Dear reviewers，

On behalf of all the contributing authors, I would like to express our sincere appreciations of your letter and reviewers' constructive comments concerning our article (Manuscript No:85084). These comments are all valuable and helpful for improving our article. The reviewer comments are laid out below in italicized font and specific concerns have been numbered. Our response is given in normal font.

Reviewer #1:

Specific Comments to Authors:

1. Are there controversies in this field? What are the most recent and important achievements in the field? In my opinion, answers to these questions should be emphasized. Perhaps, in some cases, novelty of the recent achievements should be highlighted by indicating the year of publication in the text of the manuscript.

Response: We sincerely appreciate the valuable comments. At present, it has become a new strategy to scientifically explain the effectiveness of traditional Chinese medicine by constructing multi-layer network model with network pharmacology technology. Network pharmacology helps people study traditional Chinese medicine from the whole point of view. It has been successfully applied in many aspects of Chinese medicine research. By combining the research methods of network pharmacology, more and more chemical components, action targets, pharmacological mechanisms and prescription rules of traditional Chinese medicine will be clarified. The recognition and acceptance of Chinese medicine will continue to improve, and the modernization and internationalization of Chinese medicine will be a step closer. In recent years, a large number of articles have been published to explain the effects and mechanisms of traditional Chinese medicine based on network pharmacological analysis. For example, there are articles has explained the mechanism of protective effect of Xuanbai Chengqi Decoction on LPS-induced acute lung injury, the effective inhibition of myocardial fibrosis by Buyang Huanwu Decoction, and mechanism of Huanglian Jiedu

Decoction against sepsis[1-3]. However, as a new subject, it still has some unsolved problems. For example, the sources of information in different databases may be inconsistent. There may be omissions in the chemical components of Chinese medicine. The actual distribution of the active ingredient in the body is uncertain. But network pharmacology indeed provides a new approach to the study of traditional Chinese medicine pharmacology and helps to explain the mechanism of its clinical efficacy. Moreover, with the development of network pharmacology and its combination with new technology, it will have a broad application prospect in the research of traditional Chinese medicine.

This issue is supplemented on lines 266-304 on page 10-12 of the manuscript.

2. The results and discussion section is very weak and no emphasis is given on the discussion of the results like why certain effects are coming in to existence and what could be the possible reason behind them?

Response: Thank you for your suggestions, which are of great guiding significance to my writing. We revised the discussion section of manuscript. The results of the manuscript are based on several databases and obtained through the analysis of network pharmacology methods. The results can initially predict the mechanism of action of Wuzhuyu decoction against HCC. And the more specific mechanism of action needs further experimental verification. The results of our manuscript currently show the content of the network pharmacological analysis. After reading relevant literature, we found that some of our research results were consistent with those of others and analyzed them in the discussion section. We will continue to carry out relevant experiments in the future. This is also our future research direction.

This issue is supplemented on lines 305-372 on page 12-14 of the manuscript.

3. Conclusion: not properly written.

Response: We tried our best to improve the manuscript and the conclusion of the manuscript has been revised and rewritten. We appreciate for reviewers' warm work earnestly and hope that the correction will meet with approval.

This issue is amended on lines 374-382 on page 14 of the manuscript.

4. Results and conclusion: The section devoted to the explanation of the results suffers from the same problems revealed so far. Your storyline in the results section (and conclusion) is hard to follow. Moreover, the conclusions reached are really far from what one can infer from the empirical results.

Response: The results and conclusion have been corrected. We have improved the presentation of the results and corrected errors, which can improve the readability of the article. We revised the conclusion to make the result more consistent with the conclusion. We will be happy to edit the text further based on helpful comments from reviewers.

This issue is amended on lines 170-171 page 7; lines 175-176 page 7; lines 186-191 page 7-8; lines 202-203 page 8; lines 237-238 page 9; lines 374-382 page 14 of the manuscript.

5. *The discussion should be rather organized around arguments avoiding simply describing details without providing much meaning. A real discussion should also link the findings of the study to theory and/or literature.*

Response: Thank for your suggestion. Based on your comments, we have made the modifications. The discussion of the manuscript has been revised and rewritten. We will pay more attention to the logical connection between the results of the article and the discussion.

This issue is amended on lines 259-372 page 10-14 of the manuscript.

6. *Spacing, punctuation marks, grammar, and spelling errors should be reviewed thoroughly. I found so many typos throughout the manuscript.*

Response: We sincerely thank the reviewer for careful reading. We feel sorry for our carelessness. In our resubmitted manuscript, the typo is revised.

7. *English is modest. Therefore, the authors need to improve their writing style. In addition, the whole manuscript needs to be checked by native English speakers.*

Response: We apologize for the poor language of our manuscript. We worked on the manuscript for a long time and the repeated addition and removal of sentences and sections obviously led to poor readability and the manuscript

has been checked by native English speakers. We really hope that the language level has been substantially improved.

Reviewer #2:

Specific Comments to Authors:

This article is a research article rather than a systematic review article.

Response: Thank for your careful checks and reminder. When selecting a research article category for submission, the submission system needs to submit documents such as animal ethics. This manuscript does not involve animal studies. We cannot be provided these documents. Thus, the manuscript is transferred to another article category.

revision reviewer：

Specific Comments to Authors:

Results and conclusion: The section devoted to the explanation of the results suffers from the same problems revealed so far. Your storyline in the results section (and conclusion) is hard to follow. Moreover, the conclusions reached are really far from what one can infer from the empirical results.

Response: We apologize for the previous version of the manuscript and sincerely hope that results and conclusion are better with this new version. We improved the logic of the results presentation and corrected errors. We hope to make it easier for readers to understand. We revised the conclusion to make the result more consistent with the conclusion. The statements have been modified. We will be happy to edit the text based on helpful comments from reviewers.

This issue is amended on lines 46-53 page 2-3; lines 173-176 page 7; lines 179-181 page 7; lines 186-191 page 7-8; lines 197-198 page 8; lines 248-229 page 10; lines 374-382 page 14 of the manuscript.

Thank you very much for your attention and time. We have carefully considered the suggestion of Reviewer. We tried our best to improve and made some changes in the manuscript. Look forward to hearing from you.

Yours sincerely,

Jia-Ying OuYang

Pharmaceutical department, Zhuhai People's Hospital, Zhuhai, Guangdong, China

E-mail:wangrq2020@ext.jnu.edu.cn

[1]   ZHU H, WANG S, SHAN C, et al. Mechanism of protective effect of xuan-bai-cheng-qi decoction on LPS-induced acute lung injury based on an integrated network pharmacology and RNA-sequencing approach [J]. Respir Res, 2021, 22(1): 188.

[2]   WANG T, JIANG X, RUAN Y, et al. Based on network pharmacology and in vitro experiments to prove the effective inhibition of myocardial fibrosis by Buyang Huanwu decoction [J]. Bioengineered, 2022, 13(5): 13767-83.

[3]   LI X, WEI S, NIU S, et al. Network pharmacology prediction and molecular docking-based strategy to explore the potential mechanism of Huanglian Jiedu Decoction against sepsis [J]. Comput Biol Med, 2022, 144: 105389.