REVIEW ARTICLE

Effects of Traditional Chinese Medicine on Serum Cytokines for the Dampness-heat Syndrome of Ulcerative Colitis: A Systematic Review and Meta-analysis

Yuan Xu, MM; Yu Liu, MM; Jian Lu, BM; Jiong Wu, MD

ABSTRACT

Context • Ulcerative colitis (UC) is a chronic disease affecting the large intestine. Cytokines, as inflammatory mediators, can enable pathological injury of the intestinal mucosa and play an important role in UC's pathogenesis. Traditional Chinese medicine (TCM) offers a wealth of theory and experience in UC's treatment.

Objective • The literature review and meta-analysis intended to examine TCM's effects in the treatment of UC patients who have the dampness-heat syndrome on the serum cytokines known to be related to UC's pathogenesis.

Design • The research team conducted a comprehensive literature search for randomized controlled trials (RCTs) in seven databases. The search covered all publicly published documents from the establishment of a database until August 31, 2021. The team also performed a meta-analysis of the RCTs' results to compare the levels of cytokines in the intervention and control groups.

Setting • The study took place at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai University of Traditional Chinese Medicine in Shanghai, China.

Interventions • For the meta-analysis, the research team created two intervention groups, the oral TCM only group and the TCM+ Western Medicine (WM) group and a control group, the WM group. The team determined which RCT's measured a particular cytokine and which groups those RCTs compared, the team examined the differences between the groups postintervention.

Outcome Measures • The primary outcome measures were the RCTs' levels of 13 serum cytokines—interleukin 6 (IL-6), IL-8, tumor necrosis factor alpha (TNF-α), IL-17, IL-23, interferon-gamma (IFN-γ), IL-21, IL-1, IL-1β, IL-2, IL-4, IL-10, and IL-13. The team used the random effects model to combine the results for the serum markers as standardized mean differences (SMDs) and compared the two intervention groups to the control group.

Results • The research team identified 22 studies that included 1957 participants. The team found that six proinflammatory cytokines were significantly lower in the combined TCM only and TCM+WM intervention groups than in the WM control group: (1) IL-6—SMD -2.60, 95%CI -3.37 to -1.83, $P < .00001$; (2) IL-8—SMD -2.49, 95%CI -3.34 to -1.64, $P < .00001$; (3) TNF-α—SMD -1.70, 95%CI -2.07 to -1.33, $P < .00001$; (4) IL-17 (TCM+WM group only)—SMD-2.99, 95%CI -4.66 to -1.31, $P = .0005$; (5) IL-23 (TCM+WM group only)—SMD -2.43, 95% CI -2.78 to -2.08, $P < .00001$; and (6) IFN-γ—SMD -1.47, 95% CI -1.81 to -1.12, $P < .00001$. The team found that two anti-inflammatory cytokines were significantly higher in the intervention group than in the control group: (1) IL-4—SMD 1.45, 95% CI 0.92-1.99, $P < .00001$, and (2) IL-10—SMD 1.33, 95% CI 0.97-1.69, $P < .00001$. For the results that the team couldn't combine, the levels of the proinflammatory cytokines IL-1, IL-1β, IL-2, and IL-21 were significantly lower in the combined intervention groups than in the control group ($P < .05$), and the level of the anti-inflammatory cytokine IL-13 in the intervention group was significantly higher than that in the control group ($P < .05$). The comprehensive analysis showed that oral TCM or a combination of TCM and WM could more significantly reduce the levels of the proinflammatory cytokines IL-6, IL-8, TNF-α, IL-17, IL-23, IFN-γ, IL-21, IL-1, IL-1β and IL-2 and increase the levels of the anti-inflammatory cytokines IL-4, IL-10 and IL-13.

Conclusions • Oral TCM or TCM+WM can reduce the proinflammatory response and increase the anti-inflammatory response of UC patients by regulating serum cytokines and can obtain a better clinical effect than WM only. These benefits can alleviate intestinal inflammation in patients and have a positive effect on clinical efficacy. In the future, more high-quality, large-sample, and long-term follow-up randomized controlled trial are necessary to support research analysis. (*Altern Ther Health Med.* 2023;29(5):386-395).

Yuan Xu, MM, Resident Doctor, and **Jian Lu, BM**, Associate Chief Physician, Department of Coloproctology, Kongjiang Hospital, Yangpu District, Shanghai, China. **Yu Liu, MM**, Resident Doctor, Department of Prevention of Disease, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China. **Jiong Wu, MD**, Chief physician, Department of Coloproctology, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine, Shanghai, China.

Corresponding author: Jiong Wu, MD
E-mail: tcmoctober9@163.com

Ulcerative colitis (UC) is a chronic disease affecting the large intestine, with an increasing incidence worldwide. Nearly one-million people in both the United States and Europe suffer from the disease, and it affects more people worldwide.[1] UC patients can have diarrhea—increased frequency of soft stools and defecation, rectal bleeding, an urgent need to defecate, and abdominal pain.

With the continuing study of UC, researchers have reached a deeper understanding of its pathogenesis, particularly the role of the immune system. As a core link in immune regulation, T lymphocytes are of three types, with different functions: (1) helper T (Th) cells, (2) regulatory T (Treg) cells, and (3) cytotoxic T (Tc) cells. As presently understood, the pathogenesis of UC mainly involves the former two.

Cytokines

By secreting related cytokines, Th cells participate in the regulation of cellular immunity (Th1), humoral immunity (Th2), and autoimmunity (Th17) and maintain a dynamic balance among various cytokines.

Treg cells can inhibit inflammatory reactions, to avoid excessive immune damage. In normal intestinal mucosa, the components of T lymphocytes are in dynamic balance, thus maintaining the stability of the intestinal mucosa's immune response. If any of the components is dysfunctional, whether high or low, it can cause a balance to be broken, resulting in inflammation.

Th1 secretes the proinflammatory cytokines interleukin-2 (IL-2), tumor necrosis factor alpha (TNF-α), and interferon-gamma (IFN-γ). Th2 secretes the anti-inflammatory cytokines IL-4, IL-10, and IL-13. Th17 secretes the proinflammatory cytokines IL-17 and IL-23, and Treg secretes transforming growth factor beta (TGF-β) and IL-22, which can be both pro- and anti-inflammatory.

