

Statistics

The experimental data were expressed as $\bar{x} \pm s$. The *t*-test was used to analyze the significant difference between the two groups ($p < 0.01$).

Results

Effects on the Pathological Morphology of Colon Tissue

Compared with rats in the BC group, rats in the MC group showed significant colon tissue edema and severe damage. SASP and Chang-An-Kang had varying degrees of improvement effects on the above indicators, and Chang-An-Kang had a more significant improvement effect. Under the light microscope, the mucosal epithelial cells of the colon tissue of the BC group rats

were intact, the glands were arranged neatly, and the structure was clear. The mucosal epithelium of the colon tissue in the MC group of rats was detached, damaged, and erosive, with inflammatory granulocyte infiltration and cellulose-like exudation, accompanied by necrosis and ulceration. The mucosal epithelial shedding of the colon in SASP group rats was reduced, and inflammatory granulocytes were reduced. The colon tissue of rats in the Chang-An-Kang group showed a reduction in intestinal mucosal epithelial detachment and defect, repair of epithelial hyperplasia of the surrounding intestinal mucosa, significant reduction of the ulcer area, and proliferation of granulation tissue, showing significant improvement. The results are shown in Figure 1A–D.

Levels of IL-6, IL-7, IL-10, and TNF- α in Colon Tissue

Compared with the BC group, the contents of IL-6, TNF- α , and IL-7 in the colon tissue of the MC group were significantly increased ($p < 0.01$), and the contents of IL-10 were significantly decreased ($p < 0.01$). SASP and Chang-An-Kang had different effects on the above indexes, and Chang-An-Kang had more obvious effects. The results are shown in Table 1.

Expression of NF- κ B and STAT3 Proteins in Colon Issue

Compared with the BC group, the expression of NF- κ B protein in the MC group increased, which showed that the Area of positive cells and the IOD of NF- κ B protein were increased ($p < 0.05$). SASP and Chang-An-Kang decreased the expression of NF- κ B protein, which showed that Area and IOD decreased. Chang-An-Kang had a significant effect on reducing Area ($p < 0.01$) and IOD ($p < 0.05$). SASP could decrease Area ($p < 0.05$) and IOD, but the difference was not significant. The results are shown in Figure 2A–D and Table 2.

Compared with the BC group, the expression of STAT3 protein in the colon of the MC group was decreased, which showed that STAT3 protein Area ($p < 0.05$) and IOD were decreased, but there was no significant difference between the MC and BC groups. SASP could increase the expression of STAT3 protein and Area ($p < 0.01$) and IOD ($p < 0.05$). The expression of STAT3 protein was decreased in Chang-An-Kang, which showed a significant decrease in Area and IOD ($p < 0.01$). The results are shown in Figure 3A–D and Table 2.

Discussion

The occurrence and development of UC is a very complex biological phenomenon involving multiple genes and multiple factors. The study of the NF- κ B/STAT3 signaling pathway provides a large number of favorable and reliable evidence for the pathogenesis of UC.¹¹ Intervening the key factors of the NF- κ B/STAT3 signaling pathway and then blocking the excessive inflammatory response of UC has become a hot spot in the treatment of UC.¹²

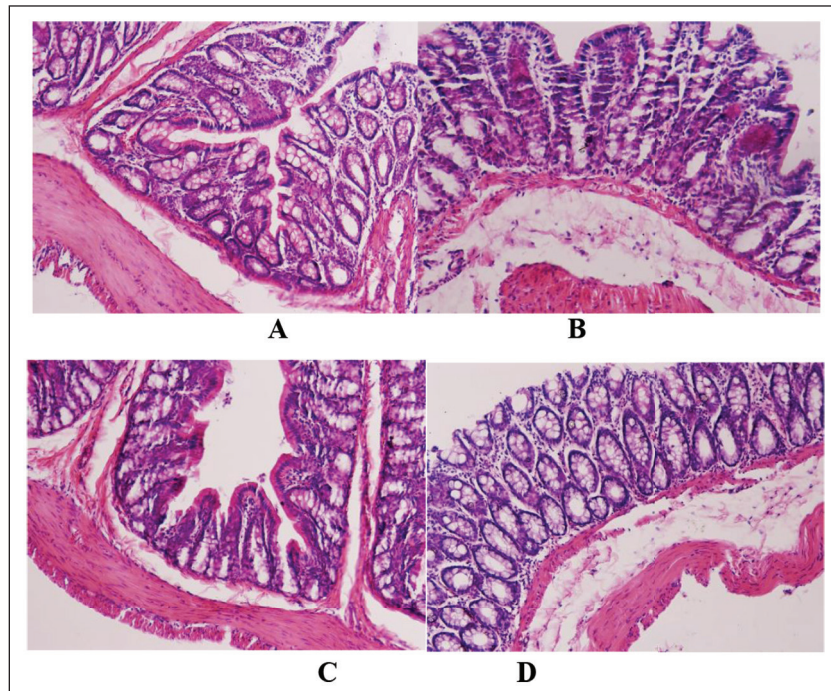


Figure 1. Effects on the Pathological Morphology of Colon Tissue. (A) BC group, (B) MC group, (C) SASP group, and (D) Chang-An-Kang group.

