Author’s response to reviews

Title: Evaluation of HuoXueHuaYu therapy for Nonalcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis of Randomized Controlled Trial

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Author’s response to reviews:

Dear Editors and Reviewers:

Thank you for your letter and for the reviewers’ comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. We have studied comments carefully and have taken the comments into consideration in preparing our revision. The responses to the reviewers’ comments and the main corrections in the paper are as following:

Reviewer: 1

1. Effectiveness of HuoXueHuaYu (HXHY) herbal drugs on non-alcoholic fatty liver disease (NAFLD) was investigated in this systematic review. While this review adheres to the basic principles of systematic review and meta-analysis methodology, detailed explanation is much lacking. To better claim the effectiveness of HXHY on NAFLD, whole analysis with overall herbal drugs, followed by subset analysis with HXHY herbal drugs, would have been desirable. From such design, any changes in the effect size or heterogeneity would have been interesting and have added more significance to the
Response: Thanks for the reviewer’s suggestion. The purpose of our systematic review and meta-analysis is to evaluate the effect of HXHY therapy on NAFLD. Therefore, we just focus on the studies which used HXHY-class herbs for NAFLD. The reviewer’s suggestions are very valuable and helpful. We will assess the whole Chinese herbal medicine and do the subgroup analysis of different therapies in TCM for NAFLD in the future.

2. Please state that this study is a systematic review in the title and the abstract.
Response: We accept the reviewer’s suggestion and have stated that the study is a systematic review and meta-analysis in the title and the abstract.

3. Figure 2 does not match what the manuscript states; while the manuscript states that the most of the studies did not properly describe of allocation concealment and blinding, the figure shows the opposite. Credibility of figures is thus questionable. All figures must be re-examined for their integrity.
Response: Thanks for the reviewer’s suggestion. We are very sorry for this kind of mistake in our manuscript. We have checked the quality assessment of all the included studies and all the figures. As the reviewer said, figure 2 does not match what the manuscript states and we have re-created the figure 2.

4. Criteria of HXHY-class herbs must be defined; without clear definition of HXHY-class herbs, omission of non-HXHY herbal trials seems much subjective and non-systematic. Disclosure of herbal composition of drugs listed in table 1 would help readers to better understand the class.
Response: Thanks for the reviewer’s suggestion. The reviewer’s suggestions are very valuable and helpful. We have defined the criteria of HXHY-class herbs in the Methods, Study Selection section with highlighting and added table 2 to show the herbal composition of formulae in the included studies.

5. For readers outside China, definition of the primary outcome, "effective rate" must be described in detail. Moreover, it would be desirable if the definition of effective rate in each original study is provided, e.g. clinical symptoms, lab results, etc. If the definition of effective rate depends on subjective judgement, more objective measures such as ultrasonic or lab results would be suitable as the primary outcome.
Response: Thanks for the reviewer’s suggestion. As the reviewer said, "effective rate" should be described in detail. We have described the definition of the effective rate in each study in the “The Effect of HuoXueHuaYu Therapy on the Effective Rate in NAFLD Patients” of Results section with highlighting. The effective rate in seven studies refers to the proportion of participants with improvement of clinical symptoms and level of type-B ultrasonic of liver. The effective rate in the other five studies refers to the proportion of participants with improvement of clinical symptoms and level of type-B ultrasonic of liver as well as ≥30% reduction in level of liver function and blood lipids. The effective rate included not only clinical symptoms, but also lab results. Therefore, we consider the effective rate might be suitable as the primary outcome.
Reviewer: 2

1. It is difficult to determine whether the analysis of this paper is the effect of the HuaXueHuaYu therapy for NAFLD or the effect of the whole Chinese herbal medicine for NAFLD. In addition, it is also necessary to suggest the criteria for judging what the author have judged the herbal medicine classified as a HuaXueHuaYu as a Chinese herbal medicine. As the herbs of included studies are diverse, table 2 should be added to show the composition of Chinese medicine.

