

# Randomized Clinical Trials of Traditional Chinese Medicines for Treating Ulcerative Colitis: A Scoping Review

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## Abstract

**Objective:** Traditional Chinese medicines (TCMs) are efficacious against ulcerative colitis (UC). In recent years, the number of randomized clinical trials (RCTs) of TCM has increased. Thus, it is very important to summarize the basic characteristics, quality, and types of TCM interventions in published RCTs. This scoping review was performed to systematically identify and describe the current situations about RCTs of TCMs for treating UC. Hope to express the focus and specifics of nowadays research in TCM interventions in RCTs and evaluate their common disadvantages exposed to help advance in TCM researching. **Materials and Methods:** A scoping review was conducted according to the PRISMA extension for scoping reviews. We searched two English databases and four Chinese databases from the date of establishment of each database to January 2020. Data from RCTs focusing on any TCM treatment for patients with UC were extracted and evaluated. Selection and characterization were performed by two independent reviewers using predefined forms. All discrepancies were resolved by consensus discussion with a third reviewer. Microsoft Excel 2010 was used to extract the following data from the included studies: (1) basic information of the included studies including research ID, article title, publication language, journal, year of publication, and funding information; (2) patient information including gender, age, disease course, disease stage, severity, sample size; and (3) information on intervention measures, types of intervention measures, drug dosage forms, and treatment courses. **Results:** The search identified 2225 RCTs published between 1987 and 2020. These studies covered 36 provinces in China. The time frame of the RCTs was <28 days in approximately one-third of the RCTs (647, 29.08%). Only one RCT was published in English. Nearly three-quarters of RCTs (1665, 74.83%) did not report the severity of the disease. Three types of interventions were included in the RCTs: pharmacotherapy (2028, 91.15%), nonpharmacotherapy (57, 2.56%), and a combination of the two (140, 6.29%). The administration modes of the intervention groups were evaluated. Drug therapy involved 12 types of TCM dosage forms, which were decoctions, troches, powders, capsules, granules, pills, suppositories, ointments, injections, gels, oral liquids, and substitute tea according to the frequency of use. Nondrug intervention measures involved 10 treatment options, namely, acupuncture, moxibustion, hemospasia, auricular point, acupoint catgut embedding, acupoint injection, scrapping, tuina, acupoint application, and five-tone therapy according to the frequency of use. Most studies included in this review were low in quality. This underscores the need for improvement in the quality of trial methodology in TCM RCTs.

**Keywords:** Dosage forms, randomized clinical trial, research status, scoping review, Traditional Chinese medicine, ulcerative colitis

## INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease affecting the colonic mucosa. Clinical manifestations include diarrhea, abdominal pain, bloody mucous stools, and systemic symptoms of different degrees, and the course of the disease is more than 4–6 weeks.<sup>[1]</sup> Current Western medicine options include treatment with 5-aminosalicylic acid preparations, glucocorticoids, immunosuppressants, biological agents, and surgical treatment.<sup>[2]</sup> Depending on the clinical severity, UC can be divided into three grades, namely mild, moderate, and

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**Received:** 09-12-2020, **Accepted:** 17-01-2021, **Published:** 29-04-2021

**How to cite this article:** Zheng YY, Wang X, Si JT, Sun YX, Hou WB, Liu JP, *et al.* Randomized clinical trials of traditional chinese medicines for treating ulcerative colitis: A scoping review. World J Tradit Chin Med 2021;7:326-31.

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**DOI:**  
10.4103/wjtcn.wjtcn\_22\_21

severe.<sup>[1]</sup> The prevalence of UC in China is approximately 11.6 per 100,000 people.<sup>[3]</sup> In recent years, the incidence of UC has been increasing. The long course of the disease and its high recurrence greatly affect the patient's quality of life.<sup>[4,5]</sup>

According to clinical manifestations, chronic diarrhea, hemostasis, mucus, and stomachaches associated with UC can be treated using Traditional Chinese Medicine (TCM).<sup>[6]</sup> TCM can improve the clinical symptoms of UC, thus improving the quality of life of patients, enhancing confidence, and creating conditions for follow-up treatment.<sup>[7]</sup>

