

**Dear Editor and reviewers,**

Thank you for your letter dated June 16th. We gratefully appreciate for the time and effort that reviewers have put into reviewing the previous version of the manuscript. Your suggestions have helped us to improve our work. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript.

Appended to this letter is our point-by-point response to the comments raised by the reviewers. Our responses to the comments are given directly as follows.

To Reviewer #1:

**Scientific Quality:** Grade D (Fair)

**Language Quality:** Grade B (Minor language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** The manuscript of Yiping Zhang et al. deals with the role of nitric oxide during hepatic ischemia reperfusion injury. The authors conducted a systematic review analyzing a series of possible molecular interaction mechanisms. The topic would be interesting with important repercussions on clinical practice, especially in transplantology. However, The bibliographic research was not performed according to standardized methodologies (e.i PRISMA guidelines).

We gratefully appreciate for your valuable comment. For this, we have made some appropriate changes to the form of the article to try to bring it into line with the standardized methodologies.

Sometimes the results are listed in difficult to understand way.

We gratefully thanks for the precious time the reviewer spent making constructive remarks. We have revised some of the presentation of the article carefully and industriously.

The discussion could be developed more extensively. Furthermore, the possible clinical implications of the research have not been reported and the study limits should be highlighted. Thanks for your suggestions. With regard to the discussion section, we have not only briefly made the summarization for the full text, but have also added some new contents. For example, the outlook on the possibilities and prospects for the clinical application of NO and eNOS, as well as the shortcomings of existing studies, such as the unclear role of iNOS and its mechanisms. We hope that the revision will improve the conclusions in this manuscript.

Reviewer #2:

**Scientific Quality:** Grade C (Good)

**Language Quality:** Grade C (A great deal of language polishing)

**Conclusion:** Major revision

**Specific Comments to Authors:** [Dear Dr Shu-long Yang, your article is very important in the medical field however I've some comments for you & your team to consider.

1st of all is the language which needs precise revision by an expert as there are some spelling mistakes ( for example in the abstract line 4 it is phase not phage as you wrote) also formulation of many sentences need to be adjusted.

We feel sorry for the spelling mistakes in our manuscript. Now we have corrected these language errors through the text carefully.

Regarding the scientific content I've some questions to raise so you can clarify or adjust in your manuscript 1st you just mentioned in the introduction that the ET/NO ratio is increased in early ischemia, however you didn't mention any details as regarding the normal ratio or even the mechanism for this increase.

Thanks for your suggestion. We make a small addition to the section on ET and NO, acting as a link between the HIRI and NO sections.

Next, you mentioned in your manuscript that iNOS may decrease the HIRI however all mentioned data in your article showed only the bad aspect and deleterious effect of iNOS you just mentioned that its action depends on length & duration of ischemia without any clarification, moreover all data in your article revealed the deleterious effect of iNOS both early & prolonged ischemia without any evidence or even a mechanism for its role in improving the HIRI so I think this needs justification.

We gratefully appreciate for your valuable suggestions. Some modifications and additions have been made to address these issues. However, due to the lack of extensive and convincing data from iNOS on this result for HIRI, the available data may be only the specific case, so it is difficult to draw uniform conclusions. This issue will be addressed again in the conclusion section.

Also the role of NO in apoptosis, you reported that it can induce or inhibits apoptosis, however you didn't even write a single evidence for its role in stimulating apoptosis or even when this happens.

Thank you for your rigorous comments. I provided some evidences about the stimulating apoptosis role of NO via inducing the mitochondrial apoptotic pathway and it may also associate to the down-regulating Bax protein expression and increasing Bcl-2 expression.

Not only this, but you also reported that inhibiting NO can reduce HIRI by cell apoptosis which I think need to be revised.

Thank you for your careful consideration. Since the previous evidences showed that NO can induce cell apoptosis. We recklessly concluded that inhibiting NO can reduce HIRI by cell apoptosis, which we think it is not a proper sentence or a conclusion. So, we deleted it. And we replaced it with some evidences below.

Finally I also would like to highlight 2 contradictory sentences in your conclusion, the 1st reporting that adding NO or increasing its bioavailability have both protective & deleterious effects then you reported that increasing NO bioavailability in hepatic tissue is a good way to prevent & treat HIRI.

We feel sorry for the errors. This is indeed an oversight in the logic of our article. It has been corrected in the text according to your suggestions, thank you!

