MAPAN-JOURNAL ,
Publisher: METROLOGY SOC INDIA , NPL PREMISES,
Address: DR K S KRISHNAN MARG, NEW DELHI, INDIA,
ISSN / eISSN:0970-3950 / 0974-9853
Volume 25-Issue 1-(2025)

The Mechanism of Action of Sishen Pills on Ulcerative Colitis and Colon Cancer Based on Network Pharmacology and Molecular Docking

LIU Chaoyue[1], JIN Tonghui[1], DU Yu[2], BAI Jiaqi[1], WANG Yinan[1], LI Guofeng[3*]

[1]College of Chinese Medicine, Changchun University of Chinese Medicine, Changchun, Ji Lin, 130117, China

[2]Anorectal Department, Affiliated Hospital of Changchun University of Traditional Chinese Medicine, Changchun, Ji Lin, 130021, China

[3] Anorectal Department, Shenzhen Bao'an Authentic TCM Therapy Hospital, Shenzhen, Guang Dong, 518000, China

[*]Corresponding E-mail: doctorlgf@163.com

Abstract Objective: This study aims to investigate how Sishen Pills function in the treatment of ulcerative colitis (UC) and colon cancer (CC) by utilizing network pharmacology combined with molecular docking techniques. Methods: Active components of Sishen Pills were identified, and potential targets were forecasted using resources like TCMSP databases. The disease-related targets of UC and CC were screened using Gene Cards, CTD, and TTD databases. The PPI network was established, followed by GO function enrichment and KEGG analysis of likely biological processes and signaling pathways, along with molecular docking validation. Results: In total, 94 active ingredients from Sishen Pills were identified, and 279 potential targets for the treatment of UC and CC associated with Sishen Pills were discovered, encompassing 3161 biological processes, 115 cellular components, 265 molecular functions, and 178 signaling pathways. Core active compounds such as quercetin, key target proteins such as TP53, and signaling pathways such as TNF and IL-17 were screened. The key targets all had strong binding activity with the core active compounds. **Conclusion**: Sishen Pills can play the role of "treating different diseases with the same treatment" for UC and CC through multiple components, multiple targets and multiple pathways.

Keywords: Sishen Pills, Ulcerative colitis, Colon cancer, Network pharmacology, Molecular docking

Ulcerative colitis (UC) is a condition characterized by inflammation of the mucosal layer, starting in the rectum and potentially impacting the entire colon. Characteristic clinical manifestations include abdominal pain, diarrhea, and bloody stools with mucus and pus [1]. The disease is chronic and recurrent, and there is currently no cure. UC is one of the precancerous lesions of colon cancer, and the transformation of UC to colon cancer conforms to the classic "inflammation-cancer transformation" process. Colon cancer (CC) is the third most common cancer in the world and the fourth most deadly[2]. As a precancerous lesion of colon cancer, its inflammatory-cancer transformation mechanism is closely related to the persistent inflammatory microenvironment. Genetic factors affect tumor susceptibility by regulating inflammatory responses, and chronic inflammation can promote the process of carcinogenesis through multiple mechanisms. Studies have shown that inflammation and tumors have a bidirectional promoting effect, and some Chinese herbal medicine ingredients may block this vicious cycle by regulating related pathways. [3-4]

Sishen Wan originated from the book Zheng Zhi Zhun Sheng, written by Wang Kentang, a physician in the Ming Dynasty. The prescription is made up of six herbs, including Psoralea corylifolia, Evodia rutaecarpa, Nutmeg, Schisandra chinensis, and two auxiliary herbs, ginger and jujube. In modern clinical practice, Si Shen Wan is mainly used to treat digestive system diseases, such as inflammatory bowel disease and CC [5-8]. Studies have shown that Si Shen Wan has good effects on the treatment of UC [9] and the inhibition of CC [10]. At present, The underlying pharmacological basis and action mechanism of Si Shen Wan in treating UC and CC remain vague. Thus, this study aims to combine network pharmacology prediction with molecular docking validation to preliminarily elucidate its potential pharmacological mechanisms, offering a scientific foundation for future systematic experimental investigations and clinical applications..

