Chinese herbal extract granules combined with 5-aminosalicylic acid for patients with moderately active ulcerative colitis: study protocol for a multicenter randomized double-blind placebo-controlled trial

Zhaofeng Shen
Affiliated Hospital of Nanjing University of Chinese Medicine https://orcid.org/0000-0002-7914-3965

Kai Zheng
Department of Gastroenterology, Jiangsu Province Hospital of Chinese Medicine

Jiandong Zou
Affiliated Hospital of Nanjing University of Chinese Medicine

Peiqing Gu
Jiangsu Province Academy of Traditional Chinese Medicine

Jing Xing
Michigan State University Eli Broad College of Business

Lu Zhang
Department of Gastroenterology, Jiangsu Province Hospital of Chinese Medicine

Lei Zhu (✉ zhulei5100@163.com)
Jiangsu Province Hospital of Chinese Medicine

Hong Shen
Department of Gastroenterology, Jiangsu Province Hospital of Chinese Medicine

Study protocol

Keywords: Ulcerative colitis, Chinese herbal medicine, 5-aminosalicylic acid, Multicenter randomized controlled trial, Study protocol

DOI: https://doi.org/10.21203/rs.3.rs-29723/v1

License: © This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

Background

Ulcerative colitis (UC) is an intestinal inflammatory disease characterized by inflammation of the colonic mucosa. With unknown pathogenesis, it has become a chronic lifetime disorder worldwide. In patients with moderately active UC, several therapies (e.g. aminosalicylates, corticosteroids, immunosuppressants and biologics) are recommended for induction (or maintenance) of remission. Given the side effects and disease burden, it is difficult for most patients to achieve ideal treatment goals in clinical practice. Chinese herbal medicine (CHM), as a complementary therapy, has been widely used in the management of UC in China. Qing-Chang-Hua-Shi granule (QCHS) is a classical Chinese herbal formula. Our preliminary study suggested that the QCHS decoction has a significant effect on patients with moderately active UC. However, its effectiveness and safety has not been evaluated convincingly. Therefore, we designed this protocol to investigate the efficacy of QCHS granule for moderately active UC.

Methods

This is a multicenter, randomized, double-blind, placebo-controlled, superiority trial. A total of 120 patients with moderately active UC will be recruited from 10 hospitals in China. Each eligible participant will be randomly assigned to receive QCHS granule or placebo twice daily for 12 weeks. Both groups will be given basic treatment with mesalazine (4 g/d). The primary outcomes are the clinical response (remission) rate. The secondary outcomes are health-related quality of life, endoscopic response rate, mucosal healing rate and inflammatory markers (e.g. Fecal calprotectin and CRP). The whole study period will last 36 weeks, including 24 weeks follow-up time. According to the intention-to-treat principle, variables will be assessed at 2, 4, 6, 8, 10 and 12 weeks after study commencement.

Discussion

This is the first prospective, multicenter, randomized, double-blind, placebo-controlled, superiority trial regarding Chinese herbal extract granules in the management of moderately active UC. We aim to investigate the superiority of QCHS granules over placebo in terms of induction of remission. The findings will provide convincing evidence on the efficacy and safety of QCHS granules for moderately active UC, which may help clinical practitioners, UC patients and policymakers make more informed choices in the decision-making.

Trial registration:

Chinese Clinical Trial Registry, ChiCTR-IOR-14005554. Registered on 27 November 2014.
Background

Ulcerative colitis (UC) refers to a subtype of inflammatory bowel disease (IBD), which is characterized by chronic idiopathic inflammation of the large intestine (e.g. colonic mucosa) [1, 2]. As a lifelong disease [3, 4], UC has a significant impact on health-related quality of life [5, 6]. To date, the pathogenesis mechanism of UC is not fully understood, associated with multiple factors (e.g. heredity, environment, immunity and behavior) [7, 8]. As a result, it has become a global refractory disease with worldwide shifting epidemiological characteristics. According to a recent survey, the incidence and prevalence in developed areas such as North America and Europe have been stable [9]. However, the data in in Asia and other developing countries have encountered a significant increase over the past decade [10, 11].