Some studies have found that serum levels of Th1 cytokines—IL-2, TNF-α, and IFN-γ—are much higher in UC patients than in healthy people.[33-35] Other studies have found that UC patients also have higher levels of Th17 cytokines —IL-17, IL-21, and IL-23—compared with healthy people.[36-38]

In addition, other studies have found that the serum levels of Th2 cytokines—IL-4, IL10, and IL-13—and the Treg cytokine TGF-β are lower in UC patients than in healthy people.[39-42] In addition, monocyte macrophages produce IL-1, IL-6, and IL-18, all proinflammatory cytokines, and IL-8, an anti-inflammatory cytokine, and all of them are highly expressed in the serum of UC patients.[43-46]

UC Pathogenesis

For patients with UC, cytokines, as inflammatory mediators, enable pathological injury of the intestinal mucosa and play an important role in UC's pathogenesis. At present, some studies have connected some proinflammatory cytokines—IL-1, IL-2, IL-18, IFN-γ, IL-6, IL-17, IL-22, IL-8, IL-21, IL-23, and TNF-α—to UC's pathogenesis.[2-5] Other studies have linked anti-inflammatory cytokines to UC's pathogenesis, such as IL-4, IL-23, TGF-β, and IL-10.[6,7]

In addition, some studies have reported that IL-13 may play a dual role in the pathogenesis of UC, both proinflammatory and anti-inflammatory.[8,9] The occurrence of UC is related to the imbalance of these cytokines, and proinflammatory cytokines are dominant.

UC Treatments

The drugs that clinicians use to treat UC include aminosalicylic acids, glucocorticoids, immunosuppressants, and biological agents, but some have side effects, and some are expensive, which can burden patients. Therefore, alternative therapies may provide more options for UC patients.

Chinese people have used traditional Chinese medicine (TCM) as an alternative therapy to treat diseases in China for over 2000 years. Also, TCM offers a wealth of theory and experience in UC's treatment.

TCM divides UC into the seven categories: (1) the dampness-heat syndrome, (2) the spleen deficiency dampness syndrome, (3) the spleen-kidney yang deficiency syndrome, (4) the liver depression and spleen deficiency syndrome, (5) the blood stasis and spleen deficiency syndrome, (6) the cold-heat mixed syndrome, and (7) the heat-toxin blazing syndrome. The corresponding treatments mainly remove the dampness, heat, blood stasis, and toxins in the body and regulate the function of the viscera.[10]

For TCM, the main symptoms of the dampness-heat syndrome in UC are diarrhea, pus and blood in the stool, tenesmus, and abdominal pain. The secondary symptoms are anal burning, red urine, red tongue, yellow and greasy tongue coating, and slippery pulse.

UC has two periods: active and remission. The theory of TCM states that the active period is mainly evil reality, with dampness and heat as the main content. Clearing heat and removing dampness to eliminate stagnation is key to the treatment of UC during the active period and can have a positive effect on the disease's prognosis.[47]

Some studies have shown that TCM can alleviate the inflammatory response in UC patients by adjusting the ratio of Th17/Treg cells and Th1/Th2 cells.[48-50] TCM, in the treatment of dampness-heat UC, not only provides a good effect against UC's symptoms but also regulates any imbalance in the serum cytokines of UC patients.

Current Study

Studies on the topic, however, usually have had small sample sizes; serum cytokines often haven't been the main outcome measure; and the measured serum cytokines have been different.

The current literature review intended to examine TCM's effects in the treatment of UC patients who have the dampness-heat syndrome on the serum cytokines known to be related to UC's pathogenesis.

METHODS

Procedures

The research team conducted a comprehensive literature search and also performed a meta-analysis of the results to

determine the levels of cytokines. The study took place at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine of Shanghai University of Traditional Chinese Medicine in Shanghai, China.

Inclusion and exclusion criteria. The research team included randomized controlled trials (RCTs): (1) with published results in Chinese or English, whether blinded or not; (2) in which participants were patients with the dampness-heat syndrome of UC; (3) in which the control group received treatment using routine western medicine (WM) and the intervention group received oral TCM combined with western medicine, TCM+WM, or oral TCM only; and (4) that included one or more of the following serum cytokines as outcome measures: IL-1, IL-18, IFN-γ, IL-2, IL-6, IL-17, IL-22, IL-21, IL-23, IL-8, IL-23, TNF-α, IL-2, TGF-β, IL-4, IL-10, or IL-13.

The research team excluded: (1) case reports, letters, and degree theses; (2) RCTs in which patients had dysentery, intestinal tuberculosis, Crohn's disease, radiation enteritis, intestinal perforations and intestinal obstructions, severe systemic diseases, or malignant tumors; or (3) RCTs in which patients were pregnant or lactating.

Data sources and searches. Two members of the research team, the reviewers, carried out an extensive search using electronic databases: Cochrane, Embase, Pubmed, the China National Knowledge Infrastructure database (CNKI), the Chinese Scientific Journals Full-Text Database (CQVIP), the Wanfang Data Knowledge Service Platform, and the Chinese Biomedical Literature Service System (SINOMED).

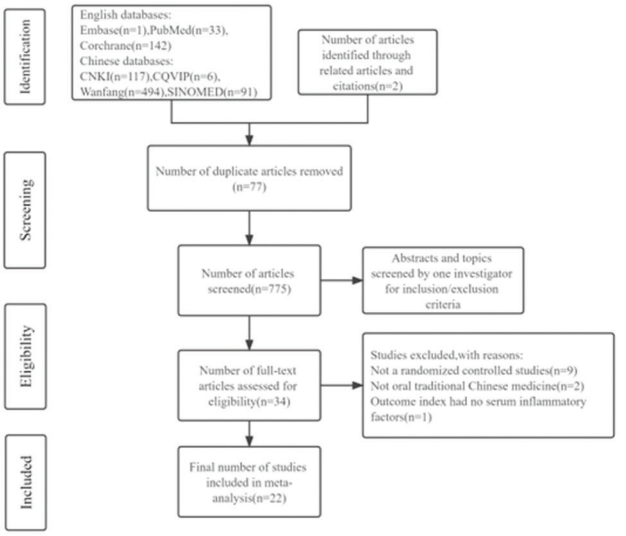
The two reviewers selected the keywords to be as broad as possible to avoid missing any study. The keywords included: ulcerative colitis, inflammatory bowel disease, UC, IBD, inflammatory factor, cytokines, immunological serum marker, TNF-α, IFN-γ, TGF-β, IL, interleukin, TNF-alpha, IFN-gamma, TGF-beta, tumor necrosis factor-α, interferon-γ, transforming growth factor-β, Chinese medicine, traditional Chinese medicine, Chinese herbal medicine, Chinese herbal drug, traditional herbal medicine, herbal medicine, TCM, dampness-heat, damp-heat, clinical trial, randomized controlled trial, and controlled clinical trial. The team retrieved all publicly published documents from the establishment of each database to August 31, 2021.

