

Dear Editor,

Thank you for your letter and the reviewers' comments concerning our manuscript entitled "**Chinese medicine formulas for nonalcoholic fatty liver disease: Overview of systematic reviews**". Those comments are all valuable and very helpful for revising and improving our manuscript. We have carefully read the comments and made relevant modifications in revision mode in the manuscript. The point-to-point response to reviewers' comments are as following:

Reviewer 1#

I agreed with the authors that most of the systematic reviews have poor methodological quality and possessed a high risk of bias. In the current Overview review, unfortunately the number of included systematic reviews is very small (7 only) so it is unrealistic to conclude results regarding the efficacy of TCM formulas for NAFLD. The authors can't rely on only two systemic reviews to decide that TCM formulas may have benefits. Actually, we can't get any reliable or trustable or informative conclusion from two reviews. Therefore, in the conclusion the authors should recommend that all future research should focus on designing rigorous RCTs rather than repeatedly conducting meaningless systematic reviews while the conclusion about the efficacy of TCM formulas for NAFLD should be removed because of poor quality and insufficient included systematic reviews.

*R: Thank you for your comments. This overview aimed to summarize the effect of TCM formulas for NAFLD. Hence, we excluded comparators involving relevant interventions and found only 7 systematic reviews were eligible. We agree that current results could not support the efficacy of TCM formulas for NAFLD. We have deleted contents regarding the efficacy of TCM formulas in the conclusion, and stated that clinical application of TCM formulas should be cautious. We have also modified relevant contents in results and supplemented a new paragraph to support this statement.*

Reviewer #2

A reasonable analysis of Chinese medicine formulas for the treatment of NAFLD. The analysis is based on an overview of systematic reviews (both RCT and non-randomized studies). The outcomes were largely focused on biochemistry or radiology, without any evidence derived from hard end-points. The authors also scored the methodological quality of studies – the best part of the study - , and concluded for a general low quality. Finally, only two formulas survived the analysis, but the end-points were soft (radiologic improvement and ALT normalization).

*R: Thank you for your comments. We are glad that this work has been recognized. Indeed, the recommendation for treating NAFLD should be established based on hard outcomes like hepatic histology and clinical endpoint events. However, based on the included systematic reviews, we did not find any relevant outcomes. Hence, we also supplemented statement that all outcomes recognized should be further downgraded when transforming to clinical practice.*

Problems 1. Needless to say that radiologic improvement, due to subjective ascertainment, is of low value. While the presence of liver fat is well described by US, a quantitative analysis is poorly representative of the burden of lipid accumulation. This point should be more clearly expressed in the discussion.

*R: We appreciate your suggestions. This problem is based on the first “high quality” outcome. We strongly agree with the comments, and certain revisions have been made. First, we modified the contents in the “efficacy and safety of TCM formulas for NAFLD” of results section, namely “both radiologic improvement and ALT normalization are considered as surrogate outcomes for NAFLD treatment. The quality of evidence should be further degraded when transforming into clinical practice”. Then, we supplemented a new paragraph regarding ultrasonic improvement the in the discussion, to further explain their indirectness in NAFLD treatment. At last, we stated that “caution is still necessary in the clinical application of TCM formulas for NAFLD management” in the conclusion section.*

2. Similarly, there is modest evidence that ALT levels are predictive of the severity of disease, although ALT reduction is frequently assumed as a therapeutic target. In principle, there is large evidence that the severity of disease appears to be totally

independent of ALT levels.

3. Also this issue should be more clearly expressed and discussed.

*R: Thank you for your comments. The two issues focused on the second “high quality” outcome, namely the ALT normalization. We have modified the relevant contents together with the ultrasonic improvement comments. To be specific, we revised the contents in the “efficacy and safety of TCM formulas for NAFLD” of results section, namely “both radiologic improvement and ALT normalization are considered as surrogate outcomes for NAFLD treatment. The quality of evidence should be further degraded when transforming into clinical practice”. Then, a new paragraph was supplemented in the discussion, to further explain the indirectness of the two surrogate outcomes in NAFLD treatment. Lastly, we claimed that “caution is still necessary in the clinical application of TCM formulas for NAFLD management” in the conclusion section.*

4. This also means that most of the final conclusions should be downgraded as to the effectiveness of treatment.

*R: Thank you for your comments. We have adjusted relevant contents in results and discussion. Among all extracted information, we did not find outcomes involving liver histology or adjudicated events. Hence, the outcomes from this overview should be further degraded when transforming into clinical practice.*

5. For non-experts in Chinese medicine, an explanatory report of the different formulas might be of help. What do they contain? Herbal medicine?

*R: Thank you for your suggestion. We have supplemented the concept of TCM formula in the introduction and discussion. In addition, based on the two relatively high-quality evidences, we have summarized the composition of TCM formulas and sorted out the frequently-used herbs. Further studies could consider exploring the efficacy of these herbs for NAFLD.*

Reviewer #3

Authors used A Measure Tool to Assess Systematic Reviews 2 (AMSTAR 2) and Risk of Bias in Systematic Review (ROBIS) in order to evaluate systematic reviews on the effectiveness of traditional Chinese's medicine (TCM) on treatment of nonalcoholic fatty

liver disease (NAFLD). They concluded that current studies are inadequate and rigorous RCTs are needed. The manuscript has too many technical data with very few clinical results. I strongly recommend the manuscript to be reviewed by a statistician who is an expert on AMSTAR2 and ROBIS methods.

*R: Thank you for your comments. We appreciated your acknowledgement of the scientific quality of our overview. This overview objectively evaluated available systematic reviews regarding TCM formulas for NAFLD using various tools. All evaluations were completed by researchers with evidence-based background. We hope this work could encourage researches to emphasize on high-quality RCT design rather than conducting systematic reviews repeatedly.*

Based on the above comments we received, we tried our best to revise our manuscript. In addition, the revised manuscript was modified by language expert and followed the requirements of revision guideline. We hope that the revision will meet the standard of *World Journal of Clinical Cases*. Once again, thank you for your supporting, and we are looking forward to your response.

Sincerely yours

Prof. Guang Ji

Institute of Digestive Diseases, Longhua Hospital

Shanghai University of Traditional Chinese Medicine