



Safety and Efficacy of Shaoyao Decoction with Anti-Inflammatory Effect in the Treatment of Ulcerative Colitis: A Meta-Analysis

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Abstract

Background: We aimed to evaluate the effectiveness and safety of Shaoyao Tang in treating ulcerative colitis (UC) through a randomized controlled meta-analysis.

Methods: Computer searches were conducted between Jan 2000 and Mar 2023 using the databases of CNKI, VIP, PubMed, the Cochrane Library, Wanfang and Web of Science in search of trials with randomization and control including Shaoyao decoction in UC. After quality assessment, The Revman 5.3 was applied.

Results: Overall, 23 articles were selected for the study totally. Shaoyao decoction improved clinical effective rate ($P<0.001$) and effective rate of syndrome ($P<0.001$), IBDQ ($P<0.001$), interleukin-4 ($P<0.001$) and interleukin-10 ($P<0.001$), reduced adverse reactions ($P=0.004$), recurrence rate ($P=0.03$), DAI ($P<0.001$), tumour necrosis component α ($P<0.001$), interleukin-1 β ($P<0.001$), interleukin-6 ($P<0.001$), and extremely sensitive C-reactive protein ($P=0.02$).

Conclusion: Shaoyao decoction has certain advantages and good safety in the treatment of UC; however the findings still need to be supported by excellent studies.

Keywords: Ulcerative colitis; Shaoyao decoction; Meta-analysis

Introduction

Ulcerative Colitis (UC) occurs in part or all of the mucosa or submucosa of the colon and manifests as recurrent diarrhea, mucus, pus and blood stools, and abdominal pain (1,2). UC directly affects the gastrointestinal tract, impacts patients' eating, and may lead to nutritional deficiencies. UC, as a chronic non-specific inflammatory disease of the rectum and colon, mainly affects the colonic mucosa and submucosa, manifested as symptoms such as diarrhea, abdominal pain, and mucous purulent bloody stools. Its pathogenesis

is complex, involving immune factors, genetic factors, environmental factors, and possible infectious factors, leading to intestinal immune imbalance and intestinal mucosal barrier damage (1,2).

The current treatment for it mainly relies on medication and surgical intervention. General medications include 5-aminosalicylic acid drugs, hormone drugs, and immunosuppressants, such as mesalazine. However, long-term use can cause allergies and drug resistance in patients. Surgical



treatment mainly includes total resection of the colon, ileostomy, total resection of the colon, and ileocecal anastomosis to control the progression of the disease, but it can easily lead to infection, anemia, and abdominal pain in patients. At present, the incidence rate of UC is about 1/1000-2500 people, and the ratio of male to female is 3:1. The onset age is mostly between 20-30 yr old, and the peak age is 25-35 yr old (3). Long-term inflammation can increase the risk of rectal cancer. Rectal cancer occurs more often in UC patients than in non-UC people—roughly 2.4 times as frequently. At 30 years after the diagnosis of UC, 20% of people will get colorectal cancer (4,5). UC's precise pathophysiology is yet unknown. Immune response disorders, changes in intestinal microflora, genetic susceptibility, and environmental factors can impact the occurrence of UC.

Glucocorticoids, aminosalicyclic acid preparations, and immunosuppressants are commonly used in the clinic, but the effect is not good, it is easy to relapse, and the side effects are relatively large (6). At present, UC can have the following impacts on patients' daily lives and work, including abdominal pain, diarrhea, general fatigue, high fever, and bloody stools during acute attacks. These symptoms can cause inconvenience to patients' daily lives and work; Inducing other diseases, UC may be accompanied by complications such as intestinal perforation and toxic megacolon, which can make the condition more complex and increase the difficulty of treatment; The third is to increase the risk of cancer. UC has a higher risk of cancer, especially in patients with recurrent episodes and no improvement in local inflammatory symptoms. In terms of treatment, relevant studies have shown that the combination of traditional Chinese and Western medicine is more effective in treating UC. In terms of treatment, relevant studies have shown that the combination of traditional Chinese and Western medicine is more effective in treating UC (7).