Quality assessment and data extraction. Two evaluators screened the literature independently using the inclusion and exclusion criteria. They: (1) read the title and abstract of each article first, (2) excluded the irrelevant literature, (3) then the read the full text and summarized the information, including the study's results, through the development of a perfect data table; and (4) determined whether to include a study or not.

If differences existed in the studies each evaluator selected, they resolved them by means of discussion or by consultation with a third party.

The extracted information included: (1) first author; (2) year of publication; (3) randomization method; (4) age of participants; (5) the study's period; (6) the course of the disease; (7) the sizes of the intervention and control groups; (8) the genders of participants; (9) the UC's severity; (10) the treatments that the intervention and control groups received; (11) the course of treatment, and (12) the outcome index.

Figure 1. Flowchart of literature search and study selection.



Quality evaluation. The evaluators then assessed the quality of all the literature that had met the criteria, using the Cochrane bias risk assessment tool and including high-quality studies and excluding low-quality studies.

The evaluators then determined the bias risk using the bias risk assessment tool for RCTs in the Cochrane manual. They evaluated the quality of seven aspects of the studies: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective reporting, and (7) any other biases.

Interventions. For the meta-analysis, the research team created two intervention groups, the oral TCM only group and the TCM+WM group and a control group, the WM group. The team determined which RCT's measured a particular cytokine and which groups those RCTs compared.

Outcome measures. The primary outcome measures were the RCTs' levels of the 13 serum cytokines—IL-6, IL-8, TNF-α, IL-17, IL-23, IFN-γ, IL-21, IL-1, IL-1β, IL-2, IL-4, IL-10, and IL-13. Because the numerical units of the included studies weren't unified, the research team used standardized mean differences (SMDs) and 95% confidence intervals as the outcomes.

Meta-analysis

The research team performed the meta-analysis using the Cochrane Collaboration Software Review Manager 5.3, and the Egger's regression using STATA 15.0 (Stata Corporation, College Station, TX, USA).

The team used the I^2 test to evaluate the degree of heterogeneity between the studies, with $I^2 > 50\%$ indicating substantial heterogeneity. In that case, team used the random-effects model to calculate the SMDs. With an $I^2 < 50\%$, the team

used the fixed effects model for analysis. The team assessed the publication bias using Egger's regression. The team performed a descriptive analysis of data that they couldn't merge.

RESULTS

Literature

The reviewers first found 886 articles, 884 in the databases and two identified through related articles and citations (Figure 1). After reading the topics, they excluded 77 repetitive articles, screened 775 articles, and excluded 584 unrelated studies. After reading the abstract, they excluded 191 studies and reviewed the full text of 34 potentially related studies to confirm their qualifications. Among them, nine studies weren't RCTS; two used an intervention that wasn't an oral TCM, a TCM enema; and one study used no serum inflammatory factors as outcome measures. Finally, the reviewers included 22 RCTs, all of which were from Chinese literature.

RCTs' Characteristics

The 22 studies included data from 1957 patients, 977 in the intervention groups and 980 in the control groups (Table 1).[11-32] The researchers had conducted all 22 studies in China and published the results in Chinese. Among them, five studies used oral TCM, and 17 used TCM+WM.

The measurement of cytokines included: (1) 13 studies—IL-6 levels,[11,13,17-20,22,25,27-29,31,32] (2) seven studies—IL-8 levels[11,21,27,29-32]; (3) 16 studies—TNF-α levels[12,16,18-25,27,28,19,30-32]; (4) four studies—IL-17 levels[14,16,24,26]; (5) four studies—IL-4 levels[15,17,23,25]; (6) six studies—IL-10 levels[17,19,24-27]; (7) two studies—IL-23[14,26]; (8) two studies—IFN-γ levels,[15,25] and (9) one study each—IL-1,[17] IL-1β,[20] IL-2,[25] IL-13,[25] and IL-21[16] levels.

Quality Evaluation

Figures 2 and 3 show the results of the bias risk assessments. Of the 22 studies, 21 mentioned randomized control, including 13 that mentioned use of random number tables for grouping. One study didn't mention randomized control.[31]

None of the studies mentioned allocation concealment, blinding of participants and personnel, or blinding of outcome assessments. One study mentioned 14 participant who were lost to follow-up, with a loss rate of 10.8%,[17] but the remaining 21 studies indicated that they had no loss to follow-up or withdrawals.

The results of all studies were complete, and the research team believed that studies' researchers hadn't selectively reported the results. In one study, the treatment time of the two groups was different, and the research team included it under "having other bias."[30]

Table 1. Characteristics of the RCTs (N = 1957). All included RCTs were from Chinese publications.

