Review Article

Chinese Herbal Medicine for the Treatment of Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome-Associated Diarrhea: A Protocol for the Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Diarrhea can occur at an early or advanced stage of acquired immunodeficiency syndrome (AIDS) as a usual symptom in people with human immunodeficiency virus (HIV) infection. While it is usually not fatal, it can influence patients’ quality of life seriously. It has shown to be efficacious and improves people’s immune status to a certain extent to treat HIV/AIDS-related diarrhea on the basis of syndrome differentiation and treatment or Chinese herbs plus conventional treatment. Therefore, it may have a good application potential. Here, we outline a protocol for the systematic review of this health-care intervention, with the aim to evaluate the beneficial effects and safety of Traditional Chinese Medicine (TCM) for patients who suffer from HIV/AIDS-associated diarrhea. Randomized controlled trials that compare Chinese herbs with placebo or other effective treatments will be searched and included, in spite of publication status or language. The primary outcomes include diarrhea frequency and fecal character. The databases we will search as follows: China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (SinoMed), Wanfang Data, China National Knowledge Infrastructure, PubMed and the CENTRAL in Cochrane Library. Two authors will respectively conduct the screening of trials, data extraction, and use the Cochrane risk of bias tool to assess the methodological quality. We will analyze the data and perform a meta-analysis if possible. We intend to identify potential therapeutic modalities that may be of benefit to inform clinical practice by supplying existing evidence of the helpful effects and safety of TCM to treat patients suffering from HIV/AIDS-associated diarrhea.

Keywords: Chinese herbal medicine, human immunodeficiency virus/acquired immune deficiency syndrome-associated diarrhea, meta-analysis, protocol, systematic review

Background

Description of the condition

Human immunodeficiency virus (HIV) gives rise to acquired immunodeficiency syndrome (AIDS), which is a chronic infectious disease. HIV can invade and damage CD4+ T-lymphocytes, leading to damage and deficiency of immune cells, and even severe opportunistic infections and tumors.[1] By 2018, 39.7 million or so people worldwide were living with HIV, about 32 million or so people among whom met death for HIV/AIDS-related causes worldwide, and most of people with HIV infection live in lower to middle-income countries in the light of the World Health Organization.[2] As one of the main reasons of death among people with AIDS, diarrhea is a common complication of AIDS.[1] The clinical symptoms are primarily chronic diarrhea with loss of weight,

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dystrophy, marasmus syndrome, and even cachexia (loss of weight, muscular dystrophy, inappetence, and malaise). In North America and Europe, the occurrence rate of HIV/AIDS-associated diarrhea is about 30%~80% and as high as 90% in developing countries.\[9\] Opportunistic infection of bacteria, viruses, fungi, and parasites accounts for approximately 50%~60% of patients with HIV/AIDS-associated diarrhea.\[5\] With decline of CD4+ T-lymphocytes counts, the incidence of diarrhea will increase. Therefore, it is more common in lower income areas where highly active antiretroviral therapy (HARRT) is unavailable or unaffordable.\[6\] In addition, in the process of AIDS progression, there may be noninfectious causes such as side effects of HAART, AIDS-related individual idiopathic factors, AIDS-related absorption disorders, and malignant tumors.\[7\] If HAART use is widespread, the side effect of HAART is more likely to be the cause of HIV/AIDS-associated diarrhea than opportunistic infections.\[10,11\] The incidence of noninfectious diarrhea rose from 32% to 70%, while the incidence of diarrhea caused by opportunistic infections fell from 53% to 13%.\[12\] The incidence of noninfectious diarrhea mainly caused by medication rose from 0% in 1995 to 45% in 1997.\[13\]

HAART has been proven to be the most effective treatment for HIV-infected patients. It is a combination of three or more drugs that can greatly reduce the incidence and mortality of AIDS.\[13\] However, diarrhea is still common in patients with HIV infection. Diarrhea caused by HARRT drugs is of concern, especially when combined with lopinavir/ritonavir. HARRT drug-related diarrhea was reported to account for up to 65.60% among those with HIV/AIDS-associated diarrhea.\[14\] On account of the HAART’s defects, poor patient compliance, the long period of drug management, high price after drug discontinuance, drug dependence, drug adverse effect, high recurrence rate and the incapability to wholly reconstruct immunity,\[15\] the current modern medical treatments are not very good at treating HIV/AIDS-associated diarrhea.\[16\] We need alternative approaches, given the limited options available to treat HIV/AIDS-associated complications like HIV/AIDS-associated diarrhea.