For example, Shaoyao Tang in traditional Chinese medicine has a profound background in traditional Chinese medicine and significant clinical effects in the treatment of ulcerative colitis. Tra-

ditional Chinese medicine categorizes ulcerative colitis as "dysentery, rectal bleeding" and believes that classic formulas such as Shaoyao Tang have unique advantages in treating it. It has the effects of clearing heat and dampness, regulating qi and blood, especially suitable for treating damp heat dysentery, such as abdominal pain, pus and bloody stools. Modern research has shown that Shaoyao Tang can improve colonic pathological damage, with the characteristics of multi-component, multi-target, and multi pathway effects. It has stable efficacy, high safety, and minimal toxic side effects (8). The methods of Shaoyao decoction in the cure of UC include Shaoyao decoction alone, Shaoyao decoction combined with other traditional Chinese medicine therapies, and Shaoyao decoction combined with western medicine.

We aimed to perform a meta-analysis addressing Shaoyao decoction published in the last 20 years on the cure of UC and to thoroughly determine the efficacy and safety of Shaoyao Decoction.

Methods

Literature retrieval

The key terms "Shaoyao Decoction" and "modified Shaoyao Decoction" in conjunction with "colitis" and "chronic colitis" were used to obtain information from the databases of CNKI, Wanfang, VIP, PubMed, Cochrane Library, and Web of Science. The data might be retrieved between Jan 2000 and Mar 2023.

Inclusion and exclusion criteria

inclusion standards: 1) RCTs; Patients's baseline levels were similar in the two groups; the language was Chinese and English; 2) UC patients with a clear diagnosis; 3) research measures in the study group contain Shaoyao Decoction, Shaoyao decoction combined with other traditional Chinese medicine therapies and Shaoyao decoction combined with western medicine; the measures in the control group were other traditional Chinese medicine therapies or western medicine; 4) primary outcome measure was clinical effective

rate; 5) Before treatment, it is important to understand the patient's nutritional status, whether there are any extraintestinal manifestations or complications, as well as their medical history and previous treatment history; 6) Clearly assess the clinical type, severity, extent, and staging of the disease to guide treatment decisions.

Exclusion criteria: 1) non-clinical trial studies (such as reviews, clinical experience, theoretical studies, case studies, and preclinical studies); 2) non-RCT studies, non-controlled trials, and historical controlled studies; 3) duplicate articles; 4) both groups used Shaoyao decoction as an intervention measure; 5) incomplete important data or no full text; 6) no clinical effective rate.

Quality assurance and data extraction

Collect relevant data in two groups, and search for keywords related to UC treatment from both Chinese and English databases. The search time is determined to be between 2000 and 2023. Among them, English platforms include Google Scholar and IEE Search, while Chinese literature platforms include Baidu Scholar, CNKI, VIP, and other platforms. Search literature abstracts from various databases to determine if they meet the requirements of the research investigation. If they do, browse the full text of the literature and recheck it. The Cochrane Handbook version 5.1 (9) was utilized to assessment the RCTs's quality, including production of random sequences, hiding of allocations, and outcomes blinding, completeness of outcome measures, outcome bias, and other biases.

Two researchers independently collected the authors, year of publication, sample size, gender, age, and illness progression, disease severity, treatment plan, treatment cycle, and research indicators (clinical effective rate, effective rate of

syndrome, incidence of adverse reactions, recurrence rate, Sutherland disease activity index (DAI), tumor necrosis factor-alpha (TNF- α), interleukin-1 β (IL-1 β), inflammatory bowel disease questionnaire (IBDQ), interleukin-4 (IL-4), interleukin-6 (IL-6), interleukin-8 (IL-8), and hyper-sensitive C-reactive protein (hs-CRP)). Two researchers extracted data from each study according to a pre-designed form and double-checked the data.

Statistic Evaluation

The collected publications were subjected to a meta-analysis Applying Revman 5.3 programme. The χ^2 test and I2 test were applied to assessment the heterogeneity among similar studies. When there was little variation across studies ($P > 0.1$, $I^2 \leq 50\%$), a fixed-effect model was used. In cases where there was statistical heterogeneity, a random effect model was applied ($P \leq 0.1$, $I^2 > 50\%$). The binary variable was analyzed using relative risk. With a 95% confidence interval (CI) and a significance threshold of 0.05, the continuous variable was analyzed using MD or SMD, respectively.