Table 1A	Intervention Groups (n = 1018)							
						Disease Condition		
RCTs	Study Period	n	Age SMD ± SD	Males/ Females n (%)	Course of UC, y SMD ± SD	Mild n (%)	Moderate n (%)	Severe n (%)
Chen et al, 2007[11]	2006	60	38.5 ± 6.3[a]	26 (43.33) / 34 (56.67)[a]	3.5 ± 0.6[a]	38[a]	22[a]	0
Zhai et al, 2017[12]	2014.1-2016.3	32	38.35 ± 2.33	18 (56.25) / 14 (43.75)	25.38 ± 10.37[b]	NR	NR	NR
Fan et al, 2018[13]	NR	48	38.33 ± 10.17	21 (43.75) / 27 (56.25)	15.58 ± 5.26[b]	22 (45.83)	26 (54.17)	0 (0.00)
Guo et al, 2017[14]	2015.1-2017.1	75	35.41 ± 7.29	42 (56.00) / 33 (44.00)	4.28 ± 1.36	32 (42.67)	37 (49.33)	6 (8.00)
Hong et al, 2019[15]	2016.2-2018.2	40	43.20 ± 6.40	18 (45.00) / 22 (55.00)	5.29 ± 1.45	0 (0.00)	40 (100.00)	0 (0.00)
Li et al, 2013[16]	NR	40	44.3 ± 7.6	26 (65.00) / 14 (35.00)	3.1 ± 1.7	NR	NR	NR
Liu et al, 2019[17]	2016.7-2018.6	65	35.08 ± 13.42	39 (60.00) / 26 (40.00)	3.91 ± 3.04	15 (23.08)	35 (53.84)	15 (23.08)
Liu et al, 2012[18]	2009.3-2012.3	30	35.3 ± 8.6	16 (53.33) / 14 (46.67)	5.8 ± 3.6	8 (26.67)	22 (73.33)	0 (0.00)
Luo, 2018[19]	2015.1-2018.1	60	38.78 ± 14.12	23 (38.33) / 37 (61.67)	3.57 ± 1.63	NR	NR	NR
Shou et al, 2020[20]	2016.8-2019.6	43	50.73 ± 10.87	24 (55.81) / 19 (44.19)	3.86 ± 0.87	22 (51.16)	18 (41.86)	3 (6.98)
Tang et al, 2017[21]	2013.4-2015.4	34	36.05 ± 13.11	18 (52.94) / 16 (47.06)	3.62 ± 1.37	15 (44.12)	19 (55.88)	0 (0.00)
Wang et al, 2017[22]	2014.2-2016.4	32	35.18 ± 5.60	18 (56.25) / 14 (43.75)	5.22 ± 1.48	15 (46.88)	17 (53.12)	0 (0.00)
Wang, 2011[23]	2009.6-2010.5	30	46 (27-70)[c]	12 (40.00) / 18 (60.00)	NR	NR	NR	NR
Zhan et al, 2019[24]	2018.9-2018.12	30	44.90 ± 9.00	15 (50.00) / 15 (50.00)	4.35 ± 3.24	14 (46.67)	7 (23.33)	9 (30.00)
Zhang et al, 2020[25]	2017.2-2018.8	41	50.47 ± 9.34	24 (58.54) / 17 (41.46)	2.61 ± 0.94	0 (0.00)	0 (0.00)	41 (100.00)
Zhu et al, 2017[26]	2015.1-2016.6	39	41.18 ± 20.32	22 (56.41) / 17 (43.59)	7.02 ± 4.76	NR	NR	NR
Zhao, 2020[27]	2016.6-2019.6	42	46.75 ± 4.96	24 (57.14) / 18 (42.86)	4.18 ± 1.43	19 (45.24)	17 (40.48)	6 (14.28)
Liu et al, 2018[28]	2015.5-2017.5	60	42.60 ± 6.43	24 (40.00) / 36 (60.00)	3.27 ± 0.89	NR	NR	NR
Wang, 2020[29]	2016.1-2018.1	48	38.42 ± 7.58	29 (60.42) / 19 (39.58)	3.11 ± 1.37	NR	NR	NR
Wu et al, 2016[30]	2013.12-2015.12	31	39.20 ± 3.60	20 (64.52) / 11 (35.48)	NR	NR	NR	NR
Gao et al, 2018[31]	2015.8-2016.9	101	33.25 ± 5.76	56 (55.45) / 45 (44.55)	3.23 ± 1.03	NR	NR	NR
Xie et al, 2017[32]	2013.4-2015.8	37	46.87 ± 6.64	21 (56.76) / 16 (43.24)	6.62 ± 0.96	NR	NR	NR

[a]Information representing Intervention groups and Control Groups;
[b]The unit is the month;
[c]The study used median and range for statistical analysis.

Abbreviations: NR, not recorded**;** RCTs, randomized controlled trials; UC, ulcerative colitis.

Table 1B	Control Groups (N = 988)							
						Disease Condition		
RCTs	Study Periods Years	n	Age SMD ± SD	Males/Females N (%)	Course of UC, y SMD ± SD	Mild n (%)	Moderate n (%)	Severe n (%)
Chen et al, 2007[11]	2006	30	-	-	-	-	-	-
Zhai et al, 2017[12]	2014.1-2016.3	32	40.51 ± 3.32	19 (59.38) / 13 (40.62)	24.75 ± 9.62	NR	NR	NR
Fan et al, 2018[13]	NR	48	39.12 ± 11.16	23 (47.92) /25 (52.08)	16.28 ± 6.87	20 (41.67)	28 (58.33)	0 (0.0)
Guo et al, 2017[14]	2015.1-2017.1	75	36.53 ± 7.60	46 (61.33) / 29 (38.67)	4.09 ± 1.15	31 (41.33)	39 (52.00)	5 (6.67)
Hong et al, 2019[15]	2016.2-2018.2	42	43.94 ± 7.22	19 (45.24) / 23 (54.76)	5.48 ± 1.62	42 (100.00)	0 (0.00)	0 (0.00)
Li et al, 2013[16]	NR	40	43.9 ± 8.1	28 (70.00) / 12 (30.00)	3.4 ± 1.5	NR	NR	NR
Liu et al, 2019[17]	2016.7-2018.6	65	36.81 ± 14.29	35 (53.85) / 30 (46.15)	3.75 ± 2.95	16 (24.62)	36 (55.38)	13 (20.00)
Liu et al, 2012[18]	2009.3-2012.3	30	36.5 ± 7.9	15 (50.00) / 15 (50.00)	5.1 ± 3.2	10 (33.33)	20 (66.67)	0 (0.00)
Luo, 2018[19]	2015.1-2018.1	60	39.67 ± 14.65	25 (41.67) / 35 (58.33)	3.94 ± 1.58	NR	NR	NR
Shou et al, 2020[20]	2016.8-2019.6	43	51.03 ± 11.08	23 (53.49) / 20 (46.51)	4.03 ± 1.04	22 (51.17)	17 (39.53)	4 (9.30)
Tang et al, 2017[21]	2013.4-2015.4	34	35.14 ± 12.27	20 (58.82) / 14 (41.18)	3.58 ± 1.24	12 (35.29)	22 (64.71)	0 (0.00)
Wang et al, 2017[22]	2014.2-2016.4	35	33.89 ± 6.01	20 (57.14) / 15 (42.86)	5.17 ± 1.59	16 (45.71)	19 (54.29)	0 (0.00)
Wang, 2011[23]	2009.6-2010.5	30	40 (22-65)[a]	14 (46.67) / 16 (53.33)	NR	NR	NR	NR
Zhan et al, 2019[24]	2018.9-2018.12	30	43.30 ± 7.85	13 (43.33) / 17 (56.67)	4.36 ± 3.39	15 (50.00)	7 (23.33)	8 (26.67)
Zhang et al, 2020[25]	2017.2-2018.8	41	49.75 ± 8.58	27 (65.85) / 14 (34.15)	2.56 ± 0.87	0 (0.00)	0 (0.00)	41 (100.00)
Zhu et al, 2017[26]	2015.1-2016.6	34	42.13 ± 20.46	20 (58.82)/ 14 (41.18)	7.34 ± 4.61	NR	NR	NR
Zhao, 2020[27]	2016.6-2019.6	42	47.21 ± 4.82	23 (54.76) / 19 (45.24)	4.02 ± 1.31	18 (42.86)	16 (38.10)	8 (19.04)
Liu et al, 2018[28]	2015.5-2017.5	60	42.79 ± 6.50	26 (43.33) / 34 (56.67)	3.44 ± 0.92	NR	NR	NR
Wang, 2020[29]	2016.1-2018.1	48	37.34 ± 6.81	31 (64.58) / 17 (35.42)	3.23 ± 1.45	NR	NR	NR
Wu et al, 2016[30]	2013.12-2015.12	31	38.90 ± 4.20	19 (61.29) / 12 (38.71)	NR	NR	NR	NR
Gao et al, 2018[31]	2015.8-2016.9	101	32.89 ± 5.81	54 (53.47) / 47 (46.53)	3.46 ± 1.06	NR	NR	NR
Xie et al, 2017[32]	2013.4-2015.8	37	47.46 ± 6.70	19 (51.35) / 18 (48.65)	6.53 ± 0.93	NR	NR	NR