**Description of the intervention**

Traditional Chinese Medicine (TCM) dated from thousands of years ago and is still developing in China. The natural medicinal plants are the source of Chinese herbs, and it is usually considered as a method that is natural, more inexpensive, and convenient and with lighter side effects to treat diseases.

It has been shown to be efficacious to treat HIV/AIDS-associated diarrhea on the basis of syndrome differentiation and treatment. It can also improve patients’ immune status to some extent\[17,18\] and could have good application potential, especially for those who cannot acquire or afford HAART.

Many clinical trials have been conducted on TCM for treating HIV/AIDS-associated diarrhea.\[19-26\] Moreover, Chinese herbs are commonly used in the treatment of diarrhea in clinical practice in China.\[27\]

**How the intervention might work**

Many clinical studies about TCM have shown that they may relieve HIV/AIDS-associated diarrhea symptoms. TCM decreases the levels of interleukin (IL)-6, IL-17, IL-21, IL-23, and other cytokines, by this means, reducing immune inflammatory damage of intestinal tract and protecting the intestinal barrier function in the treatment of diarrhea.\[28\] TCM has many mechanisms to treat diarrhea. First, it can maintain the balance of water and electrolytes. The examples are as follows: Buzhong Yiqi Tang,\[29\] Berberine (BBR),\[30\] and Atractylodolide I\[13\] can increase the absorption of Na+ and water by up-regulating the Na+/glucose cotransporter 1 and Na+/H+ exchanger 3 expression. The activity of the calcium-activated chloride channel and the cystic fibrosis transport regulator can be inhibited by dimer and tetramers of resveratrol. Therefore, the secretion of Cl- reduces with the intestinal fluid secretion reduces as well.\[32\] Rhubarb tannins play a role in the regulation of aquaporins (AQP) and inhibition of AQP2 and AQP3 expression, thus prominently decreasing fecal water in the colon;\[33\] the expression of AQP4 can be adjusted upward by Jiawei Renshen Wumei Tang\[34\] and Fuzi Lizhong Tang\[35\] to promote the intestinal absorption of water.

Second, Chinese herbal medicine can have anti-inflammatory effects and regulate immune responses. Some active components of Chinese herbs can regulate the secretion of proinflammatory cytokines by interfering with micro-ribonucleic acid (RNA)-155 (miR-155), nucleotide-binding oligomerization domain -like receptor 3 (NLRP3), nuclear factor kappa-B, and other signal pathways. Some can promote the T-helper cells’ apoptosis variously, inhibit the rapamycin signal pathway target in mammals, and raise the ratio of T regulatory cells by balancing T-lymphocytes.\[36\] For example, the level of proinflammatory cytokines like tumor necrosis factor-α and IL-1β can reduce by Chinese herbs such as BBR,\[37\] raw and bran-roasted *Puerariae lobatae Radix* (Gegen),\[38\] *Polygonum hydropiper* (Laliao),\[39\] Huangqin Tang,\[40\] Gegen Qinlian Tang\[41\] and *Chrysanthemum morifolium Ramat* (Juhua),\[42\] Shenlin Baizhu San,\[43\] coked *Atractylodes rhizome* (Cangzhu)\[44\] and *Puerariae lobatae Radix* (Gegen),\[38\] can enhance the level of IL-10 to alleviate inflammatory responses.

Thirdly, Chinese herbal medicine can improve gastrointestinal function. Taking *Rhizoma atractylodis* (Baizhu) as an example, it can have an effect on the counts of brain-gut peptide and the biological synthesis of neurotransmitters (or signaling molecules) that are amino acid derivative like gamma-aminobutyric acid, dopamine, and 5-hydroxytryptamine, so as to regulate the neuro-endocrine network homeostasis and eliminate gastrointestinal dysfunction through amino acid metabolism.\[45\] The volatile oil, which is extraction from *Alpinia oxyphylla* (Yízhi), can inhibit the secretion of gastrointestinal hormone and reduce the level of motilin and
somatostatin, achieving the aim of improving gastrointestinal function.\textsuperscript{[46]}

