

RESPONSE TO PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 60924

Title: The protective effect and mechanisms of action of Mongolian medicine Sulongga-4 on pyloric-ligation-induced gastroduodenal ulcer in rats

Reviewer's code: 00058352

Position: Peer Reviewer

Academic degree:

Professional title: Professor

Reviewer's Country/Territory: Argentina

Author's Country/Territory: China

Manuscript submission date: 2020-11-20

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2020-11-27 19:33

Reviewer performed review: 2020-11-28 10:14

Review time: 14 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

1. Demonstration of therapeutic effects of a Mongolian traditional medicine (Sulongga-4) in peptic- acid disease in rats.

Answer 1: Thank you for the affirmative comment to the paper. The current manuscript has demonstrated the therapeutic effect of a Mongolian folk medicine SL-4 on pyloric ligation-induced gastroduodenal ulcers in rats by evaluating histopathological features, tissue cytokines expression, and the microarray analysis. The overall findings support the conclusion that a Mongolian folk medicine SL-4 is a promising gastroprotective agent that can potentially be used to treat gastric ulcers.

2. Analysis of possible mechanisms involved in the eventual protection by SL4: down regulation of CYP2b2 and UGT2b1 genes in the retinol metabolism and up regulation of A2m and MASP1 genes in the complement and coagulation cascade.

Answer 2: Thanks very much for the comment! The authors discussed and analyzed the effects of CYP2b2 and UGT2b1 genes in the retinol metabolism at page16 from line 330 to 344 in Discussion section. The putative gastroprotective mechanism of A2m and MASP1 genes in the complement and coagulation cascade were discussed and speculated at page 17 from line 349 to 359 in Discussion.

3. A very important future direction is the investigation of these therapeutic effects of SL-4 in the human being.

Answer 3: Thank you for the advice! A Mongolian folk medicine SL-4 has been used for long time in Mongolian medicine clinics as a hospital preparation around Inner Mongolia region. But this medicine has not been registered and approved by CFDA. Our research group's overall aim is to develop an antiulcer herbal formula and register as a new drug



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based on traditional Mongolian medicine. In the Discussion, the authors discuss the clinical application and future directions of SL-4 on human beings at page 17 from line 339 to 344 and page 18 from line 378 to 380, respectively.

RESPONSE TO PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 60924

Title: The protective effect and mechanisms of action of Mongolian medicine Sulongga-4 on pyloric-ligation-induced gastroduodenal ulcer in rats

Reviewer's code: 00036517

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor

Reviewer's Country/Territory: Japan

Author's Country/Territory: China

Manuscript submission date: 2020-11-20

Reviewer chosen by: Jin-Lei Wang

Reviewer accepted review: 2020-11-26 06:48

Reviewer performed review: 2020-12-02 02:57

Review time: 5 Days and 20 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Major points

4. I wonder that the results of this manuscript is disjoint and less relevant. I suggest that authors need to add more speculation about relevance of each result in discussion.

Answer 4: Thank you for the advice!! The author thoroughly reedited the Discussion section following the reviewer's comment. First, we discussed the findings of histopathological changes and tissue cytokine expressions in the context with other relevant published literatures (page 14 from line 271 to 302). Second, we compared the gastroprotective effect of a Mongolian medicine SL-4 with Chinese medicine, Indian medicine and Malaysian medicine, and discussed the main active ingredients with potential therapeutic mechanisms (page 15 from line 303 to 317). Third, we discussed the microarray results and speculated the gastroprotective mechanism of SL-4 in PL-induced ulceration in rats (page 16 from line 318 to 359).

5. Authors studied the expression of cytokines. So, I suggest that authors need to add the inflammatory changes of histological findings.

Answer 5: Thanks for the advice! The author added the inflammatory changes of histological findings in the Result section (page 11 form line 215 to 218) and discussed at page 14 from line 283 to 288 and from line 299 to 302.

6. Minor point Authors should correct the style of baciterias' name, for example, *Helicobacter pylori*, and should be in italic.

Answer 6: Thanks very much for careful reading of the article! As advised, we corrected the bacterias' name and plant species' name in Italic font. The changes were made at page 6, line 107; page 12, line 248; page 13, 252; page 15, line 303, 307, 310, 312; page 18, line 360, 361.