[a]The study used median and range for statistical analysis

Abbreviations: NR, not recorded**;** RCTs, randomized controlled trials; UC, ulcerative colitis

Table 1C	Treatments			
RCTs	Intervention Group	Control Group	Course of Treatment, d	Serum Cytokines
Chen et al, 2007[11]	TCM + SASP	SASP	30	IL-6, IL-8
Zhai et al, 2017[12]	TCM + Mesalazine	Mesalazine	30	TNF-α
Fan et al, 2018[13]	TCM + Mesalazine	Mesalazine	70	IL-6
Guo et al, 2017[14]	TCM + Mesalazine	Mesalazine	28	IL-17, IL-23
Hong et al, 2019[15]	TCM + Mesalazine & Cyclosporine A	Mesalazine & Cyclosporine A	60	IL-4, IFN-γ
Li et al, 2013[16]	TCM + Mesalazine	Mesalazine	56	TNF-α, IL-17, IL-21
Liu et al, 2019[17]	TCM + Mesalazine	Mesalazine	28	IL-1, IL-4, IL-6, IL-10
Liu et al, 2012[18]	TCM	SASP	30	TNF-α, IL-6
Luo, 2018[19]	TCM	Mesalazine	30	TNF-α, IL-6, IL-10
Shou et al, 2020[20]	TCM + SASP	SASP	120	TNF-α, IL-6, IL-1β
Tang et al, 2017[21]	TCM	Mesalazine	30	TNF-α, IL-8
Wang et al, 2017[22]	TCM + Mesalazine	Mesalazine	56	TNF-α, IL-6
Wang, 2011[23]	TCM	SASP	56	TNF-α, IL-4
Zhan et al, 2019[24]	TCM + Mesalazine	Mesalazine	56	TNF-α, IL-10, IL-17
Zhang et al, 2020[25]	TCM + Mesalazine	Mesalazine	28	IL2, IL-4, IL-6, IL-10, IL-13, IFN-γ, TNF-α
Zhu et al, 2017[26]	TCM + Mesalazine	Mesalazine	28	IL-10, IL-17, IL-23
Zhao, 2020[27]	TCM+SASP	SASP	56	IL-6, IL-8, IL-10, TNF-α
Liu et al, 2018[28]	TCM + Oxalazine sodium	Oxalazine sodium	14	TNF-α, IL-6
Wang, 2020[29]	TCM + Mesalazine	Mesalazine	28	TNF-α, IL-6,IL-8
Wu et al, 2016[30]	TCM	SASP	TCM: 14; SASP: 60	TNF-α, IL-8
Gao et al, 2018[31]	TCM + Mesalazine	Mesalazine	30	IL-6, IL-8, TNF-α
Xie et al, 2017[32]	TCM + Mesalazine	Mesalazine	28	TNF-α, IL-6, IL-8

Abbreviations: IFN-γ, interferon-gamma; IL, interleukin; SASP, salazosulfapyridine; TCM, traditional Chinese medicine; TNF-α, tumor necrosis factor alpha.

Figure 2. Bias risk assessment for included studies.

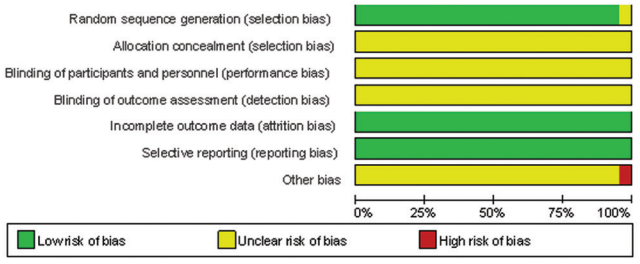
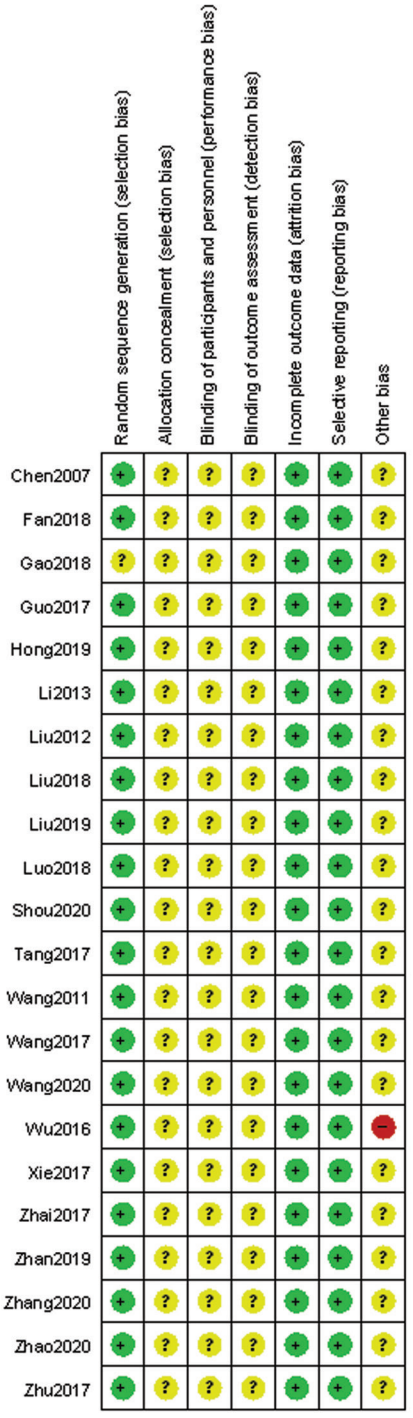


Figure 3. Summary of bias risk.



