Protocol

Chinese Herbal Medicine for Ulcerative Colitis: A Systematic Review Protocol

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ABSTRACT

Introduction: This manuscript aims to provide a protocol of systematic review to assess the safety and effectiveness of Chinese herbal medicine (CHM) for the treatment of ulcerative colitis (UC). Although CHM has been widely used for UC, its effectiveness and safety has not yet been well defined and analyzed.

Methods and analysis: Seven electronic databases were searched, including China National Knowledge Infrastructure (CNKI), Chinese Biomedical literature (CBL), VIP database, Cochrane Library, MEDLINE, PubMed and China Journals Full-text Database. Related Chinese literature will be searched in other Chinese databases. All relevant randomized controlled literature of publication type will be included. Assessment of risk of bias, data synthesis and subgroup analysis will be carried out using Review Manager 5.2.

Ethics and dissemination: The results of the systematic review will be disseminated via publication in a peer-reviewed journal and presented at a relevant conference.

Trial registration number: PROSPERO CRD42015019350.

Key Words: Chinese herbal medicine, Ulcerative colitis, Systematic review, Protocol
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Introduction

Description of the Condition

Ulcerative colitis (UC) is one of subsets of inflammatory bowel diseases that predominantly affects people in the western world, but recent data has shown that its incidence is also high in Asians[1]. As a nonspecific chronic colitis, UC is mainly located in the first distal rectum and colon, and somewhile expand to the proximal and affects the whole colon, characterized by inflammation and ulcers in mucosa and submucosa. As the etiology of UC remains unknown and no specific effective treatment is available, this disease usually becomes chronic with refractory relapses; thus, UC is seriously reducing the quality of life of patients and burdening the healthcare system.

The current medical therapies for UC include remission and preventing relapse. Medications used in the clinics are aminosalicyates, corticosteroids, immunomodulatory drugs and antibiotics. However, these western medicines (WM) have various side effects. It has been reported that allergic reactions are common, occurring in up to one third of patients taking standard maintenance doses and in up to half of those taking therapeutic doses[2]. Similarly, long-term treatment with steroids or immunosuppressant would cause serious adverse reactions such as growth retardation, hypertension, cataracts, bone marrow suppression, etc. Besides, biological agents are not only expensive and economically burdensome to patients, but also have unsatisfactory long-term efficacy for UC patients.

With unsatisfactory response to outcome of western medicines, more and more UC patients seek helps from complementary and alternative medicine (CAM) to treat their annoying bowel symptoms, especially Chinese herbal medicine (CHM), which has been practiced in eastern Asia for thousands of years. However, their uses are commonly rationalized based on their longstanding tradition in clinical practice without evidence-based analysis comparable to western medicines. Recently, some clinical trials[3] demonstrated that CHM can effectively alleviate the symptoms of UC, the efficacy of some CHM even can be comparable to western medicines. Although there are many CHM interventions available, and some have been evaluated by clinical trials, their efficacy and safety are still questioned by both patients and health care providers worldwide.

Sulfalazine (SASP) has been used for treating UC by inducing remission and accurate stage in UC for 70 years. Based on an intention to treat principle, the outcomes of interest in the treatment of UC were measured by the change of clinical symptoms such as diarrhea, bellyache and hemafecia, clinical remission, clinical improvement, endoscopic remission, or endoscopic improvement. CHM has been proven to have an effect of remission in UC. And the important reason is about the quality of clinical trial with CHM, and the fact that results of systematic reviews about CHM treatment for UC are not consistent. Many system reviews have been reported other CHM in treating inflammation bowel disease (IBD)[4], but no one reported the efficacy of CHM alone or combined with western medicine in treatment of UC. Therefore, it is necessary to conduct systematic evaluations and meta-analysis of randomizes controlled trials (RCTs) of Chinese medicine in