Results

Retrieval results

Overall, 203 Chinese articles and 11 English articles were retrieved (Table 1 and Table 2). Sixty-three duplicate essays were removed. After scanning the abstracts, 103 papers were discarded; 25 essays were removed after reading the full texts. In all, 23 articles were used for this investigation. 2068 suffers in all were recruited, the study group owns 1035 and the control group owns 1033. Fig. 1 illustrates the flow chart for including literature.

Table 1: Article characteristics (Series 1)

Authors	Year	Sample size		Sex		Age(yr)	
		Study group	Control group	Study group	Control group	Study group	Control group
Chao JF(10)	2018	40	40	41/39	43/37	45.2±12.4	44.6±11.8
Chen JL(11)	2018	36	36	20/16	21/15	38.5	37.9
Ding HH(12)	2019	38	38	20/18	22/16	34.1±3.8	34.5±3.7
He RA(13)	2020	48	49	26/22	25/24	51.47±2.03	5.44±1.12
Huang HJ(14)	2019	40	40	23/17	26/14	33.11±5.26	35.43
Huang HL(15)	2018	34	34	13/21	14/20	38.49±4.75	37.62±5.77
Jia ZJ(16)	2011	70	70	44/26	40/30	56	55.3
Li HB(17)	2018	40	40	26/14	17/23	43.24±4.82	44.12±7.20
Liang ZM(18)	2005	34	34	—	—	36.5	37.26±2.47
Lou W(19)	2021	45	45	24/21	27/18	51.48±13.53	51.52±13.78
Lu LS(20)	2010	30	30	16/14	17/13	44.03±11.7	37.37±10.39
Qi XY(21)	2016	82	83	43/39	39/44	37.9±12.8	38.8±13.4
Sun XJ(22)	2017	120	120	77/43	78/42	40.8±6.9	40.9±6.8
Tan GZ(23)	2020	34	34	16/18	19/15	41.55±9.08	40.67±10.75
Tian GD(24)	2017	38	35	18/20	16/19	38.50±10.0	38.77±10.56
Wa HF(25)	2019	18	18	10/8	11/7	54.21±5.4	53.42±5.34
Wang K(26)	2020	40	40	22/18	23/17	38.3±4.3	38.2±4.1
Xu JJ(27)	2007	27	29	14/13	14/15	20~68	24~70
Yang JK(28)	2019	30	30	12/18	11/19	46.92±10.86	47.04±11.02
Yao CJ(29)	2021	65	62	29/36	30/32	44.1±7.3	45.6±8
Zhang WH(30)	2021	36	36	20/16	19/17	45.88±5.94	45.54±5.64
Zhao FC(31)	2019	58	58	36/22	37/21	43.68±5.32	43.89±5.43
Zhong YM(32)	2010	32	32	14/18	17/15	48.75±10.50	45.25±15.75

Table 2: Article characteristics ((Series 2)