Currently, the optimal goal of management is to induce (steroid-free) remission, maintain remission, prevent disease-related complication and health-related quality of life [12]. Besides, it is believed that an emerging goal in UC management is mucosal healing. To achieve these goals, 5-aminosalicylic acid, corticosteroids, immunosuppressants, biological agents and other promising treatment (e.g. fecal microbiota transplantation) have been developed one by one [13]. As a consequence, budesonide, corticosteroids and anti-TNF therapy (e.g. adalimumab, golimumab and infliximab) have been strongly recommended to induce remission for moderately active UC with moderate to high quality of evidence [14]. However, many patients do not react well to these conventional drugs in clinical practice. What’s worse, most of these treatments have limitations in safety and efficacy, such as serious side-effects, long course of treatment, heavy burden of disease, and so on [15, 16]. Therefore, there still seems to be room for improvement in the management of moderately active UC.

Historically, in Asia (especially in China), Chinese herbal medicine (CHM) has been widely used for UC due to the unique advantages of efficacy and safety [17]. Under the circumstance, an increasing amount of evidences have shown that CHM have potentially positive effects on UC [18–20]. According to the theory of traditional Chinese medicine (TCM), CHM plays an irreplaceable role in the management of UC.

Over the past decade, our group has been searching for Chinese herbs that can be used for UC. Through years of our clinical practice, we found that QCHS formula developed from classical Chinese herbal formulas could not only relieve patients’ clinical symptoms, but also promote mucosal healing by adjusting the balance of the body. Our previous studies in vivo have proved that QCHS was associated with significant benefits regarding ameliorating the damage to colon length, suppressing inflammatory cytokines and mediators, alleviating oxidative stress through β2AR/β-arrestin2/NF-κB signaling pathway [21, 22]. Furthermore, QCHS could significantly inhibit apoptosis in HT-29 cells through MEK/ERK signaling via SGK1 [23]. However, our preliminary studies were limited to systematic top-level design (e.g. small sample size, placebo effect). Given these findings, the evidence of its effectiveness and safety was unconvincing, especially in patients with moderately active UC. Under the circumstance, we designed this protocol, a prospective, multicenter, randomized, double-blind, placebo-controlled, superiority trial, to further determine the efficacy and safety of QCHS granule combination therapy for UC patients who do not respond to 5-ASA after 4 weeks. We assume that patients with moderately active UC will benefit in terms of clinical remission, mucosal healing and quality of life.
Hypothesis and objective

In our protocol, we hypothesize that QCHS granule combined with basic treatment (5-ASA) is superior to placebo plus 5-ASA on clinical response (remission) rate, mucosal healing rate, clinical syndromes, quality of life, inflammatory mediators (e.g. Fecal calprotectin, TNF-α and hs-CRP) and adverse side-effects.

The primary objective of this trial is to investigate the efficacy of QCHS granule combined with 5-ASA in the management of patients with moderately active UC. Furthermore, the secondary objective is to explore the safety of QCHS granule for moderately active UC.

Methods

Study design

This is a prospective, multicenter, randomized, double-blind, placebo-controlled, superiority clinical trial, which conforms to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement guidelines [24] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 Statement [25]. The study began in January 2016 and will last until October 2022. A total of 120 eligible patients will be enrolled and randomized into QCHS granule group or placebo group. All patients will voluntarily sign the informed consent prior to enrollment. Prior to allocation, each of them will be screened by the eligibility criteria. According to patients’ included sequence number equally, block randomization will be performed to ensure equal group sizes with an allocation of 1:1 (permuted block sizes of 6). Participants in QCHS granule group will receive QCHS granule (125 g, twice daily, orally) for continuous 12 weeks, while patients in placebo group will receive QCHS granule placebo (125 g, twice daily, orally) for the same duration. Both groups will be given basic treatment with mesalazine (5-aminosalicylic acid, 4 g/d). Researchers and patients will be blinded from the beginning of the trial. All interested outcomes including patient-reported outcomes will be collected before (0 week) and after intervention (2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks and 12 weeks). The whole study period will last 36 weeks, including 24 weeks of follow-up. The complete SPIRIT (2013) checklist for the study is provided in Additional file 1. The overview and the SPIRIT schedule of the study are illustrated in Figs. 1 and 2, respectively.