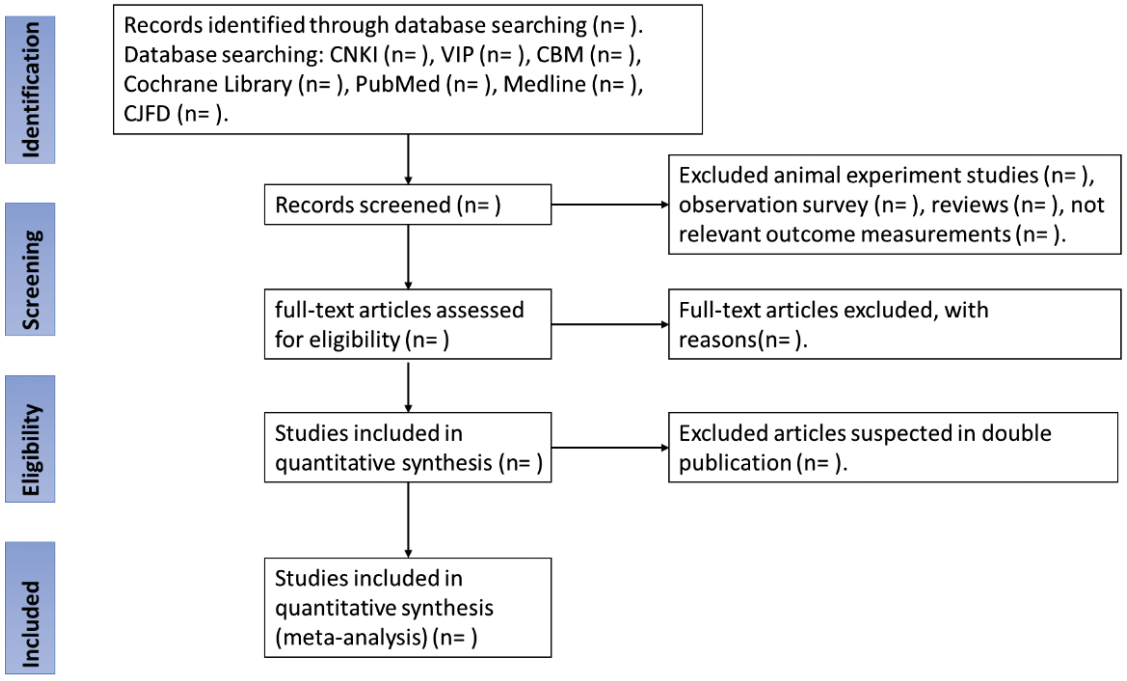

Figure 1. Process of the systematic review.

treatment of UC. Also the studies could perform a positive evaluation and provide a reference for future clinical treatment and research.

Description of the intervention

CHM is increasingly accepted by people in the developing and developed world as an alternative to conventional treatments[5]. One-third of American residents seek service from CHM practitioners every year for illnesses that do not respond to conventional treatment[6]. CHM, which is part of the important treatments in traditional Chinese medicine, has a long history of use in China.

How the intervention might work

CHM is based on the theoretical concepts of Yin-Yang and the five elements, and theories that health is maintained by a balance of energy within the body. Many in vivo studies demonstrate that cytokines are involved in the mechanisms of inflammation relief after treatment with CHM[7-9].

Objectives

This manuscript describes the protocol for a systematic review that will assess the evidence for the effectiveness and safety of CHM for UC.

Methods and analysis

Criteria for considering studies for this review

RCT with CHM for UC

All relevant randomized controlled trials (RCTs) in English and Chinese without any restrictions on publication type will be included and quasi-RCTs will be excluded.

Types of participants' patients

Studies evaluation men and women aged more than 18years of any ethnic background and nationality will be included.

Types of interventions

Chinese medicine treatment of UC includes oral and external treatment. oral treatment refers to decoction, powder, pills, tablets, oral liquid and Chinese patent medicine; external treatment contains acupoint external application, enema method, and etc.. The control intervention can include: no treatment, placebo/sham CHM or other interventions. Trials that evaluate CHM plus another therapy compared with the other therapy alone will also be included. Trials that only compare different types of CHM will be excluded.

Types of outcome measures

Primary outcomes

Only those outcomes that were thought to be the most clinically valuable assessing the efficacy of CHM for UC patients receiving therapy were included:

1 To assess the recovery rate by colonoscopy score, including mucosal hyperemia edema, mucosal erosion, and ulceration[3].
2 To assess the clinical symptom responds rate by disease activity index (DAI= (body mass index + stool form + bleeding)/3), 6-point Mayo score, simple clinical, colitis activity index (SCCAI)[4].

Secondary outcomes

1 To assess the efficacy of TCM on seroimmunity, including the mean values of post-treatment $CD3^+$, $CD4^+$cell levels, $CD4^+/CD8^+$ratio, Mast cell level, immunoglobulin (IgG, IgA, IgM), cytokine (TNF-α, IL-4).

2 To assess the efficacy of CHM on the routine biochemistry test, including stool routine, blood routine examination, fecal occult blood testing, erythrocyte sedimentation rate (ESR).

Search methods for identification of studies

Electronic searches

Table 1. Search strategy.

No	Searching item
1	clinical observation.mp
2	clinical trial.mp
3	clinical study.mp
4	efficacy.mp
5	effectiveness.mp
6	1 OR 2 OR 3 OR 4 OR 5 OR
7	random.mp
8	randomi*ed.mp
9	randomi*zation.mp
10	7 OR 8 OR 9
11	idiopathic proctocolitis.mp
12	ulcerative colitis.mp
13	colitis gravis.mp
14	inflammatory bowel disease.mp
15	ulcerative colitis type.mp
16	11 OR 12 OR 13 OR 14 OR 15
17	Chinese medicine.mp
18	herbal medicine.mp
19	herb*.mp
20	complementary medicine.mp
21	naturopathy medicine.mp
22	17 OR 18 OR 19 OR 20 OR 21
23	6 AND 7 AND 16 AND 22

"*"was used for truncation

Searching other resources

Reference texts including andragogy textbooks, integrative/alternative and complementary medicine textbooks and clinical guidelines for relevant trials will also be searched manually.