IL-6 Levels

Thirteen studies reported IL-6 levels (Figure 4).[11,13,17-20,22,25,27-29,31,32] Participants in two studies received oral TCM only, and the intervention and control groups had 90 participants each.[18,19] Participants in 11 studies received oral TCM+WM; the groups included 541 participants in the 11 intervention groups and 542 participants in the 11 control groups.

Heterogeneity existed among the studies: (1) TCM compared to WM—$I^2 = 65\%$, $P = .09$; and (2) TCM+WM compared to WM—$I^2 = 97\%$, $P < .00001$.

The TCM only and TCM+WM groups had significantly lower levels of IL-6 than the control groups did: (1) TCM compared to WM—SMD -0.95, 95%CI -1.50 to -0.41, $P = .0006$; (2) TCM+WM compared to WM—SMD -2.93, 95%CI -3.84 to -2.02, $P < .00001$; and (3) total: SMD -2.60, 95%CI -3.37 to -1.83, $P < .00001$.

IL-8 Levels

Seven studies reported IL-8 levels (Figure 5).[11,21,27,29-32] Two studies used oral TCM only, the combined intervention and the control groups had 65 participants each.[21,30] Five studies used oral TCM+WM, and the combined intervention and control groups had 258 participants each.

The evaluation revealed significant heterogeneity between the studies: (1) TCM compared to WM—$I^2 = 93\%$, $P < .00001$; and (2) TCM+WM compared to WM—$I^2 = 94\%$, $P < .00001$.

The TCM only and TCM+WM groups had significantly lower levels of serum IL-8 than the control groups did: (1) TCM compared to WM—SMD -3.27, 95%CI -5.45 to -1.08, $P = .003$; (2) TCM+WM compared to WM—SMD -2.19, 95%CI -3.11 to -1.28, $P < .00001$; and (3) total—SMD -2.49, 95%CI -3.34 to -1.64, $P < .00001$.

TNF-α Levels

Sixteen studies reported TNF-α levels (Figure 6).[12,16,18-25,27,28,19,30-32] Five studies used oral TCM only, and the combined intervention and control groups had 185 participants each.[18,19,21,23,30] Eleven studies used oral TCM+WM; the combined groups included 506 participants in the 11 intervention groups and 509 in the 11 control groups.

Significant heterogeneity existed between studies: (1) TCM compared to WM—$I^2 = 94\%$, $P < .00001$; and (2) TCM+WM compared to WM—$I^2 = 84\%$, $P < .00001$.

The TCM only and TCM+WM groups had significantly lower TNF-α levels than the control groups did: (1) TCM compared to WM—SMD -1.73, 95%CI -2.71 to -0.74, $P = .0006$; (2) TCM+WM compared to WM—SMD -1.70, 95%CI -2.07 to -1.32, $P < .00001$; and (3) total—SMD -1.70, 95%CI -2.07 to -1.33, $P < .00001$.

IL-17 Levels

Four studies reported IL-17 levels (Figure 7).[14,16,24,26] All of them used oral TCM+WM, and the combined intervention and control groups had 182 participants each. Significant heterogeneity existed between the studies ($I^2 = 97\%$, $P < .00001$). The TCM+WM groups had significantly lower

IL-17 levels than the control groups did (SMD -2.99, 95%CI -4.66 to -1.31, $P = .0005$.

IL-21 Levels

Only one study reported IL-21 levels (data not shown).[16] It used oral TCM+WM and included 40 participants in each group. The oral TCM+WM group had significantly lower serum IL-21 levels than the control group did ($P < .05$).

IL-1β Levels

Only one study reported IL-1β levels (data not shown).[20] The intervention group received oral TCM+WM, and the study had 43 participants in each group. The oral TCM+WM group had significantly lower serum IL-1β levels than the control group did ($P < .05$).

IL-1 Levels

Only one study reported IL-1 levels (data not shown).[17] The intervention group received oral TCM+WM, and the study had 59 participants in the intervention group and 57 in the control group. The TCM+WM group had significantly lower serum IL-1 levels than the control group ($P < .05$).

IL-2 Levels

One study reported IL-2 levels.[25] The intervention group received oral TCM+WM, and the study had 41 participants in each group. The TCM+WM group had significantly lower serum IL-2 levels than the control group did ($P < .05$).

IL-13 Levels

The single study mentioned in the section above also reported IL-13 levels.[25] The oral TCM+WM group had significantly higher serum IL-13 levels than the control group did ($P < .05$).

Figure 4. Meta-analysis forest map of IL-6 levels in the observation and control groups.

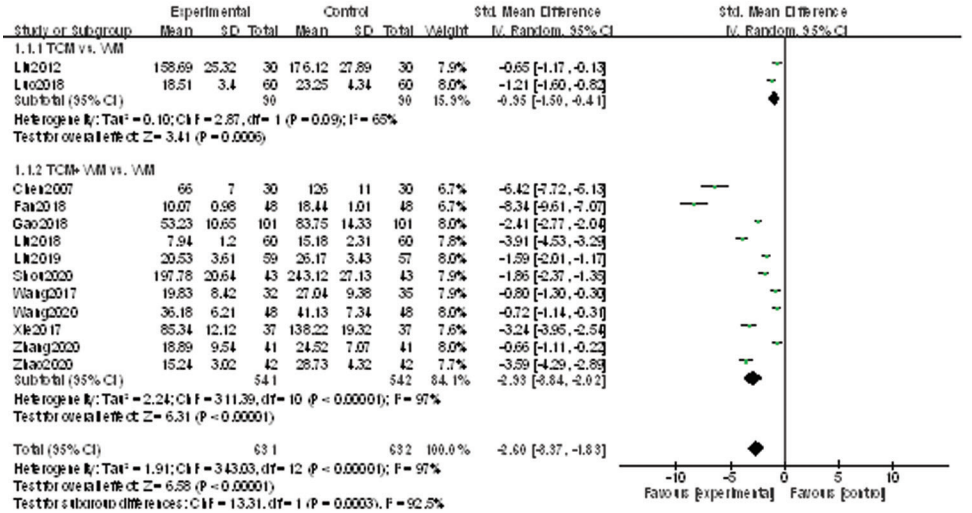


Figure 5. Meta-analysis forest map of IL-8 levels in the observation and control groups.

