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Round-1

Editorial Office,

*World Journal of Gastroenterology*

February 28, 2023

Thank you for giving us an opportunity to revise our manuscript titled, “*Cryptotanshinone Induces Apoptosis of Activated Hepatic Stellate Cells via Modulating Endoplasmic Reticulum Stress*”. The reviewers’ comments were highly valuable for revising and improving our manuscript. We have studied the reviewers’ comments carefully and have made revisions accordingly. All changes are marked in yellow in the revised text. We also provide our point-to-point responses to the comments below.

We hope that you will consider our revised manuscript for publication.

Kind regards,

Chuanlong Zhu

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We would like to express our appreciation to the Reviewers for your valuable comments and suggestions.

Reviewer #1:

(1) the authors write "Group 1 mice were not treated with CCl<sub>4</sub> or CPT. Group 2 were treated with CCl<sub>4</sub>. Group 3 mice received intraperitoneal injection of salubrinal. Group 4 mice received intraperitoneal injection of CPT. Group 5 mice were intraperitoneally injected with CPT and salubrinal at the same time.", but further describes animals that received both CCl<sub>4</sub> and CPT, but this group is not in the group description.

**Response:** Thank you for your positive and constructive comments. With regard to the experimental groupings, we have added a detailed description in the Materials and Methods section (line 11-17, page 5) and have drawn a flow chart to show animal drug treatment in Figure 5A.

(2) the list of references is not designed in accordance with the requirements of the journal.

**Response:** We have revised the format of the references.

Reviewer #2:

(1) CCl<sub>4</sub> also induces experimental hepatocarcinoma and there are many players who share both conditions (fibrosis and hepatocarcinoma), matricellular proteins such as SPARC (BM-40, osteonectin). It can be said that in 8 weeks of treatment hepatocellular carcinoma is not diagnosed, but the shared mechanisms are already working. In addition, the tumor microenvironment with

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ECM activation is already at work, including SPARC inducing ER regulation. Salubrinal directly exhibits antitumor activity and also reduces the resistance of tumor cells to other chemotherapeutic agents. In addition, Salubrinal reduces the intensity of protein synthesis processes, thus facilitating the release of a cell from a state of stress and literally saving its life (inhibition of the GADD34:PP1 holoenzyme complex) (Madden et al, 2020, Zadorozhnyi et al., 2022).

**Response:** Thank you for your positive and constructive comments. As described, CCL4 can induce liver cancer. Hepatic fibrosis is usually regarded as the first step in the trilogy of liver diseases, which gradually progresses to cirrhosis and liver cancer as the disease advances. This study mainly discusses the treatment of hepatic fibrosis using CPT, but the common mechanisms between hepatic fibrosis and liver cancer also play a role in the process of CCL4 modeling. Whether CPT can be used to treat liver cancer is worthy of further discussion. We believe this would be an interesting study and have added the above discussion to the text (line 19-23, page 9).

(2) The study by Xuiaoxue Hou et al. is of interest, but you have to clarify the methods, some of them very confusing, like ETM, "Fig.3 (G) Projection of electron fiberscope", !!!!!?? ??, and electron micrographs show that CTP induces mitochondrial damage. Were only two of all groups observed? and with this result?

**Response:** Our electron microscopic observation of endoplasmic reticulum stress allowed us to detect ultrastructural changes in the endoplasmic reticulum morphology of the HSCs before and after CPT treatment. The two groups were established to demonstrate that CPT could cause destruction of the endoplasmic reticulum in HSCs. The results showed that the endoplasmic reticulum cavity of the HSCs was swollen and that the mitochondrial membrane integrity was damaged after CPT treatment. The endoplasmic reticulum and mitochondria are important organelles related to cell function. Through the interaction of various proteins, these organelles cooperate to complete a variety of biological functions in the cell. In the early stage of endoplasmic reticulum stress, Grp78 is transported to the mitochondria, and destruction of mitochondrial membrane integrity is an early feature of apoptosis. Thus, in our model we could observe mitochondrial destruction using electron microscopy. We have added the above discussion

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in the main text (line 7-12, page 9) .

(3) The authors should add a basic graph of the experimental design, since it is very confusing, some doses are missing, some run times too, others are explained in the results.

**Response:** We have supplemented the flow chart of animal experiments according to your suggestion (see Figure 5A).

(4) Minor problem, check the English, in many paragraphs it's fine, but in others it should be rewritten, spellings too, like Annexin in Fig. 2.

**Response:** We have corrected the grammar errors and have carefully proofread the manuscript to make sure there were no additional errors. In addition, Medjaden company polished it and submitted the language qualification certificate. We also uploaded some high-resolution images to improve the quality of the figures. The content of the article has not changed.

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Round-2

Editorial Office,

*World Journal of Gastroenterology*

March 18, 2023

Thank you for giving us an opportunity to revise our manuscript. Those comments are all valuable and very helpful for revising and improving our paper. We have studied the reviewer comments carefully and have made revisions (marked in yellow) which we hope meet with approval. Point-to-point replies are as follows.

Reviewer #1:No comments.

**Response:** Thank you for your comments.

Reviewer #2:Didn't you realize that SPARC is also known as BM-40 and osteonectin? It is the same matricellular protein, although it was referenced in that paragraph with 3 references. The same with the word "Annexin", (fig.2.D and 4.H) and ccl4 (?), and also with the electron micrographs. Avoid explaining to the reviewer the reviewer's own comments.

**Response:**Thanks for your guidance.We have realized that the three proteins are the same material, and have made the correction. Moreover,we have corrected the typos in fig.2D ,fig.4H and fig.5 according to your suggestion. After that, we carefully proofread the rest of the manuscript to make sure there were no similar errors.

Once again, we would like to express our great appreciation for your comments and suggestions.