

14 April, 2020

Editorial office

*World Journal of Gastroenterology*

Dear Sir or Madam,

Re: World Journal of Gastroenterology – 54190

Thank you very much for your email concerning our manuscript entitled “Hepatoprotective effects of *Hovenia dulcis* seeds against alcoholic liver injury and related mechanisms investigated via network pharmacology”. After carefully considering the points the reviewers raised and the Editorial Office’s comments and suggestions, we have made the following revisions (I have indicated in red the changes made in one copy of the revised manuscript).

**Reviewer #1:**

Authors studied the hepatoprotective effects of *Hovenia dulcis* seed water extract (HWE) on acute alcohol-induced liver injury in mice and conducted network pharmacology. They showed that HWE had in vitro (FRAP, TEAC) and in vivo antioxidant activity (SOD, CAT, GSH etc.) and reduced hepatic lipid and hepatotoxicity. In addition, they suggested the related mechanism via analysis of network pharmacology. The manuscript contains interesting data; however, the following points should be considered in the revised version.

1. What is the reason for the dose you used in the experiment? Could please mention in methods section.

**Answer:** It has been added Line 144-149.

2. In this study, the HWE were fed to mice for 7days. How do you predict toxicity when fed it for long time?

**Answer:** *Hovenia dulcis* extracts have not been reported with detectable or significant cytotoxic effects up till now [1]. In addition, *Hovenia dulcis* seeds are stated as “non-toxic” according to the China National Administration of Traditional Chinese Medicine [2].

[1] Hyun TK, Eom SH, Yu CY, Roitsch T. *Hovenia dulcis*--an Asian traditional herb. *Planta Med.* 2010; **76**: 943–949 [DOI:10.1055/s-0030-1249776]

[2] China National Administration of Traditional Chinese Medicine (2015). *Hovenia dulcis* seeds [WWW document]. URL <https://baike.baidu.com/item/%E6%9E%B3%E6%A4%87%E5%AD%90/758262?fr=aladdin> [accessed on 2 April 2020]

3. Authors addressed *in vitro* antioxidant experiment (method and discussion) in detail; however, the data did not present in table or figure, only it was written in result section.

**Answer:** A table (Table 1) has been added with the data of *in vitro* antioxidant experiment.

4. Please avoid repeat the results in discussion section. The discussion should be lessened to focus the mechanism.

**Answer:** Some redundant sentences have been deleted.

Thank you so much for your constructive comments!

#### **Reviewer #2:**

Very interesting study. This study is very well written, results are interesting. Manuscript requires a minor editing.

**Answer:** Thank you so much for your comments, and the manuscript has been edited.

#### **Reviewer #3:**

This is an interesting study of *H. dulcis* antioxidant activity, evaluate its effects against ALD, and investigate the related mechanisms via network pharmacology. ALD can start with alcoholic liver injury, develop into alcohol-induced hepatitis and/or steatosis, and progress to fibrosis and/or cirrhosis; ALD can even lead to liver cancer. Given the poor prognosis and the limited efficacy of current treatments for ALD, it would be more effective to prevent liver disease progression at the very beginning rather than to treat advanced conditions. Certain parts of *H. dulcis* exhibit various health effects. Namely, the peduncles of *H. dulcis* showed antioxidant and immunostimulatory effects, its fruit or stem showed antidiabetic effects through the AMPK pathway, and the root could prevent proliferation of HSC-T6 cells. However,

the effects and/or mechanisms of action of *H. dulcis* seeds on ALD have not been fully illustrated. In this study, Meng et al determined the antioxidant activities of *H. dulcis* seeds, and assessed the total phenol content, total flavonoid content and polysaccharide content. The study is well designed and the results are very interesting.

Comments:

1 Title. Does the title reflect the main subject/hypothesis of the manuscript? Yes.

2 Abstract. Does the abstract summarize and reflect the work described in the manuscript? Yes.

3 Key words. Do the key words reflect the focus of the manuscript? Yes.

4 Background. Does the manuscript adequately describe the background, present status and significance of the study? Yes. The introduction is reasonable, and the references in this section are ok.

5 Methods. Does the manuscript describe methods (e.g., experiments, data analysis, surveys, and clinical trials, etc.) in adequate detail? Yes. The methods are very clear, and in detail. Animal experiment design are good, and the biochemical and histopathologic examinations are very detail.

6 Results. The results are very informative. Tables and figures are excellent. And the results were discussed with updated references.

7 Manuscript is very well written. Please take attention to the abbreviations. And some minor language polishing should be edited.

**Answer:** Thank you so much for your comments, and the manuscript has been edited with specific attention paid to the abbreviations and minor language corrections.

### **Comments and suggestions from the Editorial Office**

#### ***(1) Science Editor:***

Recommend for potential acceptance.

1 Scientific quality: 3B.

This article is about hepatoprotective effects of hovenia dulcis seeds against alcoholic liver injury and related mechanisms investigated via network pharmacology, within the scope of WJG. Summary of peer-review report: Authors studied the

hepatoprotective effects of *Hovenia dulcis* seed water extract (HWE) on acute alcohol-induced liver injury in mice and conducted network pharmacology. The study is well designed and the results are very interesting. 1 table and 6 figures. 59 references were cited, including 15 latest references from 2017-2020. 3 self-citation articles.

2 Language quality: 3B.

Edited by Wiley language editing services.

3 Academic norms and rules: Basic Study.

Copyright license agreement, The ARRIVE Guidelines, IRB, BRC and Conflict-of-Interest statement files are complete and qualified. Bing search and CrossCheck are eligible.

4 Others: Without financial support. Corresponding author has not published articles in WJG. Unsolicited manuscript.

**Answer:** Thank you so much for your comments.

**(2) Editorial Office Director:**

Recommend for potential acceptance.

1. Scientific quality:

I have checked the comments written by the science editor, and I basically agree with the science editor. The topic of the paper is the alcoholic liver injury, and is within the scope of the WJG. The reviewers stated that this manuscript is interesting and well-written, but the authors need to revise the manuscript according the reviewers' suggestions. The questions raised by the reviewers should be answered.

2. Language quality: 3B.

The language certificate is provided by Wiley Editing Services, but the reviewer 01172530 and reviewer 01630494 pointed out that the some minor language polishing should be edited.

3. Academic norms and rules:

I have checked the documents, including biostatistics review certificate, institutional animal care and use committee approval form or document, The ARRIVE Guidelines, conflict-of-interest disclosure form, and copyright license agreement, all of which are qualified. The institutional review board approval form or document is not qualified, the authors need to check and revise it. No academic misconduct was found in the CrossCheck investigation and the Bing search.

4 Supplementary comments:

(1) Unsolicited manuscript. (2) Without financial support. (3) Corresponding author

has not published articles in BPG journals.

**Answer:** Thank you so much for your comments. The institutional review board approval form or document is the official copy provided by the Animal Ethics Committee of School of Public Health, Sun Yat-Sen University.

**(3) *Company Editor-in-Chief:***

I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report and the Criteria for Manuscript Revision by Authors.

**Answer:** Thank you so much for your comments.

Thank you very much for your help!

Yours sincerely,

Xiao Meng