Study setting

This study was developed by research team in Nanjing (Jiangsu Province Hospital of Chinese Medicine) together with nine teams in China. The collaborators were selected based on the characteristics of sites as well as the strength and experience of their teams. As a result, patients will be recruited from 10 subcenters (tertiary hospitals) across China, including Affiliated Hospital of Nanjing University of Chinese Medicine, Beijing Hospital of Chinese Medicine, LongHua Hospital Shanghai University of Traditional Chinese Medicine, Guangdong Province Hospital of Chinese Medicine, The First Affiliated Hospital of Henan University of Chinese Medicine, ShengJing Hospital of China Medical University, Affiliated Hospital
of Shanxi University of Chinese Medicine, The Second Affiliated Hospital of Fujian Traditional Chinese Medical University, The First Affiliated Hospital of Heilongjiang University of Chinese Medicine, Nantong Hospital of Chinese Medicine. Each research institution will follow the same research protocol.

**Ethics and registration**

The protocol has been approved by Ethics Committee of Affiliated Hospital of Nanjing University of Chinese Medicine (approval number:2014NL-074-02, Additional file 2). Each sub-center applied for local institutional review boards (IRBs) approval. Furthermore, this trial has been registered on Chinese Clinical Trial Registry (URL: [http://www.chictr.org.cn/](http://www.chictr.org.cn/), No. ChiCTR-IOR-14005554).

**Sample size and power calculation**

The sample size was calculated according to the primary outcome (clinical response rate) at 12 weeks after initiation. The sample size calculation was based on the comparison of the proportions in the QCHS granule group versus placebo group. On the basis of our previous studies, we predicted that the clinical remission rates at 12 weeks would be 79% in the QCHS granule group and 41% in the placebo group. A difference of 10% was selected as the smallest difference that would be of clinical significance. For a two-sided significance level of 0.05 ($\alpha = 0.05$), it is estimated that a sample size of 54 subjects per group will be required to detect the superiority of QCHS granule over placebo with a test power of 80%. Under the hypothesis that some patients are unable to follow-up or unsuitable for analysis, the sample size will be inflated. Considering 10% drop out, the total planned sample size will be 60 per group.

**Randomization, allocation concealment and blinding**

Each eligible patient will be randomly allocated into QCHS granule group (5-ASA+ QCHS granule) or control group (5-ASA+ QCHS granule placebo) with an allocation ratio of 1:1. Stratified block randomization (by site) will be performed to ensure equal group sizes with permuted blocks (block size of 6). The randomization allocation sequence generated by SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was converted into unique serial numbers for each enrolled subject in subcenters. QCHS granule and placebo granule will be provided to each subcenter in advance, encoded and labelled with above serial number. To ensure blinding, the QCHS granule and placebo granule will be identical in all aspects (e.g. appearance, size, color, smell, taste, containers and doses). Participant and Principal Investigators will be blinded to group allocation throughout the research. The randomization procedure was conducted by an independent research assistant who is not involved in clinical observation or assessment. Under the supervision of Data Safety and Monitoring Board (DSMB), the randomization code will only be broken due to adverse event and statistical analysis.

**Participants**

The participants will be 120 patients with moderately active UC.

**Inclusion criteria**
Patients will be included if they meet the following criteria:

1. Confirmed diagnosis of moderately active UC after taking 5-ASA for more than 4 weeks (total Mayo score between 6 and 10, Endoscopy subscore >2)

2. Confirmed diagnosis of TCM syndrome differentiation (large intestine damp-heat syndrome)

3. Males or females with age range between 18 and 50 years

4. Ethical principle who voluntarily sign the informed consent form

**Exclusion criteria**

Patients will be excluded if they have following criteria:

1. Patients with other intestinal diseases (e.g. bacterial dysentery, intestinal tuberculosis, Crohn's disease)

2. Patients with serious complications (e.g. intestinal perforation, intestinal obstruction, toxic megacolon, colorectal cancer)

3. Patients who are pregnant, breast-feeding, or preparing for pregnancy

4. Patients with significant cardiac disease, hepatic disease, pulmonary disease, renal disease and other serious diseases (abnormal urine protein, platelet value of less than 100 × 10⁹ /l, alanine aminotransferase level above the upper limit of normal, leukocyte count of less than 4.0 × 10⁹ /l)

5. Patients who have severe physical disability (e.g. blindness, deafness, dumbness, intellectual disability, mental disability, physical disability)

6. Patients who have a history of alcohol or drug abuse

7. Patients who have a history of food allergy or drug allergy

8. Patients who are participating in other clinical trials

**Withdrawal criteria**

Patients who don't meet the inclusion criteria, have no data after randomization, have never used research medication, take forbidden drugs will be withdrawn from this study.