Recently, several single-arm trials about TCM have shown good curative effects in the treatment of UC.<sup>[8-12]</sup> Those cited reports have shown the same conclusion that TCM methods have curative effectiveness in result of curative effectiveness at TCM syndrome. In recent years, the number of randomized clinical trials (RCTs) of TCM has increased; therefore, it is very important to summarize the basic characteristics, quality, and types of intervention measures of these articles. A scoping review systematically maps a broad and diverse body of research evidence.<sup>[13]</sup> We conducted this scoping review to systematically identify and describe RCTs in TCM for the treatment of UC to generate high-quality evidence-based information for clinicians and researchers.

## MATERIALS AND METHODS

### Literature search

We searched the China National Knowledge Infrastructure, Chinese Scientific Journal Database, Wanfang Database, Chinese CBM Database, the Cochrane Library, and PubMed from inception to January 2020. Search terms included “ulcerative colitis,” “UC,” “traditional Chinese medicine,” “traditional medicine, Chinese,” “Zhong Yi Xue,” “Chinese traditional medicine,” “Chinese medicine, traditional,” “cupping,” “scraping therapy,” “guasha,” “tuina,” “moxibustion,” and “acupuncture.”

We used Note Express software (Note Express. 3.2.0.6941. April 2016. Beijing Aegean Software Co., Ltd. Beijing, China.) to filter the titles and abstracts of the included articles. After filtering the abstract, we downloaded and filtered the full text of the article.

Microsoft Excel 2010 was used to extract the following data from the included studies: (1) basic information of the included studies, such as research ID, article title, publication language, journal, year of publication, and fund information; (2) patient information, including gender, age, disease course, disease stage, severity, sample size; and (3) information on intervention measures, types of intervention measures, drug dosage forms, and treatment courses. Only RCTs of Chinese medicines for treating UC were included.

The population, intervention, control, and outcomes strategy was used to guide researchers on the studies to be included to answer the research question. The study population comprised enrolled subjects from RCTs of TCMs for treating UC who

were above 18 years of age irrespective of sex, course, and severity of illness.

The review focused on studies in which treatments were adopted based on the guidance of TCM theory or TCM treatment combined with western medicine. Those combinations are described as several TCM decoctions through oral or enema with one common medicine like mesalazine which developed and recommend by western countries. These treatments consisted of drug therapy, nondrug therapy, and a combination of drug and nondrug therapy. The included studies were compared to studies in which similar conventional western medicines for treating UC, their dosages, and course of treatment were reported. The outcome measures in the included studies were whether the patients were cured of their UC conditions or not after TCM therapy. The current scoping review was conducted and reported according to the PRISMA extension for scoping reviews.<sup>[14]</sup>

We used the Cochrane Risk of Bias Assessment Tool to assess the risk of bias which was categorized as low, high, or unclear.<sup>[15]</sup> The risk of bias assessment included random sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting, and other biases.

## RESULTS

### Description of the literature

A total of 27,854 relevant studies were retrieved and 2225 RCTs were finally included after screening. The screening process is shown in Figure 1.

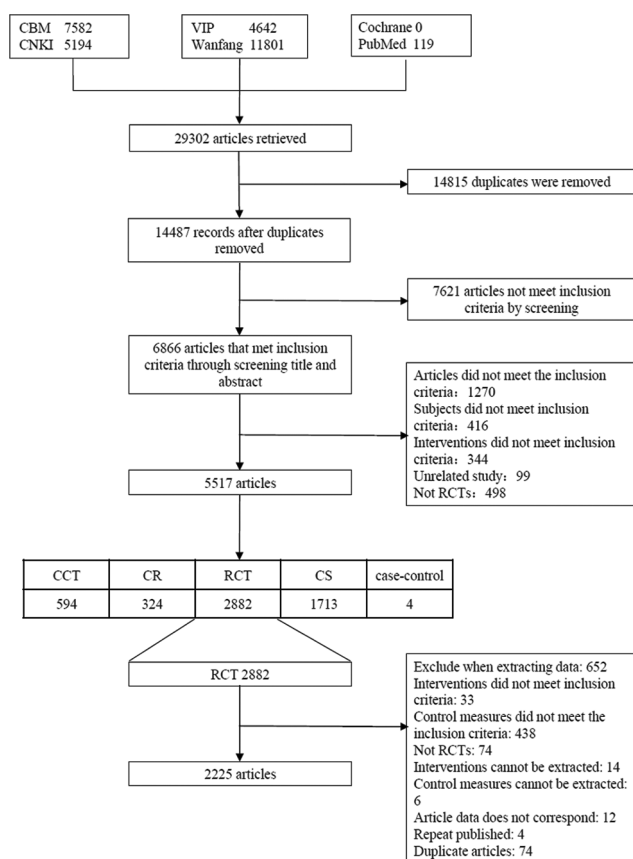
### Basic information of included trials