1 Methods

1.1 Identification of active constituents and associated targets of Sishen Pills

Initially, the Chinese Medicine System Pharmacology Database and Analysis Platform (TCMSP) was utilized to explore the chemical constituents of Sishen Pills, aiming to identify compounds that exhibit potential pharmacological effects. Among them, Psoralea corylifolia, which was not collected in the TCMSP database, was collected through the Herb database of Bencao Zujian, and

target prediction was performed.

1.2 Screening of UC&CC related targets

Targets associated with diseases were queried in both the GeneCards and OMIM databases. From the GeneCards database, only the target information with scores above the median was preserved. The results obtained from these two databases were then combined, and any redundant data were eliminated to ultimately identify the pertinent molecular targets.

1.3 Construction of a "TCM-active ingredient-disease-common target" network

The intersection of UC and CC disease targets and the active ingredient targets of Sishen Pills was taken to obtain common targets. The "TCM-active ingredient-disease-common target" network was drawn using Cytoscape software to analyze its core components.

1.4 Construction of PPI Network and Identification of Core Targets

The common targets identified through screening were entered into the STRING platform for the creation of a protein interaction network. Subsequently, the network data was transferred to Cytoscape software. Two rounds of screening were conducted, focusing on node topology characteristics, including betweenness centrality, closeness centrality, and degree centrality, ultimately leading to the identification of the key regulatory targets.

1.5 GO Function and KEGG Pathway Enrichment Analysis of Shared Targets

The bioinformatics tool in the R programming language was employed to perform an analysis of gene ontology (GO) enrichment for the potential therapeutic targets identified for UC and CC through screening. This analysis encompasses three aspects: biological process (BP), molecular function (MF), and cellular component (CC). The significance threshold P value was set to be less than 0.05, and the analysis results were presented by visualization methods. Subsequently, the KEGG enrichment function of cluster Profiler was used in combination with the Meta Scape database to conduct signal pathway enrichment research.

1.6 Molecular docking verification

Data regarding the three-dimensional crystal structures of essential target proteins were obtained from the PDB database, and the PyMol tool was used to hydrogenate, remove water, and separate non-protein ligands from the protein structure. The Grid box of the binding pocket was precisely adjusted with the help of AutoDock Tools software, The molecular docking operations

were conducted using the AutoDock Vina program to assess the binding affinity of potential active compounds with the target proteins. Additionally, the PyMol software was utilized to create a three-dimensional visualization of the complex structure.

2 Results

2.1 Sishen Pills-UC&CC Common Target Genes

Venny 2.1.0 software was used to import Sishen Pills ingredient targets and UC&CC disease common targets, and 279 TCM-disease common target genes were obtained by analysis, as shown in Figure 1.

2.2 Development and examination of the "TCM-active component-illness-common target" network

The built interaction network (Figure 2) comprises 360 nodes and 941 links. Diamond-shaped nodes indicate potential targets, circular nodes denote active components, and triangular nodes signify common elements. An analysis of the network topology reveals that the five primary active substances exhibiting the highest connectivity are quercetin, bavachin, isobavachin, bavachalcone, and isoneobavachalcone.

2.3 Construction of PPI Network and Identification of Core Targets

The 279 targets that were acquired were entered into the STRING platform, where the species was restricted to humans. A minimum interaction credibility threshold of $\geqslant$0.9 was established, leading to the construction of the protein interaction network after the removal of isolated nodes (see Figure 3). This network comprises 232 protein nodes along with 884 interaction relationships. The resulting network data was then loaded into Cytoscape software, where two rounds of screening were conducted, focusing on node topology characteristics. Ultimately, 19 core targets were identified. Among these, the five target proteins that exhibited the highest degree values were TP53, AKT1, HSP90AA1, ESR1, and JUN. This indicates their potential key regulatory roles in the treatment of UC and CC with Sishen Pills.