Authors	Time	Course of disease		Treatment plan		Treatment time
		Study group	Control group	Study group	Control group	
Chao JF(10)	2018	3.6±1.8y	3.8±1.9y	SYD+MS	MS	4w
Chen JL(11)	2018	5.62y	6.2y	SYD+MS	MS	21d
Ding HH(12)	2019	16.1±3.1y	15.9±4.0y	SYD+MS	MS	8w
He RA(13)	2020	5.36±1.07y	5.44±1.12y	SYD+AC	AC	—
Huang HJ(14)	2019	4.24±1.55y	4.12±1.53y	SYD+AC	AC	8w
Huang HL(15)	2018	—	—	SYD+BYP	BYP	2m
Jia ZJ(16)	2011	10m~11y	5m~11y	SYD+ other TCM	SAZ	10w
Li HB(17)	2018	—	—	SYD+AC	AC	2m
Liang ZM(18)	2005	22.6d	21.3d	SYD	SAZ	2w
Lou W(19)	2021	4.91±0.89y	4.89±0.87y	SYD+MS	MS	4w
Lu LS(20)	2010	3.8±2.02y	4.00±1.86y	SYD+SAZ	SAZ	60d
Qi XY(21)	2016	3.4±2.9y	3.2±2.5y	SYD+MS	MS	8w
Sun XJ(22)	2017	—	—	SYD+SAZ	SAZ	4w
Tan GZ(23)	2020	39.33±16.71y	39.70±14.2y	SYD+infliximab	infliximab	3m
Tian GD(24)	2017	5.99±4.77y	5.19±4.46y	SYD	MS	2m
Wa HF(25)	2019	8.19±0.82y	7.63±0.72y	SYD+SAZ	SAZ	—
Wang K(26)	2020	2.4±0.6y	2.3±0.3y	SYD+MS	MS	1m
Xu JJ(27)	2007	—	—	SYD	MS	8w
Yang JK(28)	2019	5.26±1.12y	5.44±1.53y	SYD+MS	MS	8w
Yao CJ(29)	2021	3.9±0.92y	4.4±0.78y	SYD+MS	MS	4w
Zhang WH(30)	2021	2.64±0.92y	2.55±0.86y	SYD+MS	MS	6w
Zhao FC(31)	2019	2.57±0.83y	2.63±0.92y	SYD	MS	6w
Zhong YM(32)	2010	4.25±2.75y	4.75±3.25y	SYD+other TCM	SAZ	30d

Note: SYD, Shaoyao Decoction; MS, mesalazine; AC, acupuncture; BYP, Buzhong Yiqi Pill; SAZ, sulfasalazine; TCM, traditional Chinese Medicine

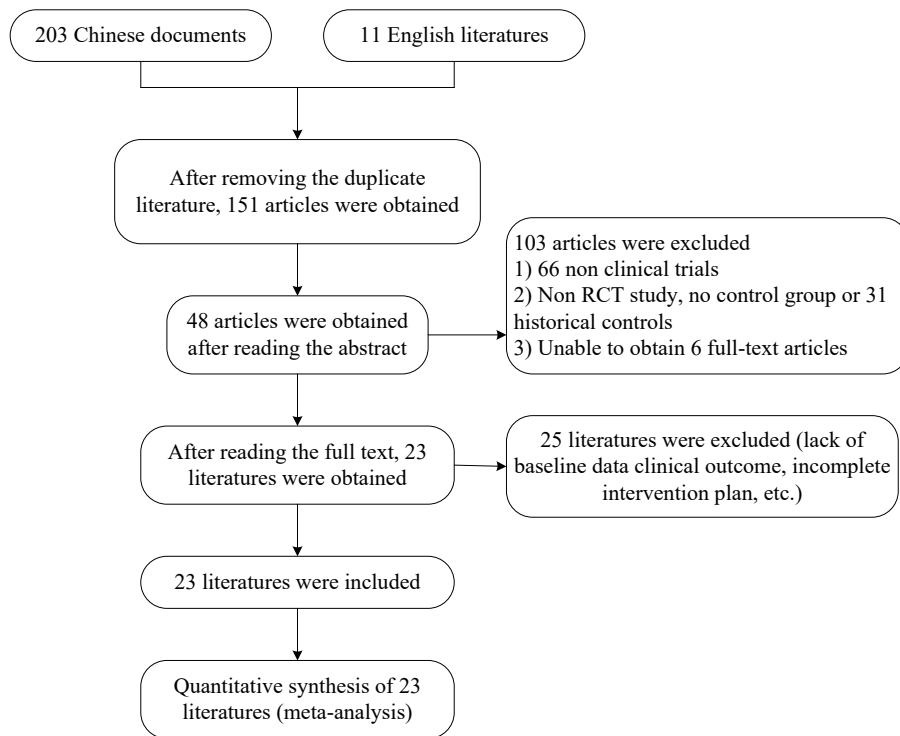


Fig. 1: Literature inclusion flowchart

Quality evaluation of included articles

All the articles (10-32) described group assignment according to the random number table method, and none of them described allocation concealment, blinding, and blinding of results. In

Fig. 2, all articles (10-32) had complete results, and did not have selective result reports or other biases.