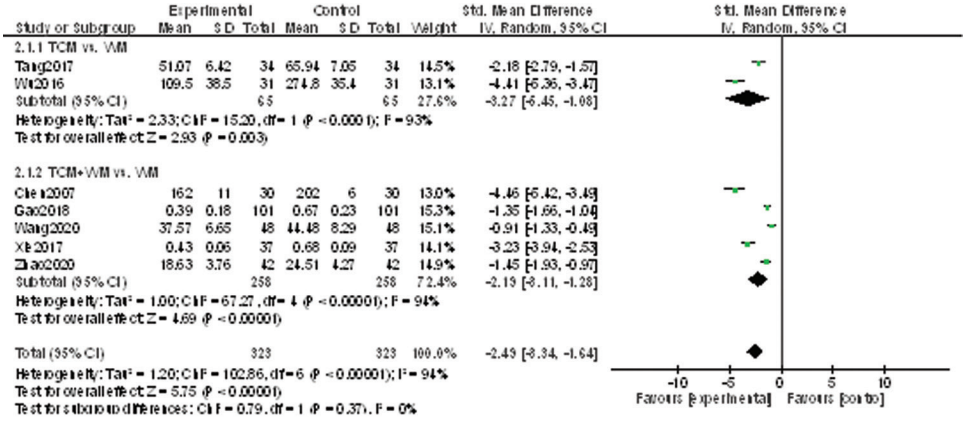


Figure 6. Meta-analysis forest map of TNF-α levels in the observation and control groups.

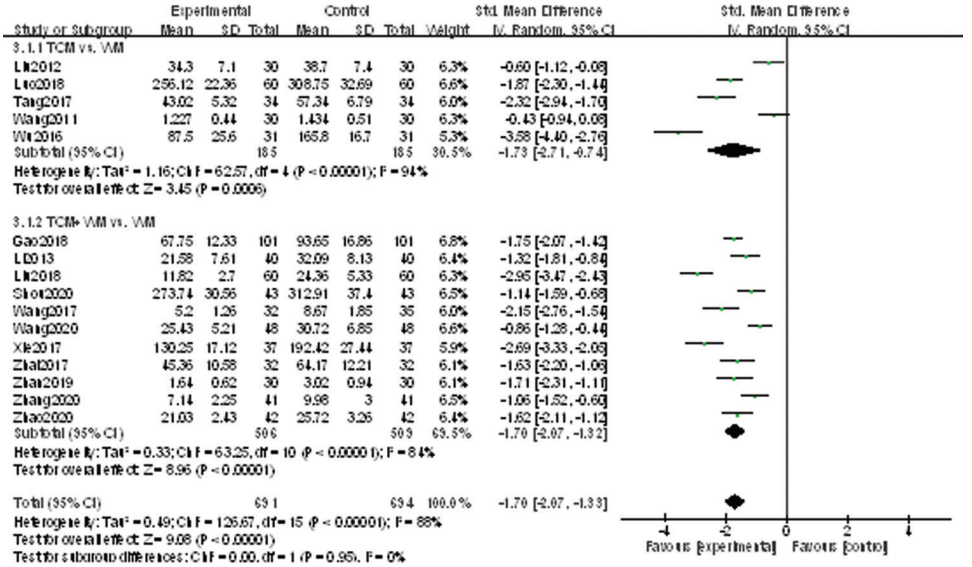


Figure 7. Meta-analysis forest map of IL-17 levels in the observation and control groups.

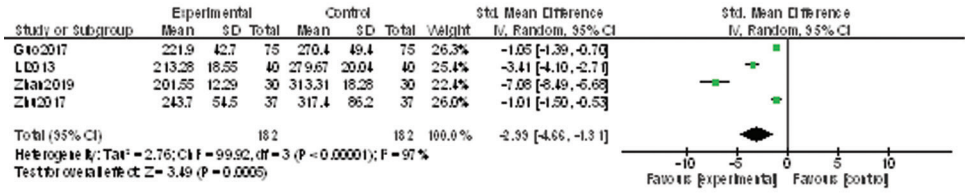


Figure 8. Meta-analysis forest map of IL-4 levels in the observation and control groups.

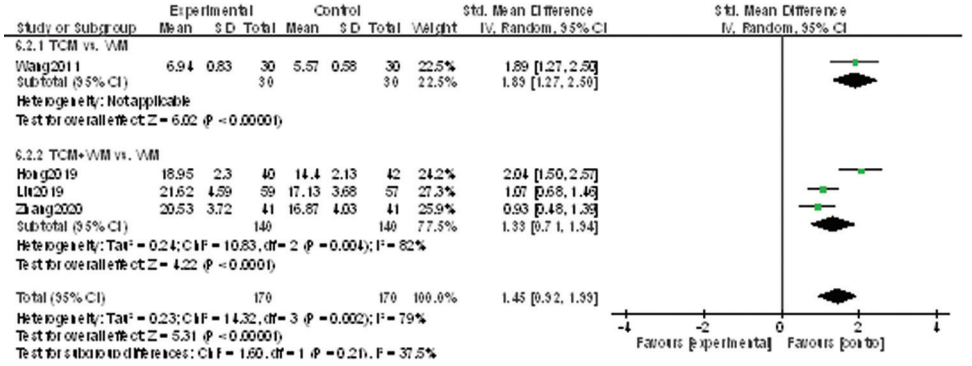


Figure 9. Meta-analysis forest map of IL-10 levels in the observation and control groups.

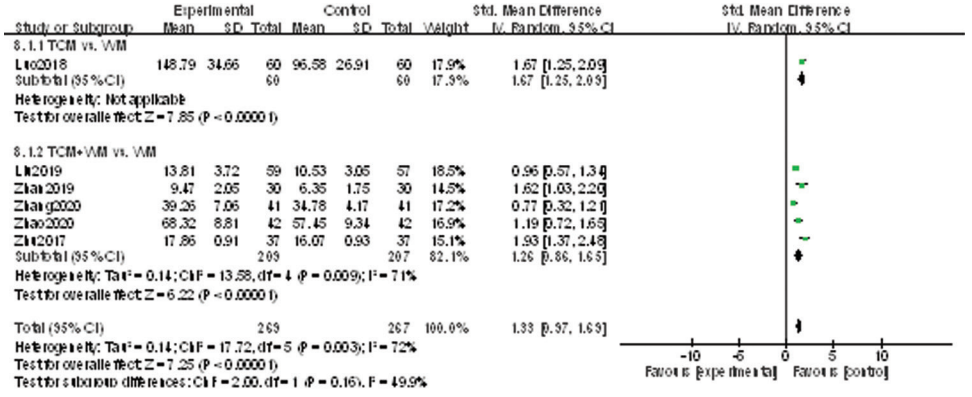


Figure 10. Meta-analysis forest map of IL-23 levels in the observation and control groups.

