**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**

Bai-Lin Chen¹, Ming-Zhu Zhang¹, Zi-Wei Huang⁴, Hong-Rui Zhang⁴, Chang Xu⁴, Jing Li⁴, Zhen-Wei Liu⁵, Feng Jiang⁴, Xun Li⁵, Nicola Robinson⁶, Jian-Ping Liu⁵

¹Department of traditional Chinese Medicine, First School of Clinical Medicine, Beijing University of Chinese Medicine, ²Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, ³AIDS Centre, Ruikang Hospital, Guangxi University, Guangxi, China, ⁴London South Bank University, UK

**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 healthcare 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.³ The clinical symptoms are primarily chronic diarrhea with loss of weight,

**Address for correspondence:** Prof. Jian-Ping Liu, Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, 100029, China. E-mail: liujp@bucm.edu.cn

This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

© 2020 World Journal of Traditional Chinese Medicine | Published by Wolters Kluwer - Medknow

Received: 20-07-2020, Accepted: 27-09-2020, Published: 16-12-2020

**How to cite this article:** Chen BL, Zhang MZ, Huang ZW, Zhang HR, Xu C, Li J, et al. 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. World J Tradit Chin Med 2020;6:370-6.
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.

Opportunistic infection of bacteria, viruses, fungi, and parasites accounts for approximately 50%~60% of patients with HIV/AIDS-associated diarrhea. 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. In addition, in the process of AIDS progression, there may be noninfectious causes such as side effects of HAART, AIDS-related individual idopathic factors, AIDS-related absorption disorders, and malignant tumors. 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.

The incidence of noninfectious diarrhea rose from 32% to 70%, while the incidence of diarrhea caused by opportunistic infections fell from 53% to 13%. The incidence of noninfectious diarrhea mainly caused by medication rose from 0% in 1995 to 45% in 1997.

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. However, diarrhea is still common in patients with HIV infection. Diarrhea caused by HAART drugs is of concern, especially when combined with lopinavir/ritonavir. HAART drug-related diarrhea was reported to account for up to 65.60% among those with HIV/AIDS-associated diarrhea.

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, the current modern medical treatments are not very good at treating HIV/AIDS-associated diarrhea.

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 slighter 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 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. Moreover, Chinese herbs are commonly used in the treatment of diarrhea in clinical practice in China.

**How the intervention might work**

Many clinical studies about TCM have shown that they may relieve HIV/AIDS-associated diarrhea symptoms. TCM increases 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.

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, and Atractylenolide I 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. 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; the expression of AQP4 can be adjusted upward by Jiawei Renshen Wumei Tang and Fuzi Lizhong Tang 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. For example, the level of proinflammatory cytokines like tumor necrosis factor-α and IL-1β can reduce by Chinese herbs such as BBR, raw and bran-roasted Puerariae lobatae Radix (Gegen), Polygonum hydropiper (Laliao), Huangqin Tang, Gegen Qinlian Tang and Chrysanthemum morifolium Ramat (Juhua), Shenlin Baizhu San, coked Atractylodes rhizome (Cangzhu) and Puerariae lobatae Radix (Gegen), 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. The volatile oil, which is extraction from Alpinia oxyphylla (Yizhi), 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-\(\beta\)1, 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, zonula occludens-1, and tight junction proteins to participate in the upregulation of the intestinal epithelial barrier function.\textsuperscript{[49]} 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, \textit{Lactobacillus acidophilus}' proliferation rate can be significantly promoted while proliferation of \textit{Escherichia coli} can be inhibited by \textit{Atractyloides macrocephala} (Baizhu).\textsuperscript{[50]} \textit{C. morifolium} (Juhua) polysaccharides can increase the number of Rikenellaceae, \textit{Lactobacillus}, \textit{Lachnospiraceae}, \textit{Clostridium}, \textit{Butyricicoccus}, and \textit{Bifidobacterium}, and decrease opportunistic pathogens, such as prevotella, \textit{Escherichia}, and \textit{Enterococcus}.\textsuperscript{[42]}

\textbf{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.

\textbf{Objectives}

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

\textbf{METHODS}

\textbf{Criteria for considering studies for this review}

\textbf{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.