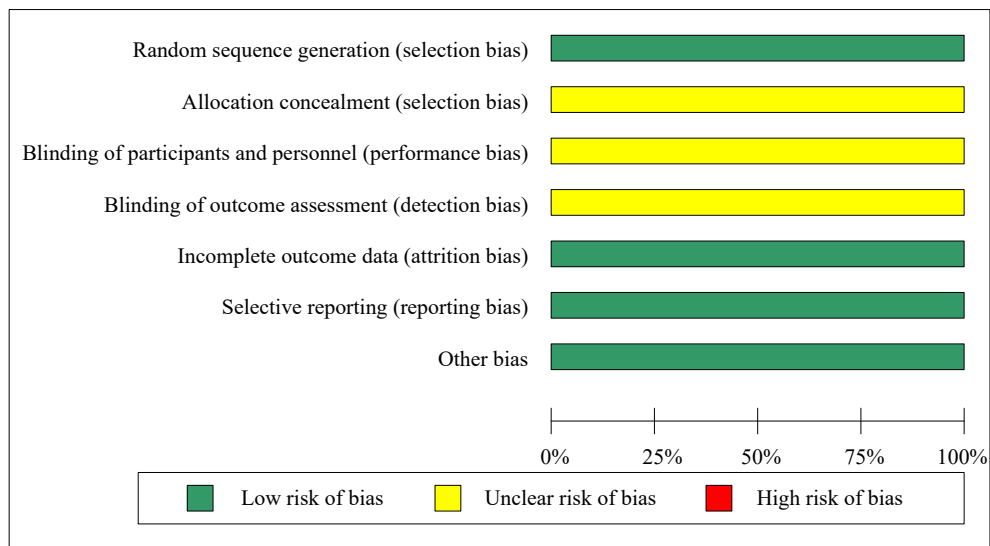


Fig. 2: Articles featured may be biased

Meta-analysis

Clinical efficacy rate

The 23 articles (10-32) all described the clinical effective rate. There was consistency amongst all of the studies ($P=0.61$, $I^2=0$), employing a fixed-effect model. The clinical efficacy rate was dramatically raised by Shaoyao decoction ($RR=1.30$, $95\%CI=1.24-1.35$, $P<0.001$). Analysis of sub-

groups revealed that Shaoyao decoction alone ($RR=1.23$, $95\%CI=1.10-1.36$, $P<0.001$), Combining Shaoyao decoction with other conventional Chinese medicine treatments ($RR=1.29$, $95\%CI=1.20-1.40$, $P<0.001$), and Shaoyao decoction combined with western medicine ($RR=1.31$, $95\%CI=1.24-1.39$, $P<0.001$) could enhance the clinical effective rate (Fig. 3).