**Dropout criteria**

Patients who are unable to be followed-up after informed consent and randomization will be considered dropout of our study.

**Termination criteria**
Patients will be terminated if they meet the following criteria:

1. Abnormality of safety index during treatment (ALT more than twice the upper limit of normal, Cr more than the upper limit of normal, platelet count less than $50 \times 10^9 / L$, white blood cells less than $3.0 \times 10^9 / L$

2. Worse condition during the course (bloody stools more than 6 times daily accompanied by body temperature $> 37.8 ^\circ C$ or $\text{Hb} < 10.5 \text{ g/dL}$)

3. Significant biases occurred in clinical research

4. Poor compliance

**Recruitment, screening and enrollment procedures**

Each subcenter need to regularly discuss the protocol and its implementation so as to have a better understanding of the trial. Site-specific implementation plans were made respectively. Specialized subject recruitment advertisement was placed in the newspaper or on the social network platform. Furthermore, fliers and brochures regarding subject recruitment have been placed inside the hospital.

According to the above-mentioned inclusion and exclusion criteria, standardized screening form was implemented to identify the potential eligible participants. After the eligible subject has been confirmed, investigators will communicate with the patient face to face explaining the purpose of the trial as well as the trial procedures. Voluntarily, participants need to sign the informed consent form if they are willing to receive them.

**Intervention**

**Basic treatment**

During intervention period, all eligible patients with moderately active UC will receive standard treatment of Mesalazine Sustained Release Granules (5-aminosalicylic acid, 5-ASA, 4g/d, 4 times daily) produced by French IPSEN Pharmaceutical Factory.

**QCHS granule group**

Those patients randomized to the intervention group will receive Qing-Chang-Hua-Shi granule (QCHS, 125 g, twice daily, orally) additionally. This Chinese herbal prescription consists of several ingredients: Rhizoma Coptidis (Huanglian) 6 g, Radix Scutellariae (Huangqin) 10 g, Herba Patriniae (Baijiangcao) 15 g, Angelicae Sinensis Radix (Danggui) 10 g, Radix Paeoniae Alba (Baishao) 20 g, Radix Angelicae Dahuricae (Baizhi) 12 g, Radix Aucklandiae (Muxiang) 6 g, Radix Sanguisorbae (Diyu) 10 g, Lithospermum Erythrorhizon (Zicao) 10 g, Rubia Cordifolia (Qiancao) 20 g, Licorice (Gancao) 6 g.

**Control group**
Patients in control group will be treated with 5-ASA plus QCHS granule placebo (125 g, twice daily, orally), which is similar to QCHS granule in terms of appearance, size, color, smell, taste, doses and containers.

According to the Good Agricultural Practice (GAP), all ingredients of Chinese herbal granule and placebo were manufactured by Jiangyin Tianjiang Pharmaceutical Co., Ltd, Jiangyin, China. Raw herbs were extracted in hot water, and the aqueous extract was concentrated, dried, and packed in sealed opaque packages. Instruction and code label will be tagged outside the container. Participants were asked to dissolve the granules by hot water and drink the mixture.

**Study period**

The total course of intervention is 12 weeks with 24 weeks follow-up. After Enrollment, the trial will last 36 weeks continuously.

**Outcomes**

The primary outcome of this study is the clinical response rate in patients with moderately active UC. The clinical response refers to a decrease (from the baseline) of the total Mayo score by at least 30% (or 3 point) together with a decrease of the rectal bleeding subscore by at least 1 point (or rectal bleeding subscore of 0 or 1 point) with no individual subscore exceeding 1 point [26].

The secondary outcomes are as follows: health-related quality of life measured by the inflammatory bowel disease questionnaire (IBDQ), endoscopic response rate defined as a decrease of Mayo disease activity index endoscopy subscore by at least 1 [26], mucosal healing rate defined as endoscopy subscore of Mayo disease activity index of 0 or 1, and improvements in inflammatory markers (e.g. Fecal calprotectin, Tumor necrosis factor -α and hypersensitive -C reactive protein, Erythrocyte sedimentation rate).