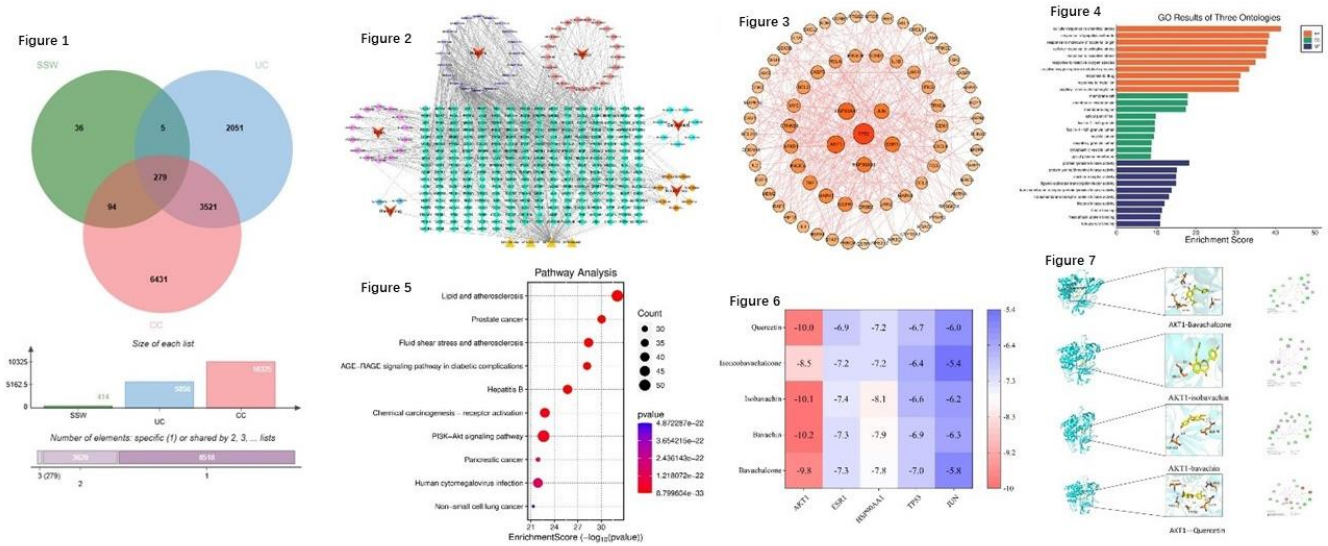
2.4 KEGG Pathway Enrichment and GO Function Analysis of Shared Targets

The Gene Ontology (GO) enrichment approach was employed to investigate the three aspects of Biological Process (BP). MF, and CC. Statistics showed that there were 3161 BP entries, 115 CC entries, and 265 MF entries. The top 10 functional entries in each dimension were selected for visualization (Figure 4). As shown in Figure 5, KEGG analysis identified a total of 178 significantly

enriched signal pathways, among which the top five pathways with the highest enrichment included: lipid metabolism and atherosclerosis, prostate cancer, Shear stress from fluids, the signaling mechanism of AGE-RAGE in complications arising from diabetes, and the pathway associated with hepatitis B virus infection.

2.5 Molecular docking verification

As shown in Figure 6, the core active ingredient was molecularly docked with the core target protein. The findings indicated that the binding energy of the majority of core components to the target was below -5 kcal • mol-1, with the lowest binding energy observed specifically for the AKT1 target, showing strong affinity. As shown in Figure 7, through the visualization of the four groups of structures, it can be clearly seen that the small molecule active substances and the receptor protein mainly rely on hydrogen bonding and π-π stacking effect to maintain a stable complex configuration, which fully proves that these active ingredients may play an important role in regulating the function of the target protein.



3 Discussion

In TCM theory, UC corresponds to symptoms such as "dysentery" and "intestinal diarrhea". The disease starts from the spleen, stomach and large intestine, and then affects the liver and kidneys over time, with a prolonged course of the disease [11-12]. Studies [13-14] have pointed out that the pathogenesis of UC is a combination of deficiency in the root and excess in the superficial symptoms, with spleen deficiency and dampness as the key. Long-term illness can lead to spleen and kidney yang deficiency. If the spleen fails to function properly, water and food