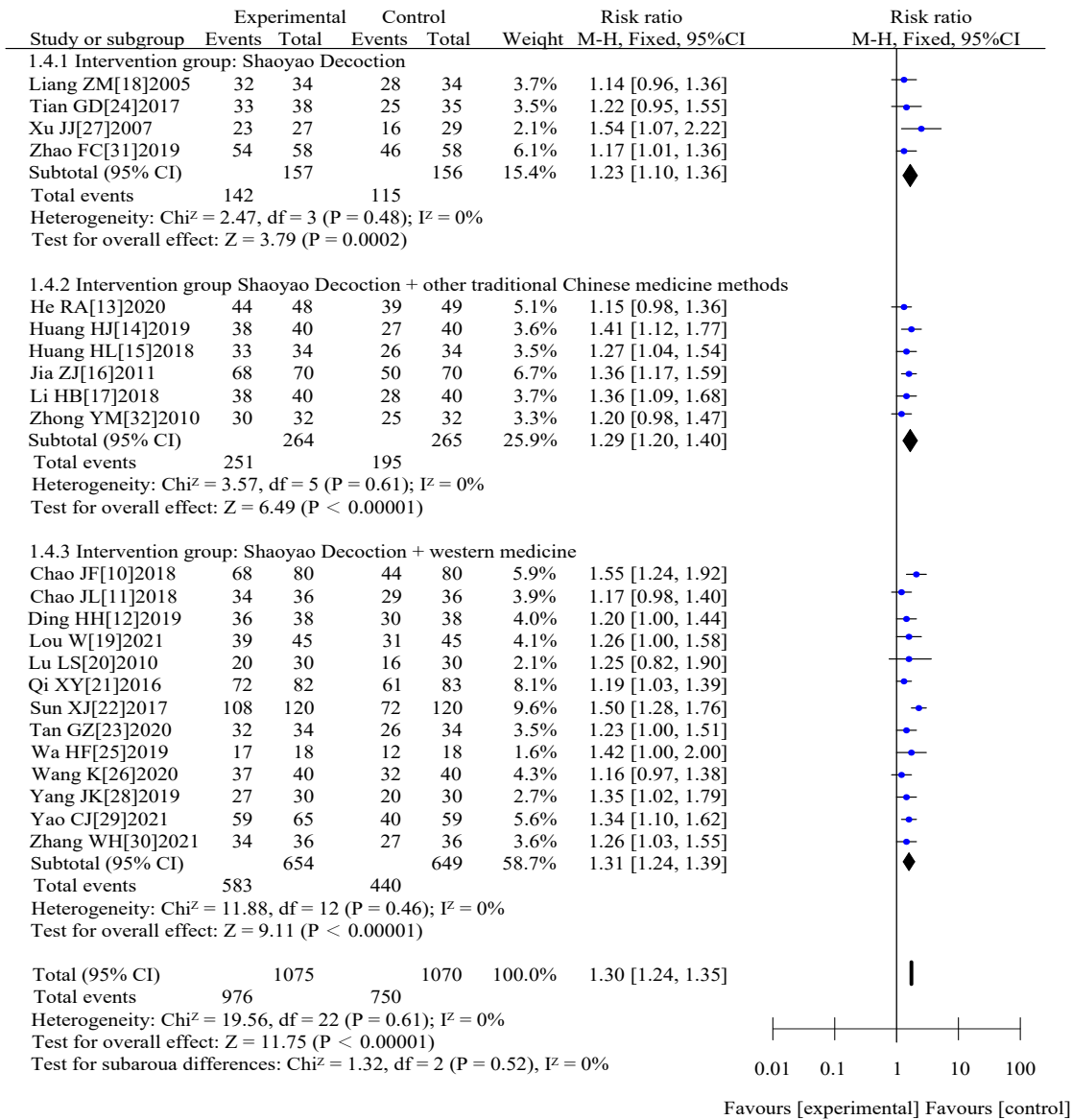


Fig. 3: Effect of Shaoyao decoction on Patients with UC, Clinical Effective Rate, Forest Plot

Effective rate of syndrome

Two articles (20-21) described the effective rate of syndrome. No studies were heterogeneous ($P=0.25$, $I^2=23\%$) and a fixed-effect model was applied. Shaoyao decoction improved the effective rate of syndrome in UC patients ($RR=1.23$, $95\%CI=1.10-1.39$, $P<0.001$).

Adverse reactions

Six studies (12, 14, 20, 22, 30-31) described adverse reactions. There was consistency amongst all of the researches ($P=0.82$, $I^2=0\%$), using a fixed-effect model. Shaoyao decoction decreased the adverse reactions of UC patients during treatment ($RR=0.52$, $95\%CI=0.33-0.82$, $P=0.004$).

Recurrence rate

Two studies (14, 24) described the recurrence rate. There was consistency amongst all of the researches ($P=0.40$, $I^2=0\%$), using a fixed-effect model. Shaoyao decoction reduced the proportion of UC patients who relapse after treatment ($RR=0.30$, $95\%CI=0.10-0.87$, $P=0.03$).

IBDQ

Two studies (21, 29) described IBDQ. Studies varied in their approaches and findings ($P=0.0003$, $I^2=92\%$), using a random-effect model. Shaoyao decoction improved IBDQ in

UC patients ($MD=26.57$, $95\%CI=14.47-38.86$, $P<0.001$).