**Additional information**

In addition, information regarding biological index (e.g. demographic characteristics, vital signs) and diagnostic index (e.g. course, status, physiological and biochemical indicators) will be obtained at baseline and follow-up. Safety index will be observed throughout the study. During the study, adverse events (AEs) will be recorded on a standard SAE form and reported to the Institutional Review Board (IRB) of the Affiliated Hospital of Nanjing University of Chinese Medicine. Those patients who experienced SAEs will be followed up for detailed reports.

**Data collecting and follow-up**

According to the protocol, assessments will be repeated 7 times during the 12 weeks intervention: at baseline, at 2 weeks, at 4 weeks, at 6 weeks, at 8 weeks, at 10 weeks, at 12 weeks. For those patients who have been induced to remission at the end of the intervention, we will follow up for 24 weeks. After enrollment, participants will attend a total of thirteen trial visits. Participants who completed our trial will
be provided with 400 RMB for transport compensation. At the beginning and the end of the study, Mayo score, colonoscopy, mucosal histology, health-related quality of life, biochemical parameters, safety index will be measured. However, partial Mayo score, symptom indicators (e.g. diarrhea, bloody stools, and abdominal pain), biochemical parameters (e.g. Fecal calprotectin, hypersensitive-C reactive protein, Erythrocyte sedimentation rate, Stool routine, Occult blood test), safety index (e.g. blood routine, liver function and kidney function) will be evaluated at 2 weeks, 4 weeks, 6 weeks, 8 weeks, 10 weeks respectively.

Data management and quality control

To ensure the quality of this trial, an external monitoring agency (a CRO located in Nanjing) will be hired to help data collection, management and analysis across all subcenters. All data will be recorded (double-entered) on electronic case report forms (eCRFs) by trained investigators and will be monitored monthly via electronic data capture system. For each abnormal or missing datum, a query will be automatically sent to the investigator. Once all the inconsistencies or queries are solved, the database will be locked for statistical analysis.

Statistical analysis

According to our protocol, all data analyses will be conducted based on pre-established statistical analysis plan. All analyses of data will be performed by SAS software (v. 9.3; SAS Institute Inc., Cary, NC, USA). To ensure the consistency and reliability of the conclusions, both Intention-to-Treat (ITT) analysis and Per-Protocol (PP) analysis will be done if necessary. All missing data will be imputed by multiple imputation. Statistical description will be performed with frequency, mean, median, standard deviation, lower quartile (P25), upper quartile (P75), minimum, maximum. Normality of all quantitative (continuous) variables (e.g. demographic characteristics, vital signs, biochemical parameters) will be tested by the Kolmogorov-Smirnov test. For normal distribution data, independent sample t-test and paired sample t-test will be employed to compare parameters at the beginning and the end of the study between and within groups, respectively. For abnormal distributions data (e.g. quality of life, inflammation markers), the Mann–Whitney U test and Wilcoxon signed-rank test will be used instead. For qualitative (categorical) variables, the chi-square test or Fisher's exact test will be used, such as clinical response rate, endoscopic response rate and mucosal healing rate. In the evaluation of efficacy and analysis of influencing factors, center and disease will be used as covariates. Covariance analysis (ANCOVA) will be used. Multiple linear regression or logistic regression will be used to analyze the influencing factors and evaluate effect of gender and condition on the efficacy of the two groups. For all analyses, P < 0.05 will be considered statistically significant.

Discussion

UC is a chronic immune-mediated (nonspecific) inflammatory condition. Patients with active UC are more likely to have comorbid psychological conditions of anxiety and depression, resulting in impaired social interactions or career progression [29]. As a difficult and incurable disease, the optimal goal of its
management is to induce (steroid-free) remission, maintain remission (especially mucosal healing), prevent disease-related complication and health-related quality of life [12]. Therapeutic options in patients with moderately active UC include 5-aminosalicylic acid, corticosteroids, anti-TNF therapy (e.g. adalimumab, golimumab and infliximab). However, many patients who do not respond to these conventional drugs recommended by the guideline. In our clinical practice, strategies for the management of moderately active UC mainly depend on following factors: the risk and benefit of the choice, preference of the patients and experience of the doctors. The use of TCM in patients with moderately active UC has increased in popularity over the past decade because of the unique advantages of efficacy, convenience, safety, and low cost [18].