Table 1. Effects of Chang-An-Kang Oral Administration on IL-6, IL-7, IL-10, and TNF- α in UC rats ($\bar{x} \pm s$).

Group (n = 10)	IL-6/ $\text{pg}\cdot\text{mL}^{-1}$	IL-7/ $\text{pg}\cdot\text{mL}^{-1}$	IL-10/ $\text{pg}\cdot\text{mL}^{-1}$	TNF- α / $\text{ng}\cdot\text{mL}^{-1}$
BC	60.47 $\pm$ 1.39	30.08 $\pm$ 1.10	184.98 $\pm$ 12.57	203.68 $\pm$ 5.54
MC	132.02 $\pm$ 28.93	46.80 $\pm$ 2.12	121.84 $\pm$ 11.38	270.83 $\pm$ 29.77
SASP	68.30 $\pm$ 2.27	33.75 $\pm$ 5.23	156.43 $\pm$ 1.21	222.12 $\pm$ 2.64
Chang-An-Kang	67.05 $\pm$ 3.71	31.70 $\pm$ 5.50	157.31 $\pm$ 18.39	212.10 $\pm$ 18.40

Table 2. Expression of Chang-An-Kang Oral Administration on the Levels of NF- κ B and STAT3 in UC rats ($\bar{x} \pm s$).

Group (n = 10)	NF- κ B		STAT3	
	Area	IOD	Area	IOD
BC	526874.20 $\pm$ 58153.32	147802.48 $\pm$ 21701.98	568483.33 $\pm$ 74242.42	145787.56 $\pm$ 14574.71
MC	546851.00 $\pm$ 42671.58	160984.12 $\pm$ 15447.95	528955.33 $\pm$ 46923.02	142400.99 $\pm$ 13563.47
SASP	508467.00 $\pm$ 67652.45	152226.50 $\pm$ 22011.55	592206.17 $\pm$ 63643.41	165324.43 $\pm$ 14803.46
Chang-An-Kang	487083.67 $\pm$ 85654.28	152452.90 $\pm$ 35844.72	432446.83 $\pm$ 35957.01	128814.15 $\pm$ 9880.71

During UC inflammation, activation of both NF- κ B and STAT3 is stimulated by various extracellular signals, and regulation of NF- κ B involves target gene expression of tumor proliferation, apoptosis, infiltration, metastasis, and angiogenesis. NF- κ B target genes, such as IL-6, are also important activators of STAT3.^{13,14} STAT3 can directly affect P65, a member of the NF- κ B family, to keep it in the nucleus and inhibit its negative feedback regulatory pathway.^{15,16} Recent studies have shown that NF- κ B is involved in the regulation of cytokines such as TNF- α , IL-6, IL-10, and IL-17 at the transcriptional level.^{17,18} IL-6 is a multifunctional, multipotent glycosylated protein factor that binds specifically

to the target cell surface receptor, participates in the local inflammatory response, and also regulates the immune response.¹⁹ Activation of NF- κ B via the STAT-3 pathway induces polarized expression of cell adhesion molecule (ICAM-1), and phosphorylated STAT dissociates from the receptor when the cell is stimulated by the signal. they enter the nucleus in the form of homogenous or heterodimerization and multimerization, bind specifically to DNA target sequences, regulate the expression of corresponding genes, and complete the whole process of cytokine-mediated signal transduction.²⁰ The role of IL-6 in acute inflammatory response is mainly manifested as pro-inflammatory effect on

