Dear Editors and Reviewers:

Thank you for your letter and for the reviewers' comments concerning our manuscript entitled "Dihydromyricetin Ameliorates Chronic Liver Injury by Reducing Pyroptosis" (NO: 56911).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 made correction which we hope meet with approval. The main corrections in the paper and the responds to the reviewer' s comments are as flowing:

Responds to the reviewer' s comments:

Reviewer #1:
[Comment 1] I congratulate the authors for Dihydromyricetin Ameliorates Chronic Liver Injury by Reducing Pyroptosis name's article. Best regards

[Answer 1] Thank you very much for your recognition, and I'll try my best to modify the manuscript to make it as perfect as possible. Best wishes!

Reviewer #2:
[Comment 2] This study investigates if hydromyricetin is able to ameliorate chronic liver injury and how this process may affect pyroptosis. Using a mouse model with carbon tetrachloride injection, the authors demonstrates that hydromyricetin when administered daily is able to reduce liver injury, steatosis, as well as the inhibition of pyroptosis related genes and proteins. Another contribution from this study is the use of a subcutaneously injected carbon tetrachloride with better safety profile as compared to the intraperitoneally injected ones. Overall, the results are affirmative of the conclusions drawn and there are room to explore the mechanism behind this effect further. Specific comments are as shown below: 1. The abstract is not written clearly. In the methods section of the abstract, it seems to suggest that the vehicle and DHM treated arms does not have carbon tetrachloride injected concurrently. 2. In the abstract, it is written that 24 mice were used in the study. Whereas in the method section, the number cited is 32. This discrepancy should be clarified. 3. From this study, it is not clear if DHM is acting on pyroptosis directly, or is it acting as an anti-oxidant that abolishes carbon tetrachloride mediated injury. The study design lacks a DHM-only treatment arm, which will help to answer this question. In such a DHM-only control, we would expect similar effect on the pyroptosis related mRNA and proteins. 4. While most of the data is consistent across the experiments, the part on Caspase-1 requires further clarification. Figure 3 shows suppression with DHM vs control, Figure 4 shows slight elevation in immunostaining, while Figure 5 shows no change with RT-PCR. Is the same antibody used in Figure 3 as for Figure 4? Is the antibody picking up pro-caspase-1 or the mature caspase-1? Clarification on this aspect should be made. 5. It would also be of interest to know how DHM affects other cell death pathway, in order to determine if the effect DHM on pyroptosis is a selective one.

[Answer 2] Thank you very much for your pertinent advice, and I have benefited a lot from it. According to your suggestions, I made the following changes:

- In the methods section of the abstract, we made it clear that the vehicle and DHM treated arms has carbon tetrachloride injected concurrently.

- All the results of this study were obtained from 32 mice, misspelled as 24 in the abstract. Thank you for your correction. Now it is being revised in the paper

- You proposed to add a DHM-only treatment arm to verify the hypothesis that DHM directly affects pyroptosis. This is a good suggestion, but as an exploratory discovery, this study shows that DHM can indeed affect the Pyroptosis pathway. On this basis, further studies will be conducted to determine the relationship between DHM regulation of pyroptosis and antioxidation in the improvement of chronic liver injury and the proportion of the two.

- The antibodies used by western blot and immunohistochemistry are both anti-caspase-1 P20, which is the antibody used to detect caspase-1 activity, namely mature caspase-1. The qRT-PCR results of Caspase-1 are not changed, which has been explained in the discussion section.
We analyzed whether DHM intervention decreased NLRP3 protein, leading to its target protein (pro-caspase 1) not being converted to mature caspase 1. Therefore, at the protein level, caspase-1 expression was downregulated after DHM intervention, but treatment did not affect the mRNA level of pro-caspase-1. Therefore, the mRNA level of pro-caspase-1 did not decrease after DHM intervention. It could also be that the sample size measured was too small to form a statistically significant downward trend.

- It would also be of interest to know how DHM affects other cell death pathway, in order to determine if the effect DHM on pyroptosis is a selective. I couldn't agree with you more, so we point out in the discussion section that whether DHM interferes with other cell death modes is still unknown, and further research on this basis is of great value.

Thanks again for your sincere comment, if there are any questions please contect me, and I'll try my best to give you a satisfactory feedback. Best wishes!

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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