In recent years, RCTs of TCM for UC have increased; the publication trend is shown in Figure 2. These studies covered several provinces in China. More than 100 related studies were carried out in Henan (257, 11.55%), Jiangsu (188, 8.45%), Shandong (167, 7.51%), Guangdong (165, 7.42%), Hebei (151, 6.79%), Hunan (117, 5.26%), and Hubei (111, 4.99%) provinces [Figure 3]. A total of 647 (29.71%) of the studies were conducted in less than a month. The basic information of the included studies is shown in Table 1. In addition, 2224 (99.96%) studies were published in Chinese, and 1665 (74.83%) of these studies did not report the severity of the disease.

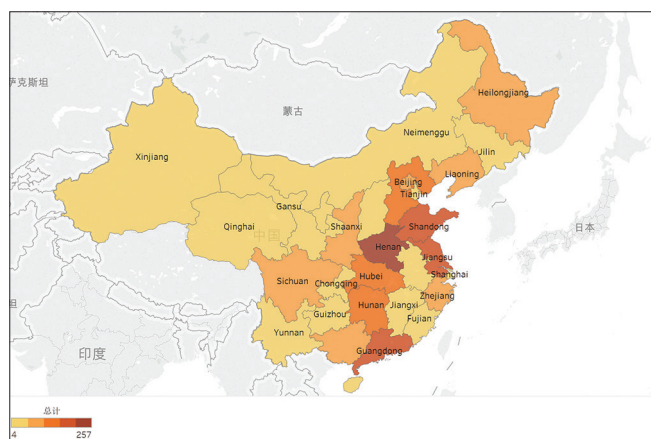
Of the included studies, 2028 (91.15%) used drug therapy, 57 (2.56%) used nondrug therapy, and 140 (6.29%) used a combination of drug therapy and nondrug therapy.

According to Table 2, most of included RCTs made comparisons of TCM drugs versus western medicine straightly 1359 (61.08%). And the second largest comparisons form are TCM drug + western medicine versus western medicine 709 (31.87%).

The administration modes of the intervention groups are shown in Table 3. Drug therapy involved 12 types of TCM dosage forms, which were decoctions, troches, powders, capsules, granules, pills, suppositories, ointments, injections, gels,



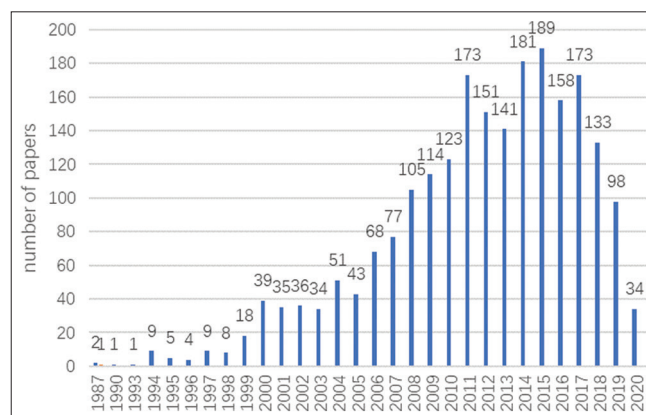
**Figure 1:** Flow chart depicting literature screening