As far as we know, QCHS is an effective treatment for moderately active UC [23]. Our previous studies have proved that QCHS could alleviate UC oxidative stress and intestinal inflammation which was related to activation of β2AR/β-arrestin2/NF-κB signaling pathway [30]. Moreover, in-depth study found paeoniflorin had the anti-inflammatory effect in UC via inhibiting MAPK/NF-kappa B pathway and apoptosis in mice [31], and astragalus and baicalein regulated inflammation of mesenchymal stem cells by MAPK/ERK pathway [32]. Based on above-mentioned results, we explored whether QCHS could help patients with moderately active UC who do not respond to 5-ASA after 4 weeks. To the best of our knowledge, this is the first prospective, multicenter, randomized, double-blind, placebo-controlled, superiority trial regarding Chinese herbal extract granules in the management of moderately active ulcerative colitis. We aim to investigate the superiority of QCHS granules combined with 5-ASA over placebo combined with 5-ASA in terms of induction of remission and maintenance of remission. The findings will provide convincing evidence on the efficacy and safety of QCHS granules for patients with moderately active UC. If the trial shows significant benefits of QCHS granules, it will help clinical practitioners, UC patients and policymakers make more informed choices in the decision-making. As a result, the current guidelines will be modified.

**Trial Status**

Recruitment for the trial was planned to start on January 2016 and last until October 2022. The first patient was enrolled on April 10, 2016. The trial is enrolling patients. The current protocol is version 2.0 and is dated 20 September 2014.

**Abbreviations**

CHM: Chinese herbal medicine; TCM: traditional Chinese medicine; UC: Ulcerative colitis; IBD: inflammatory bowel disease; QCHS: Qing-Chang-Hua-Shi granule; 5-ASA: 5-aminosalicylic acid; DSMB: Data Safety and Monitoring Board; IRBs: institutional review boards; IBDQ: inflammatory bowel disease questionnaire; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; FC: Fecal calprotectin; TNF-α: Tumor necrosis factor -α; Hs-CRF: hypersensitive -C reactive protein; AEs: adverse events; ITT: Intention-To-Treat; PP: Per-Protocol.
Declarations

Ethics approval and consent to participate

The protocol has been approved by Ethics Committee of Affiliated Hospital of Nanjing University of Chinese Medicine (approval number: 2014NL-074-02, Additional file 2). Each sub-center applied for local institutional review boards (IRBs) approval. All patients will voluntarily sign the informed consent prior to enrollment. Furthermore, this trial has been registered on Chinese Clinical Trial Registry (identification number: ChiCTR-IOR-14005554).

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

Availability of data and materials

Supporting data regarding the study protocol are available as supplementary data and have been submitted alongside the main manuscript. JDZ, ZFS, LZ and HS will have access to the final trial dataset and disclose contractual agreements.

Funding

This work is supported by the Special Scientific Research for Traditional Chinese Medicine of State Administration of Traditional Chinese Medicine of China (Grant No. 201407001) and the National Natural Science Foundation of China (Grant No. 81873260), see Additional file 3.

Authors’ contributions

LZ and HS worked out the design of the study protocol. LZ and HS provided financial support for the project. JDZ and ZFS was involved in designing the statistical methods of the study design. ZFS and LZ wrote the first draft of protocol. LZ was the principal investigator and leader of the project. PQG, KZ, PQG, JX and LZ participated in the project and provide professional guidance. LZ, HS, PQG, JDZ, KZ and JX provided critical revisions to the protocol. All authors read and approved the final version of the manuscript.
Acknowledgements

This study was supported by Jiangsu Province Hospital of Chinese Medicine (Affiliated Hospital of Nanjing University of Chinese Medicine) together with 9 subcenters (tertiary hospitals) across China. We sincerely thank the research teams who made this study possible. Furthermore, we want to express our gratitude to the patients who will participate in our study.

Author details

1 Department of Science and Technology, Jiangsu Province Hospital of Chinese Medicine, Nanjing, China
2 School of Public Health, Nanjing Medical University, Nanjing, China
3 Department of Gastroenterology, Jiangsu Province Hospital of Chinese Medicine, Nanjing, China

References

[1]. Ungaro R, Mehandru S, Allen PB, Peyrin-Biroulet L, Colombel J-F. Ulcerative colitis. Lancet. 2017; 389: 1756–1770.

[2]. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. BMJ. 2013; 346: f432.

[3]. Ordas I, Eckmann L, Talamini M, et al. Ulcerative colitis. Lancet. 2012; 380: 1606–19.