\textbf{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.

\textbf{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.

\textbf{Types of outcome measures}

\textbf{Primary outcomes}

1. Diarrhea frequency (per day or week)
2. Fecal character.

\textbf{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.

\textbf{Search method for the identification of studies}

We will search all related trials regardless of language or publication status.

\textbf{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 proper 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.$^{[57]}$ 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.$^{[58]}$

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.$^{[59,60]}$

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.$^{[60]}$ GRADEpro, a piece of software, the methods and recommendations in the Chapter 14 of Cochrane Handbook for Systematic Reviews of Interventions,$^{[61]}$ will be used.

Discussion

We searched four intervention reviews and meta-analyses about HIV/AIDS-associated diarrhea, but none evaluated TCM interventions.$^{[62-65]}$ 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.

Financial support and sponsorship

This work was supported by the National Natural Science Foundation of China (Grant No.: 81673828).

Conflicts of interest

There are no conflicts of interest.

References

1. WHO. HIV/AIDS; 2019. Available from: https://www.who.int/health-topics/hiv-aids/#tab=tab_1. [Last accessed on 25th Nov 2020].
2. WHO. 10 FACTS ON HIV/AIDS; 2019. Available from: https://www.who.int/news-room/facts-in-pictures/detail/hiv-aids. [Last accessed on 25th Nov 2020].
3. Yan L, Guo HJ. The research progress of AIDS diarrhea treated with TCM. Liao J Tradit Chin Med 2011;38:2490-3.
4. Lew EA, Poles MA, Dieterich DT. Diarrheal diseases associated with HIV infection. Gastroenterol Clin North Am 1997;26:259-90.
5. WHO. Interim WHO Clinical Staging of HIV/AIDS and HIV/AIDS Case Definitions for Surveillance; 2005. Available from: https://www.who.int/hiv/pub/guidelines/casedefinitions/en. [Last accessed on 25th
Chen, et al. A protocol of oral CHM for aids diarrhea sr

0. O.? ???. Patterns and correlates of discontinuation of the initial HAART regimen in an urban outpatient cohort. J Acquir Immune Defic Syndr 2003;34:407-14.

1. AIDS WHO GPO. Guidelines for the Clinical Management of HIV Infection in Adults. Geneva: World Health Organization; 1991.

2. Macarthur RD. Management of noninfectious diarrhea associated with HIV and highly active antiretroviral therapy. Am J Manag Care 2013;12:238-45.

3. Sherman DS, Fish DN. Management of protease inhibitor-associated diarrhea. Clin Infect Dis 2000;30:908-14.

4. Pape JW, Verdiér RI, Boney M, Boney J, Johnson WD Jr. Cyclospora infection in adults infected with HIV. Clinical manifestations, treatment, and prophylaxis. Ann Intern Med 1994;121:654-7.

5. Logan C, Beehagh MB, Beech NJ. HIV and diarrhea: What is new? Curr Opin Infect Dis 2016;26:486-94.

6. Call SA, Heudebert G, Saag M, Wilcox CM. The changing etiology of chronic diarrhea in HIV-infected patients with CD4 cell counts less than 200 cells/mm3. Am J Gastroenterol 2000;95:3142-6.

7. Dabis F, Newell ML, Hirschel B. HIV drugs for treatment, and for prevention. Lancet 2010;375:2056-7.

8. Zhang XW, Zhang AP, Li Z, Guo HJ. The analysis of the clinical features of 67 cases of HIV/AIDS related diarrhea. Chin J Dermatovenereol 2010;33:99‑102.

9. Zhao HX, Zhang FJ. Opportunities and challenges of integrated Chinese medicine treatment guidelines (2013 Edition). Acta Chin Med 2014;29:617‑20.

10. Xiao ZH, Luo XY, Cheng XX, Zheng SJ, Yang Q, Yang HW. Effect of polygoni hydropiperis herba on intestinal mucosal repair in diarrhea mice induced by Escherichia coli. Chin J Tradit Med Form 2018;24:120-6.

11. Shao MJ, Yan YX, Qi Q, Tang W, Zuo JP. Application of active components from traditional Chinese medicine in treatment of inflammatory bowel disease. Zhongguo Zhong Yao Za Zhi 2019;44:415-21.