Inflammatory factor levels

Eight studies (10-11, 20-23, 28, 30-31) described $TNF-\alpha$ ($P<0.001$, $I^2=95\%$); five studies (10,19,21,28,31) described $IL-1\beta$ ($P<0.001$, $I^2=81\%$); three studies (11,20,23) described $IL-6$ ($P<0.001$, $I^2=100\%$); four studies (10,20,28,30) described $IL-4$ ($P=0.70$, $I^2=0\%$); and four studies (10,20,23,28) described $IL-10$ ($P<0.001$, $I^2=96\%$). Shaoyao decoction reduced $TNF-\alpha$ levels in UC patients ($MD=8.16$, 95% confidence interval $-9.96-6.36$, $P<0.001$), $IL-1\beta$ levels ($MD=-0.71$, 95% $CI=-1.03\sim-0.40$, $P<0.001$), $IL-6$ levels ($MD=-23.89$, 95% $CI=-62.79$ to -15.02); Shaoyao decoction increased the levels of $IL-4$ ($MD=1.47$, 95% $CI=1.16-1.77$, $P<0.001$) and interleukin-10 ($MD=3.37$, 95% confidence interval $1.47-5.26$, $P<0.001$) in patients with UC.

Publication bias

The clinical effective rate was selected for the inverted funnel plot analysis. The inverted funnel plot displayed that the graph was symmetrical, indicating that there may not be any publishing bias. Carry out sensitivity analysis, and the results demonstrated no change significantly, suggesting that this meta-analysis is reliable (Fig. 4).

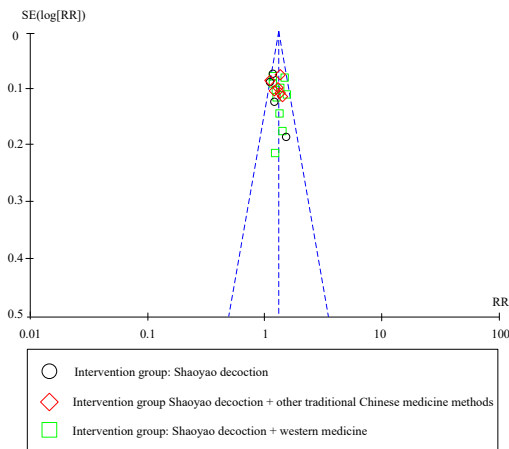


Fig. 4: Randomized controlled trials using Shaoyao decoction to treat UC are shown using an inverted funnel plot

Discussion

UC lesions often involve the rectum or distal colon and can also invade the entire colon. Chronic recurring inflammatory illness known as UC is characterized by intestinal homeostasis disturbance and mucosal epithelial destruction (33). Current management strategies for UC include corticosteroids, aminosalicic acid, antibiotics, and anti-TNF- α , but most applications have certain limitations. Aminosalicic acid drugs may cause pronounced allergies and a fever, and corticosteroids may lower bone mass and increase the risk of fractures (34). In the treatment of UC, traditional Chinese medicine has garnered a lot of attention because of its multi-component and multi-target effects. Traditional Chinese medicine believes that UC belongs to the categories of "intestinal dysentery", "dysentery", and "diarrhea" (35). Regarding medical etiology in China, there are the invasion of exogenous pathogens, injury due to diet, emotion-thought disorders, and spleen-stomach weakness. Exogenous pathogens include summer heat, dampness, cold, and heat, with dampness as the center. Because the spleen hates dampness and likes dryness, external dampness is most likely to accumulate in the spleen. Clinically, dampness combined with summer heat is considered sick. Dampness and heat invade the stomach and intestines, and damp-heat stagnation is considered sick. These symptoms can cause distant transformation disorder, stagnation of qi and blood, accumulation of heat and toxins, mutual contention and binding, and transformation into pus and blood (36). It is advisable to treat heat and dampness and regulate qi and blood (36). Shaoyao decoction is from Suwen Bingji Qiyi Bao Ming Ji and is composed of Radix Paeoniae Alba, Angelica Sinensis, Coptis Chinensis, Scutellaria Baicalensis, Areca Catechu, Aucklandia Lappa, Cinnamomum Cassia, Rhubarb, and Radix et Rhizoma Glycyrrhizae Preparata cum Melle (37). Shaoyao decoction can clear visceral heat and treat hydropyretic dysentery (37). Scutellaria Baicalensis and Coptis