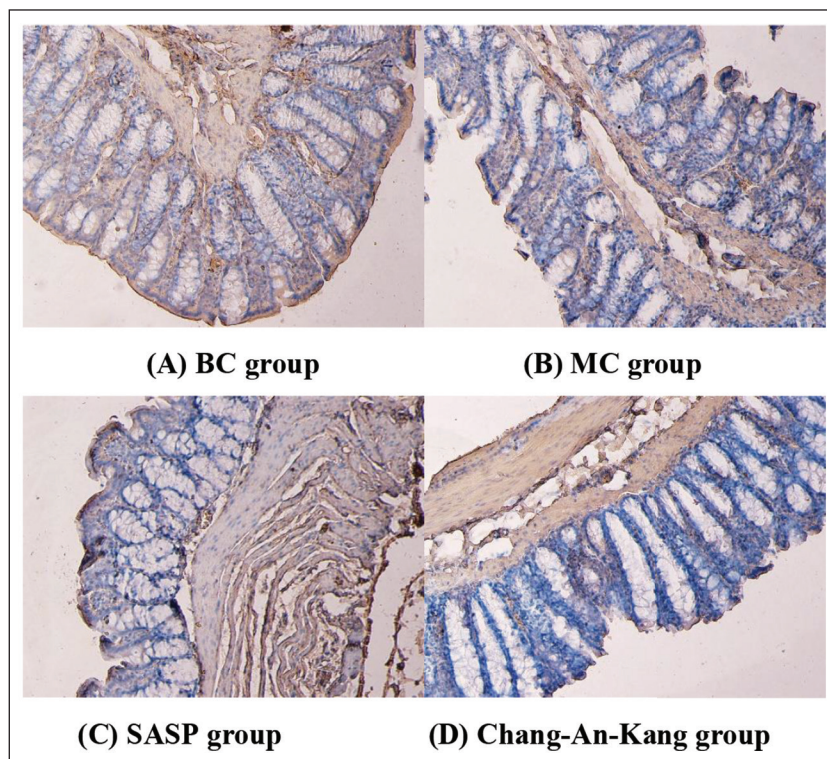


Figure 2. Expression of NF- κ B Protein in Colon Tissue. (A) BC group, (B) MC group, (C) SASP group, and (D) Chang-An-Kang group.

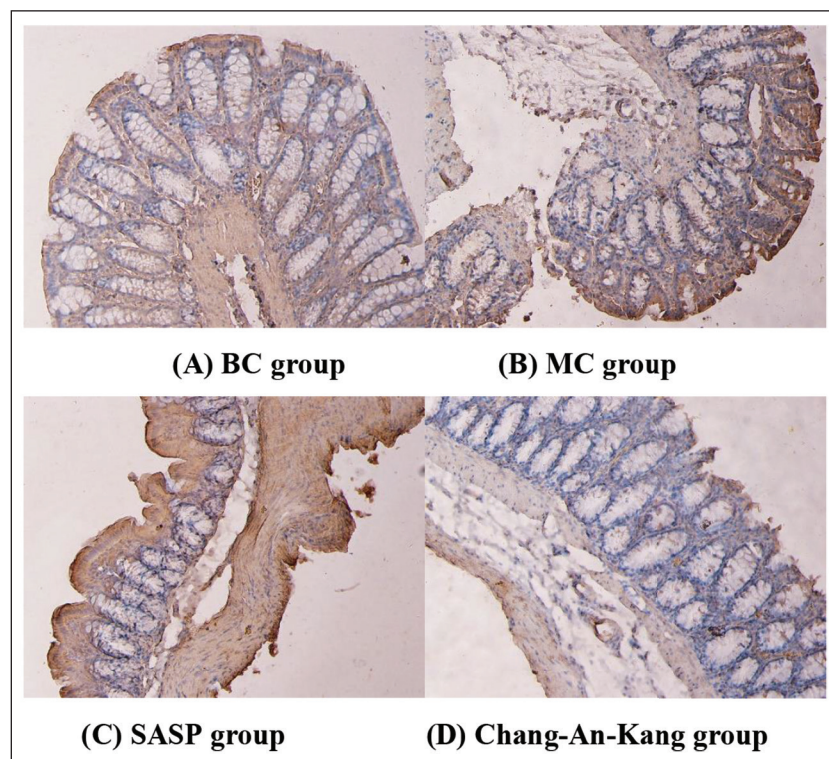


Figure 3. Expression of STAT3 Protein in Colon Tissue. (A) BC group, (B) MC group, (C) SASP group, and (D) Chang-An-Kang group.

