

Format for ANSWERING REVIEWERS



November 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13767-review.doc).

Title: Therapeutic effect of *Qingyi* decoction in severe acute pancreatitis-induced intestinal barrier injury

Author: Jing-Wen Zhang, Gui-Xin Zhang, Hai-Long Chen, Ge-Liang Liu, Lawrence Owusu, Yu-Xi Wang, Guan-Yu Wang, Cai-Ming Xu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 13767

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated followed the format for highlighted contents, the format for original articles and the revision policies of BPG for original article.

- (1) Family name was put first in full, followed by middle names and first name in abbreviation with first letter in capital for **author contributions** section.
- (2) **AIM** is no more than 20 words.
- (3) **RESULTS** is no less than 150 words.
- (4) **CONCLUSION** is no more than 26 words.

2 Revision has been made according to the suggestions of reviewer No. 2440222

(1) There are several grammar errors and vocabulary misuses in this article. Maybe it will be better understood when modified carefully.

Answer: The many grammatical errors and vocabulary suggestions by the reviewer have been carefully reviewed and corrected to better communicate the science of this paper. For example, words such as co-morbidity, expression, and protecting have been modified as complication, transcription, and protected, respectively.

(2) Several phrases and sentences have also been modified to make them clearer.

E.g. The phrase "which function..." have been changed to "the function of which...". The sentence "Verapamil (VER) can effectively reduce tissue damage to bowel by reducing intracellular calcium ion concentration which plays a decisive role in sPLA₂ activation" has been modified to read "Verapamil (VER) can effectively reduce tissue damage, especially intestinal damage, by reducing intracellular calcium ion concentration which plays a decisive role in sPLA₂ activation".

(3) There can be a better design for some experiments referred in this article, like when you set up the SAP animal model using rats, you can inject the solvent as a control rather than "only had their pancreas marginally rotated prior to closing the

abdomen” .

Answer: We agree to this experimental design proposal and did consider it during the model design but we had to forgo it to avoid any incidence of mild acute pancreatitis which could arise following the injection of the solvent (water) used to dissolve the salt. The very short time (24 h) required for the manifestation of chemically-induced SAP would not permit the complete resolution of such mild acute pancreatitis in the control rats which would in turn compromise the principal clinical differences between the control and the SAP groups. This statement has been included in the text of the **model preparation** section.

(4) Also, you can use real-time PCR to test the transcriptional level of interesting genes rather than compare the grey value.

Answer: Thank you very much for this suggestion. It is appreciated and well noted for future studies.

(5) Several results in this article is kind of confusing. Like the pictures in Figure 2, it seems that figure-2E has a different magnification times than others.

Answer: Thank you. The correct image for Figure 2E at the appropriate magnification (x200) has been provided to replace the previously incorrect image.

(6) Also, Is there any mistakes in the annotation of Figure 3-C?

Answer: Yes, and they have been ratified accordingly.

(7) And as it comes to the “Pancreas and intestinal histopathology” results, why don't you show the result in QYT group, which I think is quite important in this project?

Answer: This result is shown in Figure 1 and further description has been added (as copied below) in the text to emphasize the observed differences. “The QYT and VER groups exhibited intestinal mucosal epithelial cell swelling but generally of normal morphology while the DEX group, in addition to cell swelling deformation, showed varying degrees of inflammatory cell infiltration. Their pancreatic lobule structures were clear with only small amount of edema, hemorrhage and inflammatory cells invasion. Necrotic areas were smallest compared to DEX and SAP groups (Figure 1).”

3 Revision has been made according to the suggestions of reviewer No. 34432

(1) The major bias of the study is that the drug has been administered before the induction of acute pancreatitis whereas the other drugs were correctly administered after the induction. The response to herbal treatment is slow and the conclusions of the paper should take into account this aspect. There are several typo: for example methed instead of method.

Answer: We included the statement “to warrant enough time for the absorption of drug into blood” in the paper to support why we administered the *Qingyi* decoction (herbal preparation) 0.5 h before SAP induction in the QYT group. All typos have been corrected. Thank you.