Chinensis taste bitter and cold and enter the large intestine meridian, can clear heat, drying dampness, and detoxify to eliminate the cause of disease. Paeonia Veitchii can nourish blood, regulate *ying*, and relieve spasm and pain. Angelica Sinensis can nourish blood and promote blood circulation. This embodies the meaning of "blood circulation leads to self-healing of purulent stool", and regulates the pathogenic damp-heat toxins moulders in the intestines and collaterals and consumes *yin* blood. Aucklandia Lappa and Areca Catechu can promote *qi* and guide stagnation, meaning "tenesmus can remove automatically after regulating *qi*". The four medicines are matched to harmonize *qi* and blood. Rhubarb is bitter and cold. Its combination with Scutellaria Baicalensis and Coptis Chinensis can clear heat and drying dampness. Its combination with Angelica Sinensis and Radix Paeoniae Alba can promote blood circulation and *qi* circulation. Its purgative function can lead damp and heat away from the stool. A small amount of Cinnamomum Cassia can relieve cold with warm nature, help Angelica Sinensis and Radix Paeoniae Alba to promote blood circulation and regulate *ying*, and play a key role in anti-nausea and anti-rejection. Radix et Rhizoma Glycyrrhizae Preparata cum Melle can regulate the middle warmer. The combination of various medicines can remove dampness and heat and regulate the coordination between *qi* and blood, so diarrhea can be cured.

Shaoyao decoction has been shown to exert a therapeutic effect on UC. Treatment of UC with modified Shaoyao decoction in combination with mesalazine or sulfasalazine may increase the overall effective rate (86.67% vs 68.89%) and reduce the DAI score (10-12, 19-23, 25-26, 28-30). One of its possible mechanisms is to regulate the levels of YKL-40 and NF- κ B and reduce the degree of inflammatory response. Compared with acupuncture alone, modified Shaoyao decoction combined with acupuncture can increase the efficiency, lower the colonoscopy score, and alleviate symptoms including diarrhea, stomach discomfort, pus- and blood-filled stools, and tenesmus (13,14, 17). The TCM syndrome score after

modified Shaoyao decoction in the treatment of UC was inferior to the mesalazine control group, and the efficacy of colonoscopy for mucosal lesions was superior to the mesalazine control group (18, 24, 27, 31). By examining 23 RCTs, this research assessed the effectiveness and security of Shaoyao decoction in the treatment of UC. This meta-analysis confirmed that Shaoyao decoction alone, Combining Shaoyao decoction with other TCM treatments, and Shaoyao decoction combined with western medicine could improve the clinical efficacy.

The limitations of this study are: this study designed a search of English databases, but no relevant articles were found. The results from the current study are only applicable to UC patients in China. Whether Shaoyao decoction is suitable for UC patients outside China needs further investigation. The selected publications often lack allocation concealment or blinding and have poor methodological quality. There are some shortcomings in this study. Nevertheless, Shaoyao decoction can benefit UC patients through the analysis of clinical efficacy, syndrome efficacy, adverse reaction, recurrence rate, DAI, IBDQ, and inflammatory factor. Shaoyao decoction has a certain clinical value in the treatment of UC, and further investigations on the treatment of UC with Shaoyao decoction should expand the population, improve the methodological design, and provide high-quality literature for the clinic.

Conclusion

Shaoyao decoction can still improve the efficiency of syndromes, IBDQ, and diminish adverse reactions, recurrence rate, and DAI. Shaoyao decoction has good safety and efficacy in treating UC. Immune inflammation is the key to the aggravation of UC inflammation and tissue damage. In UC patients, the TNF- α , CRP, IL-1 β , and IL-6 rise, while the IL-4 and IL-8 fall. The TNF- α , CRP, IL-1 β , and IL-6 decreased, while the IL-4 and IL-8 increased in UC patients treated with Shaoyao Decoction. Shaoyao decoction can de-

crease the degree of inflammatory response in UC patients.

Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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