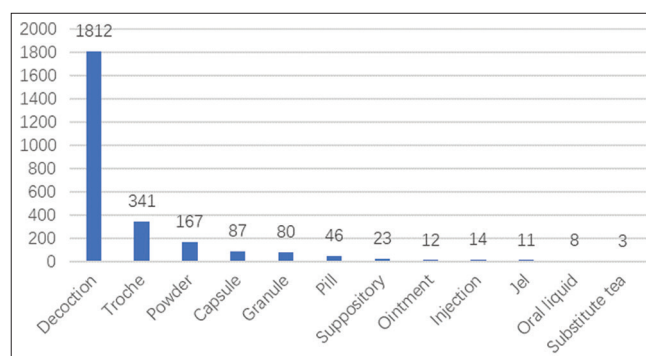
**Figure 3:** Study area distribution of the number of RCTs on TCM in the treatment of UC. RCTs: Randomized clinical trials, UC: Ulcerative colitis

oral liquids, and substitute teas according to the frequency of use [Figure 4]. Nondrug intervention measures involved 10 types of treatment measures, which were acupuncture, moxibustion, hemospasia, auricular point, acupoint catgut embedding, acupoint injection, scraping, tuina, acupoint application, and five-tone therapy according to the frequency of use [Figure 5].

Those included studies reported their results mainly in 12 forms of outcomes, which were clinical effective rate, therapeutic



**Figure 2:** Annual published trends in RCTs of TCM for UC. RCTs: Randomized clinical trials, UC: Ulcerative colitis



**Figure 4:** Distribution of TCM drug forms in the intervention group in RCT of TCM for UC. RCTs: Randomized clinical trials, UC: Ulcerative colitis

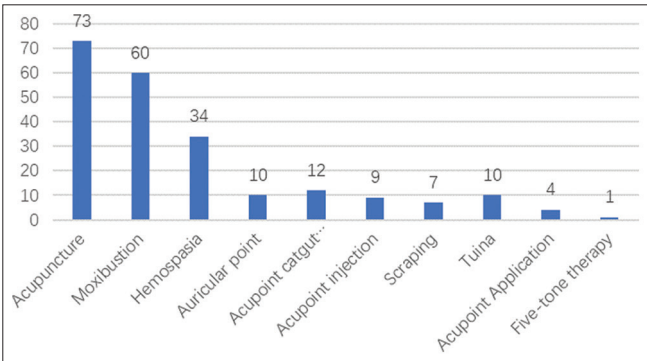
effect of TCM syndromes, score of TCM symptoms, therapeutic effect of enteroscope, Baron grade, factors of inflammation, blood routine, index of immunology, index of serum, disappearance time of the main symptom, adhesin, and flora levels.

### Risk of bias in included trials

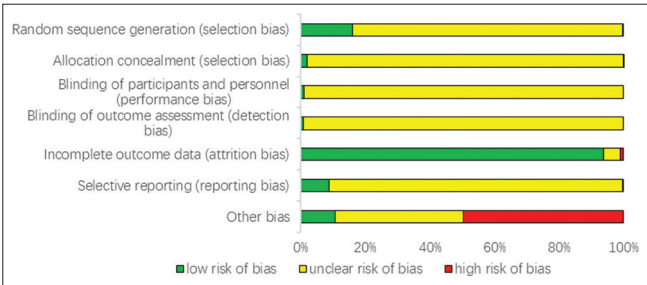
Most of the included studies did not describe random sequence generation and allocation concealment in detail or without description, and thus the risk of bias was “unclear.” There was almost no description of blinding of participants and personnel and blinding of outcome assessment [Figure 6]. A total of 1093 (49.12%) studies had only one author [Figure 7] and 414 (18.61%) studies were reported on less than one page.