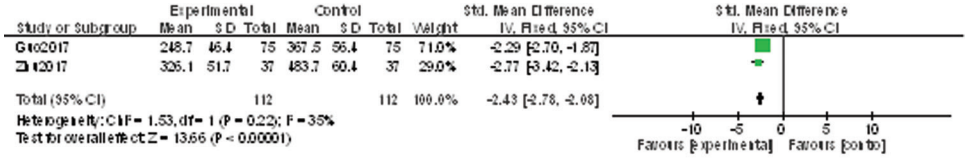
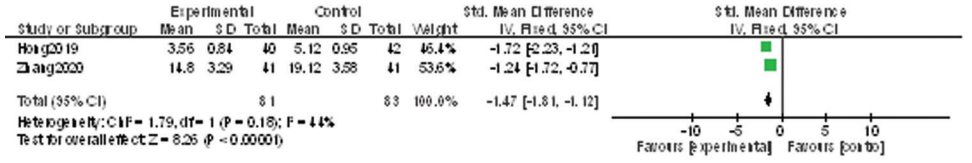


Figure 11. Meta-analysis forest map of IFN-γ levels in the observation and control groups.



IL-4 Levels

Four studies reported IL-4 levels (Figure 8).[15,17,23,25] One study used oral TCM only, and the combined intervention and control group had 30 participants each.[23] Three studies used oral TCM+WM, and the combined intervention and the control groups had 170 participants each.

Significant heterogeneity existed in the study: (1)TCM+WM compared to WM—I^2 = 82%; P = .004; and (2) total—I^2 = 79%, P = .002.

The TCM only and TCM+WM groups had significantly higher serum IL-4 levels: (1) TCM only compared to WM—SMD 1.89, 95%CI 1.27-2.50, P < .00001; (2) TCM+WM compared to WM—SMD 1.33, 95%CI 0.71-1.94, P < .00001; and (3) total—SMD 1.45, 95%CI 0.92-1.99, P < .00001.

IL-10 Levels

Six studies reported IL-10 levels (Figure 9).[17,19,24-27] One study used oral TCM only, and the combined intervention and the control groups had 60 participants each.[19] Five studies used oral TCM+WM, and the combined intervention and control groups had 209 and 207 participants, respectively.

The heterogeneity was significant between studies: (1) TCM+WM compared to WM—I^2 = 71%; P = .009; and (2) total—I^2 = 72%, P = .003).

The TCM only and TCM+WM groups had significantly higher serum IL-10 levels than the control group did: (1) TCM only compared to WM—SMD 1.67, 95%CI 1.25-2.09, P < .00001; (2) TCM+WM compared to WM—SMD 1.26, 95% CI 0.86-1.65; and (2) total—SMD 1.33, 95%CI 0.97-1.69, P < .00001.

IL-23 Levels

Two studies reported IL-23 levels, and participants in both received oral TCM+WM (Figure 10).[14,26] The combined intervention and the control groups had 112 participants each.

Homogeneity existed between the studies (I^2 = 35%, P = .22), and the research team used the fixed effect model to analyze the results. The TCM++WM had significantly lower serum IL-23 levels than the control group did (SMD -2.43, 95%CI -2.78 to -2.08, P < .00001.

IFN-γ Levels

Two studies reported IFN-γ levels (Figure 11).[15,25] Both used TCM +WM, and the combined intervention and control groups had 81 and 83 participants, respectively.

Homogeneity existed between the studies (I^2 = 44%, P = .18). The TCM+WM group had significantly lower serum IFN-γ levels than the control group did (SMD -1.47, 95% CI -1.81 to -1.12, P < .00001.

Heterogeneity Analysis

Other than IL-23 and IFN- γ, the serum cytokines had significant heterogeneity. This might have occurred due to inconsistency in the studies' baseline levels, follow-up times, and instruments, resulting in clinical heterogeneity. Using the random effects model for the meta-analysis may have corrected the heterogeneity and made the results more credible.

Sensitivity Analysis

In an analysis of the outcomes, after excluding each study in turn, the research team found that no obvious changes in the outcomes occurred, although the analysis included one less outcome measure each time, which indicates that the meta-analysis was stable and the results are reliable.

Assessment of Publication Bias

The Egger's test of the serum TNF-α levels in the related studies showed that no publication bias existed (P = .114, 95% CI -12.97to -1.56).

DISCUSSION

The current review and meta-analysis found that the use of oral TCM or a combination of TCM and WM might be more effective in reducing levels of the proinflammatory cytokines IL-6, IL-8, TNF-α, IL-17, IL-23, IFN-γ, IL-21, IL-1, IL-1β, IL-2 and in increasing the levels of the anti-inflammatory cytokines IL-4, IL-10, and IL-13 for UC patients with dampness-heat syndrome. Oral TCM or a combination of TCM and WM may control inflammation more effectively by adjusting the ratio of proinflammatory and anti-inflammatory cytokines.

The current analysis had some limitations. First, clinical heterogeneity in the study was difficult to eliminate. Second, none of the included studies mentioned blinding, which may have led to bias. Third, the cytokines mentioned in the included articles were different, resulting in a limited analysis of each cytokine. In addition, the compositions of the TCMs included in the studies weren't the same. No study has occurred on the influence of a particular TCM on serum cytokines in UC patients. Therefore, researchers need to perform more uniform and standardized studies to further explore the effects of TCM on UC.

CONCLUSIONS

Oral TCM or TCM+WM can reduce the proinflammatory response and increase the anti-inflammatory response of UC patients by regulating serum cytokines and can obtain a better clinical effect than WM only. These benefits can alleviate intestinal inflammation in patients and have a positive effect on clinical efficacy. In the future, more high-quality, large-sample, and long-term follow-up randomized controlled trial are necessary to support research analysis.

AUTHORS' DISCLOSURE STATEMENT

The authors declare that they have no conflicts of interest related to the study. The Scientific Research Program of Shanghai Science and Technology Commission (Grant/Award Number: 18401904100), and the Hospital-level fund of Yueyang Integrated Traditional Chinese and Western Medicine Hospital affiliated to Shanghai University of Traditional Chinese Medicine (Grant/Award Number: 2018YJ14) supported the study.

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