cannot be digested, causing diarrhea and abdominal pain. If the kidney yang is deficient, it will lose warmth, manifested as fear of cold and cold limbs. "Treatise on Warm Diseases" states that "cold and dampness obstruct the spleen, and yang qi does not function, resulting in abdominal distension and loose stools", and "kidney yang deficiency leads to soreness and coldness in the waist and knees, and clear and long urine." In TCM theory, CC corresponds to symptoms such as "intestinal wind" and "intestinal cyst". Its late pathogenesis is mostly a mixture of deficiency and excess, and spleen and kidney yang deficiency syndrome is common in clinical practice [13-14]. In a study on the distribution characteristics of TCM syndrome types in CC patients during the perioperative period, spleen and kidney yang deficiency syndrome accounted for 29.38% and 20.49% of CC patients in clinical stage III and IV before and after surgery, respectively[15]. In the book "Shui Zhang" of Lingshu, it is said: "What is the intestinal polyp? Qi Bo said: Cold air invades the outside of the intestines and fights with the defensive qi. The qi cannot be nourished. Because of something, it is attached to the inside, and bad air arises, and polyps are born." From the perspective of TCM, it explains the occurrence, development and changes of CC. Phlegm and poison fight for a long time, deplete qi and blood, and damage the spleen and kidney, resulting in "long-term diarrhea, qi and blood deficiency, and intestinal tract malnutrition, which leads to asthenia." It explains the key pathogenesis of spleen and kidney yang deficiency in the middle and late stages of CC. Both UC and CC have spleen and kidney yang deficiency syndrome, which can be treated the same way. Si Shen Wan may be effective for both diseases.

In this study, five key active substances of Sishen Pills for the treatment of UC and CC were obtained through multiple databases. Wang et al. [16] found that quercetin relieves UC by activating AhR-mediated TJs enhancement, thereby repairing intestinal barrier dysfunction. Some scholars [17-19] found that quercetin can inhibit the phosphorylation expression of JAK2/STAT3, thereby inhibiting the invasion and metastasis of CC. Studies [20] showed that psoralen can inhibit the invasion and metastasis of human colon cancer HCT-116 cells, and its mechanism may be related to downregulating the expression levels of βcatenin and transcription factor 4 proteins [21]. Zhao et al. found that the anti-cancer properties of psoralen flavonoids are achieved by changing the p53/Bcl-2/Bax signaling pathway related to cell apoptosis [22]. Studies have confirmed [23] that psoralen can relieve DSS-induced colitis in mice and reduce the expression of inflammatory factors such as IL-6. In summary, the active ingredients of Sishen Pills reflect their multi-target therapeutic

effects on UC and CC through immune regulation, anti-inflammatory and improvement of intestinal flora.

The results of PPI analysis showed that the core target proteins of Sishen Pills for UC and CC mainly include TP53, AKT1, HSP90AA1, ESR1 and JUN. Studies have shown that the p53 protein encoded by the TP53 gene plays an important tumor suppressor function in a variety of malignant tumors. As common genes, AKT1 and TP53 play an important role in the biological processes related to UC and CC [23]. TP53 is a tumor suppressor that can regulate cell cycle, apoptosis and senescence. Its gain-of-function mutation will aggravate the level of inflammation and may worsen the tumor [24]. Recent studies have shown that the frequency of TP53 gene mutations in colorectal tissues of UC patients is high, and there is a risk of promoting the development of UC patients to colorectal cancer [25]. AKT1 is a necessary condition for acute inflammation. It mainly works by regulating vascular permeability, leading to edema and leukocyte outflow [26]. Studies have found that AKT1 promotes the pathogenesis of UC by enhancing vascular permeability through its activation [27].