RESPONSE TO PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 60924

Title: The protective effect and mechanisms of action of Mongolian medicine Sulongga-4 on pyloric-ligation-induced gastroduodenal ulcer in rats

Reviewer's code: 02445547

Position: Associate Editor

Academic degree: DNB, FEBS, FICS, FRCS (Gen Surg), MBBS, MNAMS

Professional title: Associate Professor, Director, Surgeon, Surgical Oncologist

Reviewer's Country/Territory: Singapore

Author's Country/Territory: China

Manuscript submission date: 2020-11-20

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-11-20 03:56

Reviewer performed review: 2020-12-04 05:46

Review time: 14 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
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Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

Dear Authors i have a few minor comments and one major comment. Major comment:

7. With regards to scientific conduct, i want authors to report and include more on study design

Answer 7: Thanks for the comment! As reviewer's advice, we have added and reedited more detailed experimental design in Materials and Methods (page 7 line 139 to 146).

8. Who performed ligation?

Answer 8: Thanks for the question! The animal experiment and pyloric ligation were performed by the first author Tong Shan, who is a surgeon and an associate chief physician at the Affiliated hospital of Inner Mongolia University for Nationalities.

9. Is 18 hours adequate to develop ulcers? Did authors observe macroscopic ulcer? I say so as ulcer is a clinical diagnosis and inflammation is a biomarker / lab diagnosis based on blood / histology.

Answer 9: Thanks for the question! Dr Tong shan and Dr Wang huan have developed the pyloric ligation-induced gastric ulcer and hepatic injury model since 2011 and published around 14 relevant papers. Based on the published literature (Zhang, S., et al. (2014). Alkaloids from Mahonia bealei posses anti-H⁺/K⁺-ATPase and anti-gastrin effects on pyloric ligation-induced gastric ulcer in rats. Phytomedicine, 21(11): 1356-1363.; Paliwal Pankaj,Kumar Arepalli Sampath,Tripathi Himanshu et al. Pharmacological application of barium containing bioactive glass in gastro-duodenal ulcers.[J] .Mater Sci Eng C Mater Biol Appl, 2018, 92: 424-434.) and our previous experiences and data, 18 hours of ligation is the optimum to induce gastric and duodenal ulcers in rats. It can be confirmed by the histopathological graphs at Figure 1 in this manuscript.

10. How did you alleviate suffering?

Answer 10: All rats were housed in SPF standard animal rooms of Key Laboratory of Ministry of Education at the School of Mongolian Medicine, IMUN. The rooms were environmentally controlled (22 ± 2 °C, the relative humidity of $50 \pm 5\%$) and with a 12-h light/dark cycle to maintain the animal welfare. Oral gavage of drug was performed by well trained students and lab technician. Pyloric ligation surgery was performed by a well experienced surgeon (Tong Shan, first author of this manuscript) who are working at the Surgery Department of Affiliated Hospital of IMUN to alleviated animals suffering to the large extent.

11. How did you perform gastric lavage after surgery?

Answer 11: Thanks for the question! We did not perform gastric lavage after surgery. The drugs were pretreated via oral administration in rats for 15 consecutive days. Then, pyloric ligation surgery was performed at the end of the day to induce gastric ulceration following the methodology reported in the published literature (Zhang, S., et al. (2014). Alkaloids from Mahonia bealei posses anti-H⁺/K⁺-ATPase and anti-gastrin effects on pyloric ligation-induced gastric ulcer in rats. *Phytomedicine*, 21(11): 1356-1363).

12. Did veterinary doctor perform all these procedures?

Answer 12: The first author of this manuscript Dr Tong Shan, a specialized surgeon, performed all surgical procedures. A veterinarian Dr Li Chun from School of Animal Science IMUN was in charge of any consultant regarding all experimental procedures if necessary.

13. What was the dose of intraperitoneal pentobarbital?

Answer 13: Sodium pentobarbital was given by intraperitoneal injection with the dose of 50mg/kg for anesthesia.

14. In alignment with 3R for animal research - did authors believe small sample would have given the same results?

Answer 14: Thanks very much for the comment! This research project used the minimum quantity of animals possible to have statistically relevant results. To calculate the number of animals in the experiment, it was used the formula suggested for the National Research Council US (in Guidelines for the Use of Animals in Neurosciences and Behavioural Research) for continuous variables: $n = 1 + 2C(s/d)^2$, where C is dependent on values chosen for significance level and power.