[4]. Sedghi, S., Barreau, F., Morilla, I., Montcuquet, N., Cazalshatem, D., Pedruzzi, E, et al. Increased proliferation of the ileal epithelium as a remote effect of ulcerative colitis. Inflamm Bowel Dis. 2016; 22: 10.

[5]. Tabibian A, Tabibian JH, Beckman LJ, et al. Predictors of health-related quality of life and adherence in crohn’s Disease and ulcerative Colitis: Implications for Clinical Management. Dig Dis Sci. 2015; 60(5): 1366-1374.

[6]. Cosnes J, Gower-Rousseau C, Seksik P, Cortot A. Epidemiology and natural history of inflammatory bowel diseases. Gastroenterology. 2011; 140: 6.

[7]. Dulai, P. S., Jairath, V. Acute severe ulcerative colitis: latest evidence and therapeutic implications Therapeutic implications. Adv. Chronic Dis. 2018; 9: 2.

[8]. Kim, S. E., Choo, J., Yoon, J., Chu, J. R., Bae, Y. J., Lee, S., et al. Genome-wide analysis identifies colonic genes differentially associated with serum leptin and insulin concentrations in C57BL/6J mice fed a high-fat diet. PloS One. 2017; 12: 2.

[9]. Ng SC, Shi HY, Hamidi N, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017; 390: 2769.
[10]. Kaplan GG, Ng SC. Understanding and preventing the global increase of inflammatory bowel disease. Gastroenterology. 2017; 152: 313–21.

[11]. Cui G, Yuan A. A Systematic Review of Epidemiology and Risk Factors Associated With Chinese Inflammatory Bowel Disease. Front Med (Lausanne). 2018; 5: 183.

[12]. Feuerstein JD, Cheifetz AS. Ulcerative colitis: epidemiology, diagnosis, and management. Mayo Clin Proc. 2014; 89: 1553–63.

[13]. Gordon M, Naidoo K, Thomas AG, et al. Fecal transplantation for ulcerative colitis: current evidence and future applications. Expert Opin Biol Ther. 2011; 20: 343–51.

[14]. Rubin David T, Ananthakrishnan Ashwin N, Siegel Corey A, Sauer Bryan G, Long Millie D. ACG Clinical Guideline: Ulcerative Colitis in Adults. Am J Gastroenterol. 2019; 114: 3.

[15]. Lim WC, Wang Y, MacDonald JK, et al. Aminosalicylates for induction of remission or response in Crohn's disease. Cochrane Database Syst Rev. 2016; 7: Cd008870.

[16]. Feagan BG, Rutgeerts P, Sands BE, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2013; 369: 699–710.

[17]. Fan Y, Yi W, Huang H, et al. Efficacy of herbal medicine (Gegen Qinlian Decoction) on ulcerative colitis: a systematic review of randomized controlled trials. Medicine. 2019; 98: e18512.

[18]. Zhaofeng Shen, Qing Zhou, Yingjun Ni, et al. Traditional Chinese medicine for mild-to-moderate ulcerative colitis: Protocol for a network meta-analysis of randomized controlled trials. Medicine. 2019; 98: 33.

[19]. Zhao L, Wu H, Zhao A, et al. The in vivo and in vitro study of polysaccharides from a two-herb formula on ulcerative colitis and potential mechanism of action. J Ethnopharmacol. 2014; 153: 151–9.

[20]. Nishio M, Hirooka K, Doi Y, et al. Pulmonary arterial hypertension associated with the Chinese herb indigo naturalis for ulcerative colitis: it may be reversible. Gastroenterology. 2018; 155: 577–8.

[21]. Lu Yue-lin, Shen Hong, Yao Hong-feng, Yang Xu. Effect of qingchang huashi recipe on IL-17 in the plasma and colonic mucosa of patients with ulcerative colitis. Zhongguo Zhong xi yi jie he za zhi = Chinese journal of integrated traditional and Western medicine. 2014; 34: 10.

[22]. Zhu Lei, Shen Hong, Liu Li, Gu Pei-qing, Cheng Jia-fei, Zhang Lu. Effect of Jianpi Bushen Qingchang Huashi Recipe on Proliferation of Bone Marrow Mesenchymal Stem Cells. Zhongguo Zhong xi yi jie he za zhi = Chinese journal of integrated traditional and Western medicine. 2016; 36: 2.