Fourthly, Chinese herbal medicine can promote the intestine epithelial cells repairing and protect the intestinal epithelial cells barrier. For example, the intestinal mucosal repair factors expression can be prominently amplified by SiJun Zi Tang, including the transforming growth factor-β1, the epidermal growth factor receptor, and the proliferation of cell nuclear antigen.\textsuperscript{[47]} The mucin-1 messenger RNA and mucin-2 messenger RNA expression can be up-regulated by patchouli alcohol.\textsuperscript{[48]} Gegen Qinlian Tang may promote the expression of occludin, zona occludens-1, and tight junction proteins to participate in the upregulation of the intestinal epithelial barrier function.\textsuperscript{[41]} With enhancing lactase activity, the compound Radix pulsatillae (Baitou Weng) facilitates the intestinal epithelial cells repair.\textsuperscript{[49]}

Fifth, Chinese herbal medicine can modulate the intestinal microbiota community. Giving an example, Lactobacillus acidophilus’ proliferation rate can be significantly promoted while proliferation of Escherichia coli can be inhibited by Atractylodes macrocephala (Baizhu).\textsuperscript{[50]} C. moriformium (Juhua) polysaccharides can increase the number of Rikenellaceae, Lactobacillus, Lachnospiraceae, Clostridium, Butyricicoccus, and Bifidobacterium, and decrease opportunistic pathogens, such as prevotella, Escherichia, and Enterococcus.\textsuperscript{[42]}

Why it is important to do this review
It is important to identify potentially beneficial therapeutic modalities on account of few effective therapies in the treatment of HIV/AIDS-associated diarrhea. There is a need to support people suffer from HIV/AIDS-associated diarrhea by using Chinese herbs to relieve symptoms and attenuate the side effects of antiretrovirals. However, there is mainly theoretical and empirical evidence that supports to treat HIV/AIDS-associated diarrhea with TCM. In addition, the growing studies reports that some herbal products have hepatotoxicity or other adverse effects,\textsuperscript{[51,52]} and there is the possibility of herb-drug interactions. These literature are also worthy of evaluation.\textsuperscript{[53]} The curative effects, harm, and cost-benefit of herbal medicine has not been well demonstrated. Consequently, a systematic review should be conducted according to PRISMA-P.

Objectives
To assess the beneficial effect and safety of Chinese herbal medicine for HIV/AIDS-associated diarrhea.

Methods
Criteria for considering studies for this review
Types of studies
Randomized controlled trials (RCTs) comparing Chinese herbal medicine with placebo or other effective treatments will be included, in spite of publication status or language.

Types of participants
Patients suffer from chronic or acute HIV/AIDS-associated diarrhea will be included in spite of ethnicity, gender, age, or economic status.

Patients suffer from diarrhea caused by cholera, systemic diseases, poisoning, and dysentery will be excluded.

Types of intervention
The experimental interventions are any herbs, which include herbs extraction, single Chinese herb, and compound formulas that are administered orally and are either taken alone or with another effective therapy.

Control intervention can be no treatment, placebo, or another active treatment.

Co-intervention is permitted only if it is applied in both groups.

A combination of different Chinese herbal medicines will be excluded.

Types of outcome measures
Primary outcomes
1. Diarrhea frequency (per day or week)
2. Fecal character.

Secondary outcomes
1. Recovery duration of diarrhea
2. Length of hospital stay
3. Bodyweight
4. Recurrence
5. Condition of nutrition
6. Living quality
7. Adverse effect: all adverse effects reported or the incidence of all adverse events. The adverse events will be classified as serious and non-serious based on available data. The exterior medical events that threat to life, lead to death, significant or persistent disability, and the medical happen that might endanger people or require to be stopped will be considered a serious adverse event.\textsuperscript{[54]} Others will be considered non-serious.

The outcomes with identical constituents will be in the use of analyzing data for the composite result index. The composite result index will be divided into effective and ineffective if it is an ordered categorical variable like ineffective, effective, prominent effect, and cure.

Search method for the identification of studies
We will search all related trials regardless of language or publication status.