### DISCUSSION

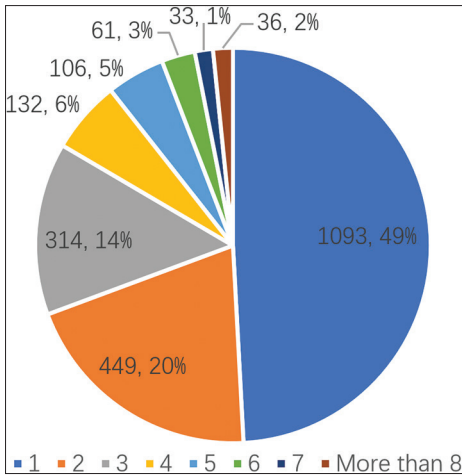
The incidence and prevalence of UC have increased gradually.<sup>[4,16]</sup> TCM plays an important role in the treatment of UC and has attracted the attention of researchers in recent years.<sup>[17,18]</sup> This review showed that more research on UC has been conducted in southern China than in northern China. This may be related to the higher incidence of UC in the former region.<sup>[18]</sup> As UC is a chronic disease, its treatment must be observed to determine its long-term effectiveness. A course of treatment that lasts <28 days may affect outcomes



**Figure 5:** Distribution of TCM no-drug forms in the intervention group in RCT of TCM for UC (TCM no-drug forms informs that therapies performed in articles are not decoction or finished drug forms absorbed through oral or enema ways to patients). RCTs: Randomized clinical trials, UC: Ulcerative colitis



**Figure 6:** Risk of bias of RCTs of UC (based on Cochrane risk of bias assessment tool). RCTs: Randomized clinical trials, UC: Ulcerative colitis



**Figure 7:** The number of authors of RCTs on TCM in the treatment of UC. RCTs: Randomized clinical trials, TCM: Traditional Chinese medicines, UC: Ulcerative colitis

and therefore, contribute to bias in the study results. Some studies did not report clear diagnostic criteria or the severity of UC. The internal validity of RCTs is affected if the subjects included are not strictly defined. Only one study was published in English, whereas others were published in Chinese, which is not conducive for international scholars to understand the effectiveness of TCM in treating UC.

**Table 1: Basic information of included randomized clinical trials of traditional Chinese medicines for ulcerative colitis**

Characteristics	RCTs, n (%)
Source of articles	
Journal articles	1999 (89.84)
Academic dissertations	202 (9.08)
Conference papers	24 (1.08)
Type of magazines	
Core journals	1037 (46.61)
SCI	1 (0.05)
General journals	961 (43.19)
Funding	
Yes	93 (4.18)
No	2128 (95.64)
Not reported	1 (0.05)
Language	
English	1 (0.05)
Chinese	2224 (99.96)
Diagnostic criteria	
Yes	1715 (77.08)
No	117 (5.26)
Not reported	393 (17.66)
Severity of the disease	
Mild	3 (0.14)
Moderate	3 (0.14)
Severe	4 (0.18)
Mild and moderate	239 (10.74)
Mild and severe	5 (0.23)
Moderate and severe	3 (0.14)
Mild, moderate, and severe	303 (13.62)
Not reported	1665 (74.83)

RCTs: Randomized clinical trials, SCI: Science citation index

**Table 2: Status of comparisons to different interventions**

Comparisons forms	RCTs, n (%)
TCM drug versus western medicine	1359 (61.08)
TCM drug versus western medicine + TCM drug	1 (0.05)
TCM drug + western medicine versus western medicine	709 (31.87)
TCM drug + TCM no-drug intervention versus western medicine	67 (3.01)
TCM drug + TCM no-drug intervention versus TCM drug	2 (0.09)
TCM drug + TCM no-drug intervention + western medicine versus TCM drug	14 (0.62)
TCM drug + TCM no-drug intervention versus TCM no-drug intervention	2 (0.09)
TCM no-drug intervention versus western medicine	49 (2.20)
TCM no-drug intervention + western medicine versus western medicine	20 (0.90)
TCM no-drug intervention versus TCM no-drug intervention	2 (0.09)

RCTs: Randomized clinical trials, TCM: Traditional Chinese medicines

The descriptions of random sequence generation and allocation concealment for the included RCTs are insufficient but are key links in the implementation of RCTs. Studies that did not