Data collection and analysis

Selection of studies

An electronic search strategy will be designed to search relevant references in China National Knowledge Infrastructure (CNKI), Chinese biomedical literature database (CBM), VIP database (VIP), Cochrane Library, Medline®, PubMed, China Journals Full-text Database. The search will be performed in English and Chinese. The search terms will be translated into Chinese when reviewers search the Chinese databases. The following literature sources in Chinese will also be searched: dissertations in CNKI, and conference papers in China Conference Paper Database. Relevant references cited in selected studies will also be searched. (Table 1 details of the search strategy for EMBASE).

Searching other resources

Reference texts including UC textbooks, integrative/alternative and clinical guidelines for relevant trials will also be searched manually.

Data extraction and management

Assessment of risk of bias in included studies

The risk of bias in the included studies will be assessed independently by two authors and presented in a risk of bias table. Decisions will be made based on the domains and criteria of the Cochrane Collaboration's tool[10] for assessing risk of bias. The following domains will be assessed:

Selection bias: random sequence generation and allocation concealment.

1 Performance bias: blinding of investigators, participants and care providers.
2 Detection bias: blinding of outcome assessment.
3 Attrition bias: incomplete data/differential dropout.
4 Reporting bias: selective reporting.
5 Other bias: for example, conflicts of interest, follow-up, non-intention-to-treat or per protocol analysis.

For each domain, the following description will be used to assess proper management of the risk of bias: 'low risk,' 'high risk,' or 'unclear.' We will grade the quality of included studies and risk of bias using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) tool[11].

Measures of treatment effect

For continuous data, the mean difference (MD) will be used to measure treatment effect with 95% CIs(Cochrane Handbook Verion 5.0.2). In case outcome variables have different scales, the standardized mean difference will be used with 95% CIs. For dichotomous data, treatment effects are presented as a risk ratio (RR) with 95% CIs. Other binary data will be changed into the RR form.

Discussion

Emerging evidences showed that CHM could suppress the inflammatory factors and improve immune system factors in different mechanism[8]. Several clinical trials demonstrated that some WM and immunosuppressant can cause serious adverse reactions or other side effects[12]. Comparing the therapeutic effects of mesalazine or SASP, studies showed that the UC patients had to stop taking medicine because of various side effects during the course of treatment[13-14], and WM will lead to adverse effects and patients may be forced to stop further treatment.

The flow chart of this systematic review is show in figure 1. This review will be helpful to clinicians treating UC and may provide evidence for researchers. Patients with UC may also benefit from CHM.

In this systematic review, it comprises the current RCTs available to prove evidence for using CHM as a major therapy for UC with oral administration. We found that the therapy significantly improved clinical symptoms such as diarrhea, bellyache and hemafecia, clinical remission, clinical improvement, endoscopic remission, or endoscopic improvement, according to basic theories and traditional diagnosis of CHM. It is suggested that using CHM could improve UC development and the adverse effects, meaning that CHM may increase the whole body immune response to prevent pathology.

In addition, it is common to treat UC patients combining CHM and WM in China, and in this review, we also found that there are advantages of efficacy for UC. Combining with WM, CHM may regulate human body function, reduce the dosage of WM, and make up the side effects of WM in treatment UC[15].

However, there are several limitations in the study. Firstly, clinical trials in the studies were not strictly designed and published following the golden standard, which may put the results of meta-analysis in risk. Allocation concealment and blinding were not clearly described in most of the included trials, which may result in the emergence of bias and overestimation of the efficacy of the treatment group. There are variations among the studies in terms of interventions, CHM composition (single or combination herbs), dosage preparation, and manufacturing standards, which may contribute to heterogeneity among the studies. Secondly, publication bias may exist in the present study. Most of the findings presented in the included studies are positive results. Some negative results may be unreported and therefore are not included in the review. Finally, the same as all previously published meta-analysis of CHM combined with conventional therapy, most of the trials included in this study did not provide enough information on demography and methodology such as duration of UC, random sequence, and intention-to-treat analyses.

Some researches indicated obvious and curative effects of CHM for UC, and were given priority to clearing heat and expelling damp, and more multi-purpose dispelling dampness, heat detoxification. This systematic review provides moderate evidence that using CHM as a major therapy alone and/or combined with SASP has a significantly efficacy in terms of each phase in UC process, and improvement of immunoregulation to prevent damage. With the small sample size, the findings of this review may not apply to all patients with UC. For further research, more clinical trials with high quality are worth performing to study the other potential interest of CHM in UC therapy, such as recurrence rate, local and distant metastasis, etc. Investigation of whether CHM as other new therapeutic agents may also be worth the effort.

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Author contributions

Zhao-xiang Bian and Feng-bin Liu designed the protocol and supervised the review, Hong Mi drafted the manuscript. Linda Zhong and Hong Mi conducted the literature review. Hong Mi, Tao Huang, Cheng-yuan Lin, Ling Zhao, Dong-dong Hu, Hai-tao Xiao retrieved the data.

Conflict of interest

The authors declare that there are no conflicts of interest.

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