The results from GO function and KEGG pathway enrichment analysis indicated that Sishen Pills may exert their therapeutic effects on UC and CC by modulating crucial signaling pathways, including TNF, IL-17, and HIF-1, and biological processes such as Toll-like receptor-mediated immune response and Th17 cell differentiation. Studies have found that Sishen Pills significantly improves the pathological state of UC by regulating key inflammatory mediators such as TNF-α and IL-17, effectively reduces the expression of proinflammatory factors, alleviates inflammatory response, and reduces the possibility of intestinal epithelial malignancy [28-29]. Studies have shown that in chronic inflammation-related CC, the HIF-1 pathway drives tumor development by promoting angiogenesis and hypoxic adaptation of cancer cells. Sishen Pills may inhibit its tumor-promoting effect and restore intestinal homeostasis by intervening in HIF-1 signaling [30]. Toll-like receptors (TLRs) also play a key role in mediating intestinal immune responses. By regulating TLR signaling, Sishen Pills may inhibit excessive inflammatory responses, which are associated with the progression of UC and CC [31-32]. The transformation of UC into a malignant state is significantly influenced by Th17 cells and the pro-inflammatory factors they secrete, including IL-17. Sishen Pills can improve the intestinal inflammatory microenvironment by regulating the function of Th17 cells, thereby reducing tissue damage and inhibiting the progression of cancer [33-34]. In short,

Sishen Pills exerts its effects by regulating the complex mechanism of multiple signaling pathways related to inflammation and immune regulation. This multi-target characteristic gives it a unique advantage in the treatment of UC and the prevention of cancer, reflecting the potential value of Chinese herbal compound in the treatment of chronic inflammatory diseases [35-36].

Based on network pharmacology and molecular docking technology, this study revealed the molecular mechanism of Sishen Pills in intervening in UC and CC, confirming its scientific connotation of "treating different diseases with the same method", and providing new ideas for the study of the mechanism of action of Chinese herbal compound.

Funding: Jilin Province Science and Technology Development Plan Project Project No.: (YDZJ202401132ZYTS)

Reference

[1] Ordás I, Eckmann L, Talamini M, Baumgart DC, Sandborn WJ. Ulcerative colitis. Lancet. 2012 Nov 3;380(9853):1606-19. doi: 10.1016/S0140-6736(12)60150-0. Epub 2012 Aug 20. PMID: 22914296.

[2] Araghi M, Soerjomataram I, Jenkins M, Brierley J, Morris E, Bray F, Arnold M. Global trends in colorectal cancer mortality: projections to the year 2035. Int J Cancer. 2019 Jun 15;144(12):2992-3000. doi: 10.1002/ijc.32055. Epub 2019 Jan 8. PMID: 30536395.

[3] Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? Lancet. 2001 Feb 17;357(9255):539-45. doi: 10.1016/S0140-6736(00)04046-0. PMID: 11229684.

[4] Xinghan Liu, Lijie Yin, Sunan Shen, Yayi Hou,Inflammation and cancer: paradoxical roles in tumorigenesis and implications in immunotherapies,Genes & Diseases,Volume 10, Issue 1,2023,Pages 151-164,ISSN 2352-3042,

[5] Chen F, Yin Y T, Zhao H M, et al. Sishen Pill treatment of DSS-induced colitis via regulating interaction with inflammatory dendritic cells and gut microbiota [J]. Front Physiol, 2020, 11: 801.

[6] Zhu J Y, Li X Y, Deng N, et al. Intestinal mucosal flora of the intestine-kidney remediation process of diarrhea with deficiency kidney-Yang syndrome in Sishen Pill treatment: Association with interactions between Lactobacillus johnsonii, Ca2+-Mg2+-ATP-ase, and Na+-K+ ATP-ase [J]. Heliyon, 2023, 9(5): e16166.

[7] Su Xiaolan, Wei Ruhan, Wei Wei, et al. Effect of warming kidney and strengthening spleen

method on the expression of serum T cell subsets in rats with diarrhea-predominant irritable bowel syndrome [J]. Chinese Journal of Integrated Traditional and Western Medicine, 2015, 35(4): 457-460.

[8] Cao Yang, Wang Yanjie, Xie Xin, et al. Effect of Sishen Pill on CD133 protein expression in colitis-induced colon cancer in mice [J]. Modern Distance Education of Traditional Chinese Medicine, 2013, 11(8): 145-146.Jia Wang. Knowledge Map Analysis of Sini San Research Based on CiteSpace. Traditional Chinese Medicine. 2022;11 (05):774-783. doi:10.12677/tcm.2022.115110.