Electronic searches
The search terms and strategy described in Additional File 1 will be used to search the following databases: China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (SinoMed), Wanfang Data, China National Knowledge Infrastructure, PubMed and the CENTRAL in the Cochrane Library.
Searching other resources
We will check the reference lists and related reviews of the retrieved studies to identify other studies that may be relevant.
We will manually search relevant Chinese journals which are most possible to publish studies about AIDS-associated diarrhea.
We will also search unpublished and ongoing studies by contacting researchers in the field.

Data collection and analysis
Two review authors (BLC and MZZ) will independently carry out each step for the screening of trials and extraction of data before discussing their findings together. Any disagreements will be resolved by discussing with another author (JPL).

Selection of studies
Two reviewers (ZWH and BLC) will eliminate duplications and examine titles and abstracts of studies retrieved through the database search independently. If a study cannot be excluded by its title and abstract, we will further evaluate its full text. If eligibility of a trial is unclear, we will contact the authors to clarify. Any disagreements will be resolved through discussion with a third author (JPL). The excluded studies and the reasons for excluding them will be listed in the “Characteristics of excluded studies” table. And we will draw the flowchart showing the screening procedure for the study.

Data extraction and management
We will import screened studies from miscellaneous search databases into EndNote and then examine duplicates. We will arrange two authors (BLC and MZZ) to extract the data by using a data extraction forms which we prepare in advance. The data that we need to extract include basic information (study author, title and study ID), methodological information (study design, the number of groups, baseline comparability, sequence generation, allocation sequence concealment, blinding, selective outcome reporting), the peculiarity of participants (inclusion criteria, exclusion criteria, diagnostic criteria, acute/chronic, TCM pattern, sex, age, setting, country, total number of intervention groups, number of loss, disease course), intervention (the drug name, formulation, dose, usage, drug combination, other interventions, course of therapy), and outcome measures. And we will make a form to record the related data. Any disagreements will be resolved through discussion with a third author (JPL) and we will touch the author if there is missing or unclear data in the trial.

Assessment of risk of bias in the included studies
Two authors (CX and HRZ) will use the Cochrane “Risk of bias” tool to evaluate each trial’s methodological quality and then record in the “Risk of bias” table. We will systematically evaluate the risk of bias based on the “Risk of bias” assessment tool of Cochrane Handbook for Systematic Reviews of Interventions, taking into account the following factors:
1. Sequence generation
2. Allocation concealment
3. Blinding of participants, personnel, and outcome assessors
4. Incomplete outcome data
5. Selective outcome reporting
6. Other possible sources of bias. The baseline differences between groups will be assessed. The risk of bias will be determined to be low in the case that the baseline differences are not significant. The risk of bias will be determined to be high if the baseline differences are significant. The risk of bias will be determined as unclear under other conditions.
We will try to contact the trial authors if the information we need is not specified. Any disagreements will be resolved through discussion with a third author (JPL).

Measures of the treatment effect
We will use risk ratios (RR) and 95% confidence intervals (CIs) to report dichotomous outcomes. If the trials included measure the continuous outcomes differently, standardized mean difference (SMDs) and 95% CI will be used as effect measure, or mean differences (MDs) and 95% CIs will be used. We will use hazard ratios and 95% CIs to present time-to-event outcomes.

Unit of analysis issues
Individual patients will be the unit of analysis if the studies are individual trials. Clusters will be the unit of analysis in the case of a cluster-randomized study design. We will conduct an appropriate analysis to adjust for the effect of cluster randomization prior to we include effects estimates in the meta-analysis. In the case that the cluster-randomized trials meet the inclusion criteria. We will extract adjusted effect measures from trials if possible. We will choose intracluster correlation coefficient (ICC) to adjust data if adjusted data are unavailable. We will also contact the authors to acquire the ICC, estimate the ICC, or refer to an ICC value in a semblable study if the it is not provided. We will carry out a sensitivity analysis to explore the robustness of analysis if the ICC is estimated.