4 Revision has been made according to the suggestions of reviewer No. 158184

Comments to authors: It was a pleasure to read such a well written article like yours
Classification is Grade B (very good)

Language evaluation is Grade A (priority publishing)

Answer: Thank you very much. We appreciate your praise, and recommendation of our paper for publication.

5 Revision has been made according to the suggestions of reviewer No. 2445032

(1) Language evaluation: Grade B: Minor language polishing Introduction - Page 3, lines 6-7: "is a damage factor **whose function is** dependent on intracellular calcium ion concentration" Material and methods - Rewrite Page 7 (Statistical analyses): "were accessed by ANOVA??"

Answer: This phrase has been replaced with "the function of which" -Page 3, lines 6-7. Material and methods - Page 7 (Statistical analyses): has been rewritten as "ANOVA was used for comparisons among the groups".

(2) SPECIFIC COMMENTS Introduction Page 3, line 13 from the bottom: the authors cite a previous study of their group as reference no. 7. Is this correct?

Answer: The incorrect citation of reference 7 in the introduction has been corrected as reference 6, accordingly.

(3) Materials and Methods The authors may include (either in this section or perhaps as supplementary on line information) details about the composition of Qingyi decoction: ingredients (roots and herbs used) and amounts of each one. It would be also useful to know the proportion of total crude ingredient/volume (i.e. 1 g/ml).

Answer: The composition of Qingyi decoction has been provided as a supplementary file (Supplementary 1).

(4) Serum TNF- α data in Table 1 seem to be expressed in ng/L, while in the Materials and Methods section it is read that "TNF- α levels are expressed in ng/mL". Which statement is correct?

Answer: Serum TNF- α was indeed measured in ng/L. The inconsistency in the "Material and Methods section" and "Table 1 data" has been ratified.

(5) If serum TNF- α data in Table 1 are indeed expressed in ng/L, the values are very different to those reported by the authors in another study (Experimental and Therapeutic Medicine 7: 565-572, 2014) by using the same model of SAP in Sprague-Dawley rats. Even though some aspects of the treatment protocol might be slightly different, at least TNF- α values in control (sham) rats should be more alike. It is true that the analytical methods for measuring TNF- α are different (radioimmunoassay vs. enzyme-linked immune sorbent assay), but I am not sure that this alone can explain the marked differences between the values reported here and in the above-mentioned article.

Answer: We agree to the observed differences in serum TNF- α level between the previous report and the data in this manuscript but currently, we do not have the precise explanation for the observed differences other than the different methods employed. However, the trend of the biological information is conserved and consistent with the previous report, irrespective of the method used for the serum TNF- α level detection.

(6) Figure 1 legend: Perhaps the authors can rephrase the text in order to avoid multiple repetitions of "pancreas tissue" and "intestinal tissues". - Figures 3C and 4C. Using +/- symbols in the X axis is confusing. I think it would be clearer if the authors simply include in the Figure legend information about which pattern (shading) corresponds to each group.

Answer: Figure legends have been revised according to the reviewer's suggestions.

(7) Qingyi decoction is given orally to rats. Have the authors information about how well tolerated is this decoction when given orally to SAP patients? Perhaps a comment about this aspect could be included somewhere in the manuscript.

Answer: Abdominal pain after drinking any fluid is a common occurrence in SAP patients and is no different upon drinking Qingyi decoction. However, drinking Qingyi decoction is well tolerated by patients and its purgative function quickly promotes relief of abdominal pain and discomfort in the patients. We have added this in introduction section.

6 References and typesetting have been corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*

Sincerely yours,

A handwritten signature in black ink that reads "Chen Hailong". The signature is written in a cursive, flowing style with a long, sweeping tail on the final character.

Hai-Long Chen, PhD, Professor of Medicine,
Department of Surgery, the First Affiliated Hospital
of Dalian Medical University,
222 Zhongshan Road, Dalian 116011,
Liaoning Province, China.
Fax: +86-411-83631284
E-mail: hailongchen2007@163.com