**Table 3: Intervention approaches in the intervention groups**

Administration in the intervention group	RCTs, n (%)
Oral administration	828 (37.21)
Clysis	581 (26.11)
Oral administration and clysis	688 (30.92)
Acupoint application	13 (0.58)
Venous transfusion	7 (0.31)
Anal plug	10 (0.45)
Hot compress	1 (0.05)
Iontophoresis	1 (0.05)
Aerosol inhalation	1 (0.05)
Use of two or more administration methods	45 (2.02)

RCTs: Randomized clinical trials

clearly report these factors or failed to allocate hiding tended to exaggerate their effect values, which ranged from 30% to 41%.<sup>[19]</sup> Nearly half of the included studies had only one author and did not mention the contributions of other investigators in their acknowledgments. However, random sequence generation and allocation hiding cannot be performed by a single person. Therefore, some bias is likely to occur. Evidence-based medicine considers a systematic review of RCTs as the highest level of evidence. The study showed that there was also a relationship between the quality of RCT reports and length of the report. Short RCTs containing few details exhibit low quality, which was a common feature in the current study, as 414 articles were no more than one page and did not report essential details. Apart from the length of the RCT reports, the number of articles used in scoping reviews impacts their quality.<sup>[20]</sup> Using a few articles for scoping reviews generates evidence that is not generalizable.

As a developing country, China has less funding invested in clinical trials of TCM, which may have contributed to the low quality of the TCM RCTs.<sup>[21]</sup> The credibility of the results of a systematic/scoping review of an RCT shows a linear relationship with the quality of the included RCTs. Low-quality RCTs lead to less credible systematic/scoping reviews and meta-analyses.<sup>[22,23]</sup> We recommend that future RCT studies be conducted in consultation with clinical researchers and methodologists to develop and register rigorous trial protocols and strictly adhere to them when trials are conducted. Moreover, relevant changes should be performed in the receiver of those researches. In order to avoid risk of bias, the journal should execute a stricter standard in reviewing of RCT submissions which paid insufficient attention in methodology. Especially self-made standards should be reconsidered carefully while there are common reviews or guidelines have existed. It is necessary to table roper suggestions about the author's methodology and performance of their RCTs. Submission should be rejected when its data, methodology, and record of intervention are not described clearly and correctly enough.

## CONCLUSIONS

The methodological quality of most of the studies included

in this review was low. Trials with rigorous methodology and improved quality of reporting are necessary to ensure that high-quality evidence exists to support clinical decision-making in UC. We, therefore, recommend that strategies to improve the quality of RCT of TCM are identified and implemented to strengthen the evidence supporting the curative properties of traditional medicines for treating UC.

## Study limitations

In this review, although we systematically searched multiple databases, there may still be omissions. In addition, the selection and extraction of data may lead to some bias. Among the RCTs included in this study, oral, clysis, and oral combined clysis were the most frequent modes of administration. The use of decoctions was highest in drug-based treatment modalities, whereas the use of acupuncture was the most common modality as a nondrug treatment approach. The results generated in the current study are based on published clinical research literature only; as such, the frequency of use of various treatments in practice may differ. Therefore, it is necessary to conduct investigations in a clinical setting to fully understand the use of various TCM treatment measures in clinical practice.

## Future research

Future research should consider the following topics: (1) how to optimally obtain research data, utilize the data, and design research studies; (2) how to identify efficacious drugs with high safety profiles to further carry out high-quality original research, providing a foundation for condensing and developing the essence of TCM; 3. The appropriate endeavor should be spent in formulating the standard of RCTs about TCM methods' publication in the future.

## Acknowledgments

The authors would like to thank Yuan-Xi Li, a postgraduate student at the College of Statistics and Data Science, Faculty of Science, Beijing University of Technology, for help with research design.

## Financial support and sponsorship

This study was financially supported by The National Natural Science Foundation of China (81904052) and The 13<sup>th</sup> Five-Year Plan for National Key R&D Program of China (2018YFC1705401).

## Conflicts of interest

Prof. Jian-Ping Liu is an associate editors-in-chief of World Journal of Traditional Chinese Medicine. The article was subject to the journal's standard procedures, with peer review handled independently of this editorial board member and their research groups.

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