[23]. Zhu Lei, Dai Lu-Ming, Shen Hong, Gu Pei-Qing, Zheng Kai, Liu Ya-Jun, Zhang Lu, Cheng Jia-Fei. Qing Chang Hua Shi granule ameliorate inflammation in experimental rats and cell model of ulcerative colitis...
through MEK/ERK signaling pathway. Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie. 2019, 116.

[24] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010; 340:c332.

[25] Chan A-W, Tetzlaff JM, Altman DG, et al. Spirit 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013; 158: 200–7.

[26] Sandborn WJ, Ghosh S, Panes J, et al. Tofacitinib, an oral Janus kinase inhibitor, in active ulcerative colitis. N Engl J Med. 2012; 367:616–24.

[27] Laharie D, Bourreille A, Branche J, et al. Ciclosporin versus infliximab in patients with severe ulcerative colitis refractory to intravenous steroids: a parallel, open-label randomised controlled trial. Lancet. 2012; 380: 1909–15.

[28] Panaccione R, Ghosh S, Middleton S, et al. Combination therapy with infliximab and azathioprine is superior to monotherapy with either agent in ulcerative colitis. Gastroenterology. 2014; 146: 392–400.

[29] Regueiro M, Greer JB, Szigethy E. Etiology and treatment of pain and psychosocial issues in patients with inflammatory bowel diseases. Gastroenterology. 2017; 152: 430–9.

[30] L. Dai, L. Zhu, H. Shen, Effect of Qingchang Huashi granule on β2AR/β-arrestin2/ NF-κB signaling pathway in experimental ulcerative colitis rats and cell. Chin. J. ETMF. 2018; 24: 86–94.

[31] P. Gu, L. Zhu, Y. Liu, L. Zhang, J. Liu, H. Shen, Protective effects of paeoniflorin on TNBS-induced ulcerative colitis through inhibiting NF-kappa B pathway and apoptosis in mice, Int. Immunopharmacol. 2017; 50: 152–160.

[32] L. Zhu, Y. Liu, H. Shen, Astragalus and baicalein regulate inflammation of mesenchymal stem cells (MSCs) by the mitogen-activated protein kinase (MAPK)/ERK pathway, Med. Sci. Monit.. 2017; 23: 3209–3216.

Figures
**Fig. 1** Overview (flowchart) of the protocol

**Figure 1**

Overview (flowchart) of the protocol
### Figure 2 Schedule of enrolment, interventions, assessments and follow-up

| TIMEPOINT** | -1 | 0 | 2  | 4  | 6  | 8  | 10 | 12 | 4  | 8  | 16 | 20 | 24 |
|-------------|----|---|----|----|----|----|----|----|----|----|----|----|----|
| **ENROLMENT:** |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Eligibility screen | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Informed consent | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Trial registration | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Baseline assessment |     | X |    |    |    |    |    |    |    |    |    |    |    |
| Allocation |     |   |    |    |    |    |    |    |    |    |    |    |    |
| **INTERVENTIONS:** |    |    |    |    |    |    |    |    |    |    |    |    |    |
| QCHS granule |     |   |    |    |    |    |    |    |    |    |    |    |    |
| QCHS granule placebo |     |   |    |    |    |    |    |    |    |    |    |    |    |
| **ASSESSMENTS:** |    |    |    |    |    |    |    |    |    |    |    |    |    |
| Demographics | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Blood routine | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Urine routine | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Stool routine | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Liver and kidney function | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Erythrocyte sedimentation rate | X | X | X | X | X | X | X | X | X | X | X | X | X |
| C-reactive protein | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Fecal calprotectin | X | X | X | X | X | X | X | X | X | X | X | X | X |
| Electrocardiogram | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Enteroscopy and histopathology | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Mayo score | X | X | X | X | X | X | X | X | X | X | X | X | X |
| partial Mayo score | X | X | X | X | X | X | X | X | X | X | X | X | X |
| TCM syndrome scale | X | X | X | X | X | X | X | X | X | X | X | X | X |
| IBD questionnaire | X |    |    |    |    |    |    |    |    |    |    |    |    |
| Adverse events | X | X | X | X | X | X | X | X | X | X | X | X | X |

Fig. 2 Schedule of enrolment, interventions, assessments and follow-up

**Figure 2**

Schedule of enrolment, interventions, assessments and follow-up

**Supplementary Files**

This is a list of supplementary files associated with this preprint. Click to download.
• SPIRIT2013Checklist.pdf