various cells, induction of acute response protein in liver tissue, promotion of electrolyte secretion of intestinal epithelial cells, increase of permeability of endothelial cells, and migration of neutrophils to inflammatory sites to cause lesions.²¹ IL-10 is an anti-inflammatory factor mainly produced by activated macrophages and monocytes, and TNF- α is a multifunctional cytokine secreted by mononuclear macrophages and activated T lymphocytes, which has the effect of promoting inflammatory response and cellular immune regulation.²² IL-10 can reduce inflammatory mediator TNF- α and inhibit antigen presentation and plays an important role in maintaining a normal intestinal non-inflammatory immune state and preventing and controlling excessive immune response under the biological activity of B cells and T cells.^{23,24} Studies have shown that mice develop spontaneous UC due to the absence of IL-10, a decrease in the anti-inflammatory factor IL-10, and an increase in the pro-inflammatory factors IL-6 and TNF- α .²⁵ IL-17 can induce the expression of innate immune inflammatory cytokines, acute response protein, granulocyte-macrophage stimulating factor (G-CSF), and prostaglandin E2 and also has a synergistic effect with TNF- α to enhance its inflammatory effect.²⁶ IL-17 induces the expression of several genes associated with inflammation, including IL-6, cell adhesion molecules, and so on.^{27–29} Studies have shown that the expression of IL-17 in intestinal mucosal tissue and serum of active UC patients is significantly higher than that of healthy people, and it gradually increases with the increase of disease activity.³⁰

In this study, we investigated the effect of Chang-An-Kang on the NF- κ B/STAT3 signaling pathway and revealed that Chang-An-Kang may inhibit the abnormal activation of STAT3 and NF- κ B signaling pathway in the treatment of UC, to maintain the dynamic equilibrium of pro-and anti-inflammatory factors, so as to control and alleviate the inflammation of colonic mucosa, protect the colonic mucosa, and provide a theoretical basis for clinical application.

Authors' Contributions

LZ conceived ideas, completed the experiments, and implemented the animal experiment. WG collected and arranged the data. CR and LY revised the article and contributed to supportive work. CX designed and funded the experiments.

Availability of Data and Material

All relevant data are contained within the article: The original contributions presented in the study are included in the article/supplementary material, and further inquiries can be directed to the corresponding author/s.

Consent for Publication

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient/

parent/guardian/ relative of the patient. A copy of the consent form is available for review by the Editor of this journal.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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Statement of Ethics Approval and Consent to Participate

This study was reviewed by the Ethics Committee of the Heilongjiang Academy of Chinese Medicine Sciences (No. 2015-64), and the experiments were conducted by the Chinese Government's "Guidelines on the Care and Use of Laboratory Animals" to minimize their suffering.

References

1. Zhendong C, Xudong T. Progress of TCM microscopic syndrome differentiation in ulcerative colitis Proceedings of the First and Fourth Academic Exchange Meeting of Digestive Endoscopy Committee of Chinese Society of Integrated Chinese and Western Medicine. Vol. 2019. Heilongjiang: Chinese Society of Integrated Chinese and Western Medicine, 2019. pp. 107–115. doi: 10.26914/c.cnkihy.2019.001268
2. Jiang X. Gastroenterology ODLZ, University MMSTOHC, et al. The features of ulcerative colitis in China. Proceedings of the Compilation of papers from the eighth International Conference on treating Endoscopic and Digestive Diseases. Hong Kong: Chinese Medical Association of digestive endoscopy society, *Hong Kong society of digestive endoscopy*, 2006. pp. 173–174.
3. Qi W, Zhang QA. Case-control study on the risk factors of ulcerative colitis. Singapore Manag Sports Sci Inst (Singapore). Proceedings of the 2018 6th ICPEM International Conference on Educational Research, Leisure, Sport and Tourism (EIST 2018) (Lecture Notes in Management Science, Vol. 105). Texas City, TX: American Applied Sciences Research Institute, Information Engineering Research Institute; 2018. pp. 339–341.
4. Hai Food Y, Hao C, Ying H, et al. Mechanism of ulcerative colitis rats. *China Pharmacol Bull* 2012; 28(2): 282–285.
5. Xiankun W, Jiayu H, Xiaohe Z, et al. Pharmacodynamic test study of intestinal Ankang Capsule. *Shaanxi Trad Chin Med* 2004; 12: 1142–1144.
6. Guoqing Y, Finland H, Shifang X, et al. 'Health kang' acute toxicity test study. *Tradit Chinese Med Forum* 2003; 1: 33–34.
7. Cai L. Replication of animal models of human disease. Vol. 7. Beijing: People's Health Publishing House; 2008. p. 282.
8. Xiaofeng Z, Peiqing S, Jiansu R, et al. Effect of Chinese medicine clearing on a rat experimental model of ulcerative colitis. *Hebei Med* 1998; 4(5): 1–3.
9. Xiankun W, Jiayu H, Jianfeng X, et al. The therapeutic effect and mechanism of intestinal Ankang capsule on ulcerative colitis in rats. *J Beijing Univ Trad Chin Med* 2004; 27(4): 31–34.
10. Hai Food Y, Hao C, Ying H, et al. Mechanism of ulcerative colitis rats. *China Pharmacol Bull* 2012; 28(2): 282–285.