12. Li CZ, Chen GJ. Study on the mechanism of berberine in treating inflammatory bowel disease. Curr Immunol 2013;3:74-6.

13. Zhang D, Zhu LL, Xu M, Xiu Y. Anti-diarrhea effect of raw and roasted Puerariae lobatae Radix and its mechanism. Chin Tradit Patented Med 2014;36:2140-4.

14. Wu Y, Wang D, Yang X, Fu C, Zou L, Zhang J. Traditional Chinese medicine gegen qinian decorateur ameliorates irinotecan chemotherapy-induced gut toxicity in mice. Biomed Pharmacother 2019;109:2252-61.

15. Chen XZ. AIDS-associated diarrhea. Int J Epidemiol Infect Dis 1997;24:77-80.

16. Feitosa G, Bandeira AC, Sampaio DP, Badaró R, Brites C. High prevalence of giardiasis and stronglyloidiassiasis among HIV-infected patients in Bahia, Brazil. Braz J Infect Dis 2001;5:339-44.

17. Marshall GD. HIV-associated diarrhea and wasting. Lancet 1995;346:1304.

18. Li Z, Yuan J, Zhang XW, Guo HJ. 19 cases of AIDS-related diarrhea with spleen-kidney yang deficiency treated by Jianpi Zhixie decoction. Tradit Chin Med Res 2016;29:11-3.

19. Dong SQ. Clinical research of Xieli Kang capsule treatment of chronic diarrhea. Acta Chin Med 2014;29:1549-51.

20. Xu Z, Yang XJ, Ni L, Zhang ML, Guo CH, Wang DX, et al. Clinical study on Xieli Kang capsule in treatment of AIDS-related chronic diarrhea. Global Tradit Chin Med 2011;4:197-200.

21. Zhou LH, Tang Y, Yang GH, Zhang HL, Guo CH. Clinical study on TCM treatment of AIDS-related diarrhea. Chin J Inform Tradit Chin Med 2007;9:10-2.

22. Chen RE, Yang QE, Xu SF, Lu YH, Jiang YM. Clinical analysis of Zhenqi Fuzheng capsule combined with HAART in the treatment of AIDS. Modern J Integr Tradit Chin Western Med 2014;23:2664-5.

23. Wang Y, Wang D, Yang X, Fu C, Zou L, Zhang J. Traditional Chinese medicine gegen qinian decorateur ameliorates irinotecan chemotherapy-induced gut toxicity in mice. Biomed Pharmacother 2019;109:2252-61.

24. Tao JH, Duan JA, Jiang S, Feng NN, Qiu WQ, Ling Y. Polysaccharides from Chrysanthemum morifolium ramat ameliorate colitis rats by modulating the intestinal microbiota community. Oncotarget 2017;8:30299.

25. Li XB, Cui LH, Chen YL, Zhan JP, Xie ZL, Zhu YQ, et al. Immunomodulatory effect of Shen Ling Bai Zhu powder on intestinal regulatory T cells in mice with ulcerative colitis. Chin Tradit Patented Med 2014;36:1295-7.

26. Chen XS. Study on Material Basis and Mechanism of Coked Atractyloides Rhizome Non-volatile Invigorating Spleen and Stopping Diarrhea, Ph.D Thesis. Wuhan, China: Hubei University of Chinese Medicine; 2019.

27. Xiao MF, Zhou SL. Prescription rules and mechanism analysis of Chinese patent medicines containing rhizoma Atractylidis for diarrhea based on data mining. China Pharm 2019;22:969-75.

28. Wang S, Li YH, Xu P, Wei N, Chen F, Zhang QJ. Preliminary study on warm spleen and anti-diarrheal activity of volatile oil extracted from Alpinia oxyphylla. J Hainan Med Univ 2013;19:433-8.

29. Cao LZ. The Study on Prevention Mechanism of Si Jun Zi Tang on E.-coli-induced Diarrhea of Mice, Master’s Thesis. Baoding, China: Hebei Agricultural University; 2009.