Dealing with missing data
We will obtain the missing data by contacting the trial’s authors. If we cannot obtain it, we will explore the impact of missing data on primary outcomes by conducting a sensitivity analysis. Loss of follow-up reduces data credibility. However, studies with more than a 50% drop-out rate will be included given the limited evidence base. A worst-case scenario approach will be adopted to analyze data if the study reports the number of people for whom the outcome data are missing. It means that we will consider people with missing data in control group as having been successfully treated, and people with missing data in treatment group as having been failed treat. We will point out which trials have used imputation and what measures are used. If the effect estimates are same and there the differences between groups are significant, we will come to conclusions more confidently. if the effect estimates of two analyses are different, we will explain the results more prudently as well as concluding more conservatively about the treatment effect.
Assessment of heterogeneity
We will use forest plots to assess the heterogeneity to determine the point estimates’ closeness and the overlap of CIs. We will use the Chi-square test, with a $P = 0.10$ to indicate the statistical significance. We will use the $I^2$ statistic to assess the heterogeneity with a value of 50%, indicating substantial heterogeneity. The random-effects model will be used if the heterogeneity is significant, or the fixed effects model will be chosen. We will use statistical analysis of the Cochrane software to conduct the analyses.

Assessment of reporting biases
We will check the funnel plots to assess the impact of small studies (publication bias). The symmetry of funnel plot will be checked if we include sufficient trials (over ten trials) in a meta-analysis. If it is not symmetrical, we will explore the publication bias quantitatively using Egger’s test.

Data synthesis
We will analyze data using The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.4. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2020. If there are adequate similar studies, we will pool meta-analysis results using a random-effects model and RR with 95% CIs. We will figure up the RR for every trial and summarize data for dichotomous outcomes. If results of studies are measured by the same standards, the MDs will be chosen for continuous outcomes. Or, the SMDs will be chosen. We will record the data in tables if it is inappropriate for a meta-analysis.

Subgroup analysis and investigation of heterogeneity
The subgroup analysis as follows for patients suffering from AIDS-associated diarrhea will be conducted to explore the heterogeneity:
1. Chronic or acute
2. TCM pattern
3. Etiology causing diarrhea
4. Interventions including prescriptions of herbs, compound patent medicine, a single herb, and so on
5. Ethnicity, age, and sex.

Sensitivity analysis
We will investigate the impact of loss of follow-up on primary outcomes by performing sensitivity analyses and exclude studies that are considered to have a high risk of bias. Moreover, we will conduct sensitivity analyses based on the reporting of randomization methods, allocation concealment, or blinding. We will vary the incidence of missing patients in the intervention group and the control group within reasonable limits for dichotomous outcomes. We will conduct a sensitivity analysis on the continuous data using the methods in Ebrahim et al., 2013 and Ebrahim et al., 2014.

Summary of findings and assessment of the certainty of the evidence
The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach will be used to assess the evidence quality, and it will be presented in the “Summary of Findings” tables. We will make use of the five GRADE considerations (publication bias, study limitations, imprecision, effect consistency, and indirectness) to assess the determinacy of a series of evidence related to the trials. GRADEpro, a piece of software, the methods and recommendations in the Chapter 14 of Cochrane Handbook for Systematic Reviews of Interventions, will be used.

Discussion
We searched four intervention reviews and meta-analyses about HIV/AIDS-associated diarrhea, but none evaluated TCM interventions. The strengths of this study consist in its value as a guide to clinical practice and exploring new methods for treating HIV/AIDS-associated diarrhea. TCM with approved safety profile that can be used to treat people suffer from HIV/AIDS-associated diarrhea, expected for not only relieving symptoms but also side effects after antiviral treatment, is in demand.

There are still several limitations in this protocol. Some trials that reported the efficacy of TCM to treat HIV/AIDS-associated diarrhea are generally poor in quality. Moreover, as there are large variations among the herbal remedies tested, it is challenging for a meta-analysis to be conducted. Lack of sufficient English literature remains a problem, even though the search strategy is comprehensive and the language is not limited. In foreign countries, the public does not accept TCM as commonly as in China, which may have an impact on the generalization of the study results. Accordingly, we are looking forward to more large-sample and high-quality RCTs that can support the results of our study and inform people all over the world about the use of TCM in treating patients with HIV/AIDS-associated diarrhea.

The systematic review was registered in INPLASY (https://inplasy.com/inplasy-2020-7-0093/). The registration number is INPLASY202070093.

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Conflicts of interest
There are no conflicts of interest.

References


A protocol of oral CHM for aids diarrhea