Response: Thanks for the reviewer’s suggestion. We have defined the criteria of HXHY-class herbs in the Methods, Study Selection section with highlighting and added table 2 to show the herbal composition of formulae in the included studies.

2. In introduction, the author mentioned that "Blood stasis syndrome is one of the basic syndromes of NAFLD". For those unfamiliar with the TCM, it is necessary to present all types of syndromes in NAFLD, among other things, which it is necessary to provide a reference for why HuaXueHuaYu therapy is the most important treatment.

Response: The reviewer’s suggestions are very valuable and helpful. We have listed all types of syndromes in NAFLD and added three references [1-3] for why HuaXueHuaYu therapy is the most important treatment in the Introduction section.

3. Conventional medicine is presented as a control group, but there are a wide variety of drugs in Table 1, and the introduction suggests that these drugs have a limited benefit depending on the drug. Due to the wide diversity of control units, I could not expect a consistent effect of control group, it is needed to add a limitation to that. It may also be necessary to specify whether or not to consider lifestyle intervention as a control group.

Response: Thanks for the reviewer’s suggestion. It is really true as reviewer said that there are a wide variety of drugs in the control group. We have added a limitation of our meta-analysis in the Discussion section. Lifestyle intervention has several limitations, such as a lack of compliance and consistent effect, which we stated in the Background section. In addition, in the process of searching articles, we found that lifestyle intervention is rarely used as a control group. Therefore, we did not consider lifestyle intervention as a control group.

4. In Result, it is mentioned to as none of the studies reported allocation concealment, but the actual figure 2 shows different results. Modifications and presentation of judgment evidence are required. If you have also evaluated the selective reporting or incomplete outcome data domains, you should be provide a rationale for this in the text.

Response: Thanks for the reviewer’s suggestion. We are very sorry for this kind of mistake in our manuscript. We have checked the quality assessment of all the included studies and re-created the figure 2. We also have added the evaluation of blinding of outcome assessment, incomplete outcome data and selective outcome reporting in the “Study Description and Quality Assessment” of Results section.

5. Although the effect rate is analyzed as the primary outcome, it is not known what the effect is defined in each study. Also, unless it is a validated tool, it can be a subjective outcome indicator, making it difficult to admit reliability and validity. If the results of each study were to indicate what the effect was, or if there was a possibility that the same criteria were not applied in each study, it would be necessary to set the type-B ultrasonic of liver as the primary outcome (except the effect rate). In
general, the effect rate, which is assessed by a tool that is not objective, may result low heterogeneity due to the bias of the study.

Response: Thanks for the reviewer’s suggestion. We have described the definition of the effective rate in each study in the “The Effect of HuoXueHuaYu Therapy on the Effective Rate in NAFLD Patients” of Results section with highlighting. The effective rate in seven studies refers to the proportion of participants with improvement of clinical symptoms and level of type-B ultrasonic of liver. The effective rate in the other five studies refers to the proportion of participants with improvement of clinical symptoms and level of type-B ultrasonic of liver as well as ≥30% reduction in level of liver function and blood lipids. The effective rate included not only clinical symptoms, but also lab results. Therefore, we consider the effective rate might be suitable as the primary outcome.

6. In the NAFLD guidelines for 2018, "Pharmacological treatments aimed primarily at improving liver disease are generally limited to those with biopsy-proven NASH and fibrosis." Therefore, NAFLD Diagnostic criteria and severity of participants in included studies should be provided.

Response: Thanks for the reviewer’s advice. The reviewer’s suggestions are very valuable and helpful. We have added NAFLD diagnostic criteria and severity of participants in each study in the Table 1.

References

Other modifications about the language have been highlighted in the text.

We appreciate for Editors/Reviewers’ warm work earnestly and hope that the correction will meet with approval.

Once again, thank you very much for your comments and suggestions

Yours sincerely,

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