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Dr. Jing Yu

Scientific Editor

World Journal of Gastroenterology

RE: Manuscript No.: 18992

We thank you for your email dated on 27th of June 2015, regarding our manuscript, entitled "Optimal management for alcoholic liver disease: conventional medications, natural therapy or combination?"

I appreciate both the Editor and the Reviewer for their scholarly and thoughtful comments. My response and modification to the reviewers' comments are in a point by point manner as below and inserted in the revised manuscript. We believe that these revisions have improved the quality of the manuscript substantially.

In regards to language certificate, we feel as though the grammar and spelling changes are sufficient because we have a native English speaker as one of the co-authors. With the time-limitation we were unable to complete the CrossCheck, however have completed the copyright assignment, audio core-tip and google scholar check as required. We thank you for considering our revised manuscript for publication in World Journal of Gastroenterology**.**

Yours Sincerely,

Xianqin Qu

List of Changes and Rebuttal

Correction and modification for the editor's comments

1. Conflict-of-interest statement: "No conflict of interest" has been added in the title page.
2. Audio core tip: attached in mp3 file
3. All the spacing problems related to the footnoted references have been corrected

Correction and modification for the reviewer's comments

1. What's the specific definition of conventional medicines and natural medicines (Table 1 and Table 2)? For example, colchicine in Table 1, silymarin in Table 2.

Response:

We appreciate reviewer's comment. Conventional medicine is often referred to as Western medicine and pertains to the modern, scientific-based treatments. *Conventional medicines* in this article are presented in the treatment for ALD with chemical pharmacotherapies. Conversely, natural medicines mainly use substances of herbal origins. To clarify this definition, we have added the following sentences highlighted in the introduction.

The treatment for ALD with conventional medicines, mainly pharmaceutical medications, has limited success with side-effects. Recently, natural medicines, which mainly apply herb-derived agents, are emphasized as alternative therapies to manage the various alcoholic related liver diseases.

Although colchicine is herbal derived, it has been isolated and purified to be a pharmaceutical medication and has been approved as prescribed medicine by the US FDA. Therefore it has been listed with other pharmaceutical medications in Table 1.

Differently, silymarin is a standardised extract of the herb (milk thistle seeds), containing a mixture of flavonolignans consisting of silibinin, isosilibinin, silicristin, silidianin and others. Silymarin has been used as a natural therapy for the most common forms of liver injuries, including ALD. Thus, silymarin is listed in Table 2.

2. All references in Table 1 and Table 2 should be formatted according to Journal requirement.

Response: We have changed the format of citing references in the tables according to the journal's instruction.

3. What does each column represent in Table 1?

We appreciate the reviewer's comment. The subtitle of each column has been added in Table 1.

4. In Fig.1, how do GSH, ROS/RNS affect PPAR-alpha, SREBP-1c and its downstream target genes? Circulating adiponectin achieves their bioactivity by binding to specific membrane-bound receptors, especially adiponectin receptor 2 (ADIPOR2), the activated adiponectin signaling leads to activation of AMPK pathway, which modulates hepatic lipid metabolism by simultaneously inhibiting de novo lipogenesis and stimulating fatty acid β-oxidation. However, these recognized pathway could be not reflected in Fig. 1.

We appreciate the reviewer's scholarly comment regarding the role of adiponectin-AMPK pathway in modulating hepatic lipid metabolism. The modified Figure 1 at the bottom line shows the decreased adiponectin by alcohol consumption causes inactive AMPK pathway, leading to elevated *de novo* lipogenesis and inflammatory process in the liver, simultaneously decreased fatty acid β-oxidation. The revised Figure legend illustrates relevant pathways involved in pathogenesis of ALD.

This figure is adapted from references[8,13,159]. When alcohol intake is chronic and heavy, alcohol oxidation occurs via cytochrome P450s, resulting in increased levels of CYP2E1, which in turn causes oxidative stress through the generation of reactive oxygen species (ROS) which are responsible for lipid peroxidation and alcoholic liver injury. ROS also negatively regulates the activation AMPK and leads to overexpression of SREBP-1, resulting in an increase of *de novo* lipogenesis. GSH also has been reported to its depletion by CYP2E1 followed by the development of oxidative stress. Alcohol consumption negatively affects adiponectin secretion from adipocytes then causes inactive AMPK pathway, leading to elevated *de novo* lipogenesis and inflammatory process in the liver, while simultaneously decreasing fatty acid β-oxidation and contributing to hepatocyte necrosis. The red, italicised font indicates the end-point of pathology in the liver.

5. The present study focus on the therapy of ALD, however, liver injury induced by other reagents, such as LPS, also involves (No 15, pubmed 1799417). Please delete the relevant content.

Response: We appreciate this suggestion and have deleted the reference that is involved in liver injury being triggered by other agents in the text and table.

6. Authors should correct the typing and grammatic errors throughout this manuscript.

We have thoroughly checked and modified the typing and grammatical errors.