11. Bannwart CF, Nakaira-Takahagi E, Golim MA, et al. Downregulation of nuclear factor-kappa B(NF- κ B) pathway by silibinin in human monocytes challenged with *Paracoccidioides brasiliensis*. *Life Sci* 2018; 86(23): 880–886.
12. Matricon J. Immunopathogenesis of inflammatory bowel disease. *Med Sci (Paris)* 2010; 26(4): 405–410. doi: 10.1051/medsci/2010264405
13. Legaki E, Gazouli M. Influence of environmental factors in the development of inflammatory bowel diseases. *World J Gastrointest Pharmacol Ther* 2016; 1: 14. doi: 10.4292/wjgpt.v7.i1.112
14. Hong L, Qun D, Rujun W. Progress in the TLRs / NF- κ B pathway and ulcerative colitis. *J Mod Integr Trad Chin West Med* 2007; 16(30): 4577–4579.
15. Xiao C. Progress in signaling of toll-like receptor 4 and ulcerative colitis. *J Gastroenterol Hepatol* 2010; 19(1): 87–89.
16. Hayden MS, Ghosh S. Shared principles in NF-kappaB signaling. *Cell* 2008; 132(3): 344–62. doi: 10.1016/j.cell.2008.01.020
17. Vallabhapurapu S, Karin M. Regulation and function of NF-kappaB transcription factors in the immune system. *Annu Rev Immunol* 2009; 27(5): 693–733. doi: 10.1146/annurev.immunol.021908.132641
18. Bidere N, Ngo VN. Casein kinase 1 α governs antigen-receptor-induced NF-kappaB activation and human lymphoma cell survival. *Nature* 2019; 458(7234): 92–96.
19. Moynagh PN. The NF-kappa B pathway. *J Cell Sci* 2005; 118(20): 4589–92. doi:10.1242/jcs.02579
20. Ke Z, Changsheng D, Youqing Z, et al. Significance of NF- κ B, COX-2, and iNOS expression in ulcerative colitis tissue. *World Chin Digest Mag* 2002; 10(5): 575–578.
21. Jatiani SS, Baker SJ, Silverman LR, et al. JAK/STAT pathways in cytokine signaling and myeloproliferative disorders approaches for targeted therapies. *Genes Cancer* 2019; 1(10): 979–993.
22. Bin L, Ning J, Song G. Effect of plum pill and its removal on IL-6 / JAK / STAT 3 signaling pathway and pathological changes of colonic mucosa in rats with ulcerative colitis. *Trad Chin Med Pharmacol Clin Pract* 2016; 32(1): 14–17.
23. Ghavami S, Eshraghi M, Kadkhoda K, et al. Role of BN IP3 in TNF-induced cell death TNF up regulates BN IP3 expression. *Biochim Biophys Acta* 2019; 1793(3): 546.
24. Pitman H, Innes BA, Robson SC, et al. Altered expression of interleukin-6, interleukin-8 and their receptors in decidua of women with sporadic miscarriage. *Hum Reprod* 2013; 28(8): 2075–2086. doi: 10.1093/humrep/det233
25. Jee SH, Chu CY, Chiu HC, et al. Interleukin-6 induced basic fibroblast growth factor-dependent angiogenesis in basal cell carcinoma cell line via JAK/STAT3 and PI3-kinase/Akt pathways. *J Invest Dermatol* 2004; 123(6): 1169–1175. doi: 10.1111/j.0022-202X.2004.23497.x
26. Zhang F, Yao S, Zhang M, et al. Roles of circulating soluble interleukin (IL)-6 receptor and IL-6 receptor expression on CD4+ T cells in patients with chronic hepatitis B. *Int J Infect Dis* 2011; 15(4): e267–271. doi: 10.1016/j.ijid.2010.12.008
27. Komiyama YS, Nakae T, Matsuki A, et al. IL-17 plays an important role in the development of experimental autoimmune encephalomyelitis. *Immunol* 2016; 177(1): 566–573.
28. Fossiez F, Djossou O, Chomarat P, et al. T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. *J Exp Med* 1996; 183(6): 2593–2603. doi: 10.1084/jem.183.6.2593
29. Chabaud M, Fossiez F, Taupin JL, et al. Enhancing effect of IL-17 on IL-1-induced IL-6 and leukemia inhibitory factor production by Rheumatoid arthritis synovial cells and its regulation by Th2 cytokines. *J Immunol* 2018; 161: 409–414.
30. Sabat R, Grutz G, Bamba S, et al. Biology of interleukin-10. *Cytokine Growth Factor Rev* 2019; 21(5): 331.