30. Yu XT. Main active component of Pogostemon cablin or Captis chinensis Protects Against Dextran Sulfate Sodium-induced Colitis in Mice: Effect and Mechanism Research. China: Guangzhou University of Chinese Medicine; 2016.

31. Zhang XL, Wang YC, Xu QQ, Wang LY, Huo XQ, Cao LZ, et al. The influence of decoction of compound radix pulsatilae on the lactase activity in diarrheal mice intestinal mucosa. J Agric Univ Hebei 2010;33:99-102.

32. Ye QQ, Wang VR, Fang WB, Liu GF, Feng J, Guan SY. Study on the regulation effect of 8 herbs on intestinal diagnostic flora growth. J Guangdong Pharm Univ 2016;32:291-4.

33. Ishizaki T, Sasaki F, Shiozaki K, Takahashi H, Abe Y, et al. Pneumonitis during interferon and/or herbal drug therapy in patients with chronic active hepatitis. Eur Respir J 1996;9:2691-6.
52. Melchart D, Linde K, Weidenhammer W, Hager S, Shaw D, Bayer R. Liver enzyme elevations in patients treated with traditional Chinese medicine. J Am Med Assoc 1999;282:28-9.

53. Izzo AA, Ernst E. Interactions between herbal medicines and prescribed drugs: An updated systematic review. Drugs 2009;69:1777-98.

54. International Conference on Harmonisation Expert Working Group. Code of Federal Regulations and International Conference on Harmonisation Guidelines. Pennsylvania: Parexel/Barnett; 1997.

55. Xia J, Adams C, Bhagat N, Bhagat V, Bhoopathi P, El-Sayeh H, et al. Losing participants before the trial ends erodes credibility of findings. Psychiatr Bull 2009;33:254-7.

56. Gamble C, Hollis S. Uncertainty method improved on best-worst case analysis in a binary meta-analysis. J Clin Epidemiol 2005;58:579-88.

57. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA, editors. Cochrane Handbook for Systematic Reviews of Interventions. United States: Wiley; 2019. Available from: https://training.cochrane.org/cochrane-handbook-systematic-reviews-interventions. [Last accessed on 25th Nov. 2020].

58. van Enst WA, Ochodo E, Scholten RJ, Hooft L, Leeflang MM. Investigation of publication bias in meta-analyses of diagnostic test accuracy: A meta-epidemiological study. BMC Med Res Methodol 2014;14:70.

59. Ebrahim S, Akl EA, Mustafa RA, Sun X, Walter SD, Heels-Ansdell D, et al. Addressing continuous data for participants excluded from trial analysis: A guide for systematic reviewers. J Clin Epidemiol 2013;66:1014-21.

60. Ebrahim S, Johnston BC, Akl EA, Mustafa RA, Sun X, Walter SD, et al. Addressing continuous data measured with different instruments for participants excluded from trial analysis: A guide for systematic reviewers. J Clin Epidemiol 2014;67:560-70.

61. Schünemann HJ, Vist GE, Glasziou P, Akl EA, Søe N, Guyatt GH. In: Higgins JP, Thomas J, Chandler J, Cumpston MS, Li T, Page MJ, et al., editors. Completing Summary of Findings Tables and Grading the Certainty of the Evidence, Cochrane Ch. 14. United States: Wiley; 2019. Available from: https://training.cochrane.org/handbook/current/chapter-14 [Last accessed on 25th Nov. 2020].

62. Humphreys EH, Smith NA, Azman H, McLeod D, Rutherford GW. Prevention of diarrhoea in children with HIV infection or exposure to maternal HIV infection. Cochrane Database Syst Rev 2010;6:CD008563.

63. Mbakaya BC, Kalembo FW, Zgambo M. Community-based interventions for preventing diarrhoea in people living with HIV in Sub-Saharan Africa: A systematic review. Malawi Med J 2019;31:86-94.

64. Motaze NV, Nwachukwu C, Humphreys E. Treatment interventions for diarrhoea in HIV-infected and HIV-exposed children: A systematic review. Pan Afr Med J 2018;29:208.

65. Nwachukwu CE, Okebe IU. Antimotility agents for chronic diarrhoea in people with HIV/AIDS. Cochrane Database Syst Rev 2008;4:CD005644.