[9] Hu, Y., Zhou, P., Deng, K. et al. Targeting the gut microbiota: a new strategy for colorectal cancer treatment. J Transl Med 22, 915 (2024).

[10] Zhihua Yang,Shanshan Lin,Wanying Feng, et al. A potential therapeutic target in traditional Chinese medicine for ulcerative colitis: Macrophage polarization. Frontiers in Pharmacology. 2022;13 (0):0-0. doi:10.3389/fphar.2022.999179

[11] Teng Huang,Junlu Chen,Lína Zhang, et al. Traditional Chinese medicine understanding of ulcerative colitis. Journal of Drug Delivery and Therapeutics. 2019;9 (1-s):390-392.doi:10.22270/jddt.v9i1-s.228

[12] Tiancheng Wang, Xinyue Liu, Weijie Zhang, Jing Wang, Tingting Wang, Wei Yue, Lan Ming, Jun Cheng, Juan Sun,Traditional Chinese medicine treats ulcerative colitis by regulating gut microbiota, signaling pathway and cytokine: Future novel method option for pharmacotherapy,Heliyon,Volume 10, Issue 6,2024,e27530,ISSN 2405-8440.

[13] Shengsheng Zhang,Luqing Zhao,Hong Shen, et al. International clinical practice guideline on the use of traditional Chinese medicine for ulcerative colitis by Board of Specialty Committee of Digestive System Disease of World Federation of Chinese Medicine Societies (2023). Phytotherapy Research. 2023;0 (0):0-0. doi:10.1002/ptr.8087

[14] Tuo Luyao, Xin Hong, Lü Kun, et al. Study on the distribution characteristics of TCM syndrome types in 405 patients with colon cancer during perioperative period[J]. World Journal of Traditional Chinese Medicine, 2023, 18(16): 2349-2353.

[15] Wang X, Xie X, Li Y, Xie X, Huang S, Pan S, Zou Y, Pan Z, Wang Q, Chen J, Zhou L, Luo X. Quercetin ameliorates ulcerative colitis by activating aryl hydrocarbon receptor to improve intestinal barrier integrity. Phytother Res. 2024 Jan;38(1):253-264. doi: 10.1002/ptr.8027. Epub 2023 Oct 23. PMID: 37873559.

[16] Asgharian, P., Tazekand, A.P., Hosseini, K. et al. Potential mechanisms of quercetin in cancer prevention: focus on cellular and molecular targets. Cancer Cell Int 22, 257 (2022).

[17] Asgharian P, Tazekand AP, Hosseini K, Forouhandeh H, Ghasemnejad T, Ranjbar M, Hasan M, Kumar M, Beirami SM, Tarhriz V, Soofiyani SR, Kozhamzharova L, Sharifi-Rad J, Calina D, Cho WC. Potential mechanisms of quercetin in cancer prevention: focus on cellular and molecular targets. Cancer Cell Int. 2022 Aug 15;22(1):257. doi: 10.1186/s12935-022-02677-w. PMID: 35971151; PMCID: PMC9380290.

[18] Piero Alex Silva-Pinto, Janaína Teixeira Costa de Pontes, Brigitte Aguilar-Morón, Christian Shleider Carnero Canales, Fernando Rogério Pavan, Cesar Augusto Roque-Borda,Phytochemical insights into flavonoids in cancer: Mechanisms, therapeutic potential, and the case of quercetin,Heliyon,Volume 11, Issue 4,2025,e42682,ISSN 2405-8440.

[19] Liu Gaiting, Gou Wenfeng, Xu Feifei, et al. Research progress on the anti-tumor mechanism of psoralea corylifolia[J]. Chinese Herbal Medicine, 2024, 55(10): 3529-3538.

[20] Feng Yuanyuan, Zhou Lihong, Liu Ningning, et al. Effects of psoralen on invasion and metastasis of human colon cancer cells and β-catenin/TCF4-MMP-9 signaling pathway[J]. Chinese Journal of Traditional Chinese Medicine, 2021, 36(12): 7033-7037.