## **6 EDITORIAL OFFICE'S COMMENTS**

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

### **(1) *Science editor:***

1 Scientific quality: The manuscript describes a minireview of the hepatic ischemia reperfusion injury. The topic is within the scope of the WJH.

(1) Classification: Grade D and Grade C;

That is OK, thank you!

(2) Summary of the Peer-Review Report: The manuscript deals with the role of nitric oxide during hepatic ischemia reperfusion injury. The authors conducted a systematic review analyzing a series of possible molecular interaction mechanisms. The topic would be interesting with important repercussions on clinical practice, especially in transplantology. Sometimes the results are listed in difficult to understand way. The discussion could be developed more extensively. Furthermore, the possible clinical implications of the research have not been reported and the study limits should be highlighted. The questions raised by the reviewers should be answered;

We have made some changes to the discussion section, adding a little to address limitations and clinical aspects of application. Thank you!

(3) Format: There is 1 table and 1 figure.

It has been done according to your suggestions.

(4) References: A total of 62 references are cited, including 19 references published in the last 3 years;

We have adjusted some references in our manuscript.

(5) Self-cited references: There are 5 self-cited references. The self-referencing rates should be less than 10%. Please keep the reasonable self-citations (i.e., those that are most closely related to the topic of the manuscript) and remove all other improper self-citations. If the authors fail to address the critical issue of self-citation, the editing process of this manuscript will be terminated;

Thank you for your rigorous consideration. For this point of self-referencing, we have made some substitutions in the citation of references.

(6) References recommendations: The authors have the right to refuse to cite improper references recommended by the peer reviewer(s), especially references published by the peer reviewer(s) him/herself (themselves). If the authors find the peer reviewer(s) request for the authors to cite improper references published by him/herself (themselves), please send the peer reviewer's ID number to [editorialoffice@wjgnet.com](mailto:editorialoffice@wjgnet.com). The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

That is OK, we will do as you suggested, thank you!

2 Language evaluation: Classification: Grade B and Grade C. The authors need to provide the language certificate of professional language company.

I am sorry for this Language evaluation. However, the authors Yi-ping Zhang and Xin-ran Liu are from Queen Mary Collage in Nanchang University, they are also major in English Language who responsible for the revision of language editing in our manuscript. We hope that it will improve the text, thank you!

3 Academic norms and rules: The authors need to provide the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement. No academic misconduct was found in the Bing search.

We are sorry for this omit! Now the signed Conflict-of-Interest Disclosure Form and Copyright License Agreement have been uploaded, thank you!

4 Supplementary comments: This is an invited manuscript. The study was supported by National Natural Science Foundation of China. The topic has not previously been published in the WJH. The corresponding author has not published articles in the BPG.

The corresponding author has published two article in the BPG. They are as follows:

- 1) Zhang YQ, Ding N, Zeng YF, Xiang YY, Yang MW, Hong FF, **Yang SL**<sup>(\*)</sup>. New progress in roles of nitric oxide during hepatic ischemia reperfusion injury, *World J Gastroenterol* 23(14):2505-2510. Published online Apr 14, 2017. doi:10.3748/wjg.v23.i14.2505
- 2) Shao-Jie Hu, Sha-Sha Jiang, Jin Zhang, Dan Luo, Bo Yu, Liang-Yan Yang, Hua-Hua Zhong, Mei-Wen Yang, Li-Yu Liu<sup>(\*)</sup>, Fen-Fang Hong<sup>(\*)</sup>, **Shu-Long Yang**<sup>(\*)</sup>. Effects of apoptosis on liver aging. *World J Clin Cases* 2019 Mar 26;7(6):691-704. doi: 10.12998/wjcc.v7.i6.691. If: 1.153;1.013.

5 Issues raised: (1) I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

Thank you so much for your check. We have added to this information.

And (2) I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

Thank you so much for your careful check. Figure 1 will be uploaded in PowerPoint, and each graph, arrow and text box can be processed individually.

6 Re-Review: Required.

We are grateful to the reviewer and editor for the hard work, thank you!

7 Recommendation: Conditionally accepted.

We are looking forward to hear good news from you !

**(2) *Company editor-in-chief:*** I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Hepatology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

Thank you very much for your suggestion. In accordance with the guidelines, we have modified the formatting of the citation section.

We would like to thank you again for your rigorous consideration and constructive suggestions.

We are looking forward to your reply.

Best wishes!

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