[21] Zhao C, Ghosh B, Chakraborty T, et al. Bavachinin mitigates DMH induced colon cancer in rats by altering p53/Bcl2/Bax signaling associated with apoptosis [J]. Biotech Histochem, 2021, 96(3): 179-190.

[22] Akbari S,Hosseini M,Rezaei-Tavirani M,et al.Common and differential genetically pathways between ulcerative colitis and colon adenocarcinoma[J]. Gastroenterol Hepatol Bed Bench,2017 ,10(Suppl1):S93-S101.

[23] Ham S W,Jeon H Y,Jin X,et al. TP53 gain-of-function mutation pro- motes inflammation in glioblastoma[J]. Cell Death Differ,2019,26(3):409- 425.

[24] Hirsch D, Hardt J, Sauer C, et al. Molecular characterization of ulcera- tive colitis-associated colorectal carcinomas[J]. Modern Pathology,2021,34(6):1153-1166.

[25] YANG J,ChENG M,GU B,et al. CircRNA_09505 aggravates inflamma- tion and joint damage in collagen-induced arthritis mice via miR-6089/ Akt1/ NF-κB axis[J]. Cell Death Dis,2020,11(10):833.

[26] ZHANG C,CHEN H,HE Q,et al. Fibrinogen/AKT/Microfilament Axis Promotes Colitis by

Enhancing Vascular Permeability[J]. Cellular and Mo- lecular Gastroenterology and Hepatology,2020,11(3):683-696.

[27] Chen F,Yin YT,Zhao HM, et al. Sishen Pill Treatment of DSS-Induced Colitis via Regulating Interaction With Inflammatory Dendritic Cells and Gut Microbiota. Front Physiol. 2020;11:801. doi:10.3389/fphys.2020.00801

[28] Ge W,Wang HY,Zhao HM, et al. Effect of Sishen Pill on Memory T Cells From Experimental Colitis Induced by Dextran Sulfate Sodium. Front Pharmacol. 2020;11:908. Doi:10.3389/fphar.2020.00908

[29] Sishen Wan ® Ameliorated Trinitrobenzene-Sulfonic-Acid-Induced Chronic Colitis via NEMO/NLK Signaling Pathway

[30] Al-Kishali HA,Abd El Fattah MA,Mohammad WA, et al. Cilostazol against 2,4,6-trinitrobenzene sulfonic acid-induced colitis: Effect on tight junction, inflammation, and apoptosis. JGH Open. 2019;3 (4):281-289. doi:10.1002/jgh3.12148

[31] Kiran S,Rakib A,Moore BM, et al. Cannabinoid Receptor 2 (CB2) Inverse Agonist SMM-189 Induces Expression of Endogenous CB2 and Protein Kinase A That Differentially Modulates the Immune Response and Suppresses Experimental Colitis. Pharmaceutics. 2022;14 (5):. doi:10.3390/pharmaceutics14050936

[32] Zhu J,Li X,Deng N, et al. Intestinal mucosal flora of the intestine-kidney remediation process of diarrhea with deficiency kidney-yang syndrome in Sishen Pill treatment: Association with interactions between Lactobacillus johnsonii , Ca2+ -Mg 2+ -ATP-ase, and Na + -K + -ATP-ase. Heliyon. 2023;9 (5):e16166. doi:10.1016/j.heliyon.2023.e16166

[33] Liu DY,Xu R,Huang MF, et al. Si Shen Wan Regulates Phospholipase Cγ-1 and PI3K/Akt Signal in Colonic Mucosa from Rats with Colitis. Evid Based Complement Alternat Med. 2015;2015:392405. doi:10.1155/2015/392405

[34] Xu Y,Dong H,Ge C, et al. CBLB502 administration protects gut mucosal tissue in ulcerative colitis by inhibiting inflammation. Ann Transl Med. 2016;4 (16):301. doi:10.21037/atm.2016.08.25

[35] Xiao J,Zhang G,Gao S, et al. Combined administration of SHP2 inhibitor SHP099 and the α7nAChR agonist PNU282987 protect mice against DSS-induced colitis. Mol Med Rep. 2020;22 (3):2235-2244. doi:10.3892/mmr.2020.11324