15. What justification for 12 rats in 1 group?

Answer 15: Thanks very much for the comment! Animal numbers used in this research have been calculated by the Sample Size Determination equation published by the National Research Council (US) Committee on Guidelines for the Care and Use of Animals in Neuroscience and Behavioral Research (Washington DC, National Academies Press, US, 2003; <http://www.ncbi.nlm.nih.gov/books/NBK43321/>). In contrast to chemical drugs, the biological activity of traditional herbal formula is milder and less toxic. According to the previous pyloric-ligated ulceration studies, the standard deviation in inflammatory cytokines such as TNF- α is 4.9 pg/ml in trials involving 8 rats in each experimental group. We expect to detect a 6 pg/ml reduction in inflammatory cytokines expression between model and SL-4 treatment with a power of 80% and a significance level of 5%. Thus, 12 experimental animals (11.47 for calculation) were required per treatment for a total of 60 animals (5 treatments x 12 rats/group).

Minor comment:

16. In introduction, you have included so many citations for different statements about

peptic ulcer disease. I suggest to delete citations 1,3,6,7 and 8 and they are irrelevant to study and instead include the paper published in sister journal - Chung KT, Shelat VG. Perforated peptic ulcer - an update. World J Gastrointest Surg. 2017 Jan 27;9(1):1-12. doi: 10.4240/wjgs.v9.i1.1. PMID: 28138363; PMCID: PMC5237817. After all the focus is not on NSAIDs and thus omit those citations please.

Answer 16: : Thank you for the advice! The author deleted the part regarding NSAIDs at page 4 from line 64 to 86, and omit all relevant citation as reviewer's advice. Instead, the authors described the peptic ulcer diseases by citing Chung et al., 2017 and some other related papers as recommended (page 5 from line 86 to 101).

17. I want authors to discuss these results and compare with other herbs - malaysian herb (Al-Wajeeh NS, Hajerezaie M, Noor SM, Halabi MF, Al-Henhena N, Azizan AH, Kamran S, Hassandarvish P, Shwter AN, Karimian H, Ali HM, Abdulla MA. The gastro protective effects of Cibotium barometz hair on ethanol-induced gastric ulcer in Sprague-Dawley rats. BMC Vet Res. 2017 Jan 19;13(1):27. doi: 10.1186/s12917-017-0949-z. PMID: 28103938; PMCID: PMC5244617.), chinese herb (Al-Wajeeh NS, Hajerezaie M, Noor SM, Halabi MF, Al-Henhena N, Azizan AH, Kamran S, Hassandarvish P, Shwter AN, Karimian H, Ali HM, Abdulla MA. The gastro protective effects of Cibotium barometz hair on ethanol-induced gastric ulcer in Sprague-Dawley rats. BMC Vet Res. 2017 Jan 19;13(1):27. doi: 10.1186/s12917-017-0949-z. PMID: 28103938; PMCID: PMC5244617.), and Indian Ayurvedic herb (Kumar A, Singh V, Chaudhary AK. Gastric antisecretory and antiulcer activities of Cedrus deodara (Roxb.) Loud. in Wistar rats. J Ethnopharmacol. 2011 Mar 24;134(2):294-7. doi: 10.1016/j.jep.2010.12.019. Epub 2010 Dec 21. PMID: 21182918.)

Answer 17: Thank you very much for the advice! The authors discussed our current findings on antiulcer effect of SL-4 with comparison of Chinese medicine, Indian medicine and Malaysian medicine and cited the above mentioned literature as reviewer's advice

(page 15 from line 303 to 317).

18. Lastly, all basic scientific benchwork must eventually translate to clinical practise. In discussion i dont see that link. I want authors to discuss more about clinical relevance, clinical application and some future direction. After all 60 rats were sacrificed and thus, need to see tangible foreward direction from authors.

Answer 18: Thanks for the comment! The authors discussed the gastroprotective effect of Mongolian medicine SL-4 and its potential clinical applications and the future direction in Discussion and Conclusion sections as advised (page 17 from line 339 to 344; page 18 from line 364 to 369 and line 378 to 380).

19. IACUC and Ethics approval are in mandarin and if possible furnish in english language please.

Answer 19: As reviewer's advice, we translated the IACUC and Ethics approval into English and attached with the revised manuscript resubmission.

20. Company editor-in-chief: I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, 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, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. The title of the manuscript is too long and must be shortened to meet the requirement of the journal (Title: The title should be no more than 18 words). Before final acceptance, the author(s) must provide the English Language Certificate issued by a professional English language editing company. Please visit the following website for the professional English language editing companies we recommend: <https://www.wjgnet.com/bpg/gerinfo/240>.

Answer 20: As company editor-in-chief's advice, the manuscript title is changed to <The protective effect and mechanisms of action of Mongolian medicine Sulongga-4 on pyloric-ligation-induced gastroduodenal ulcer in rats (17 words)>.

The final manuscript was sent for English language review of a professional English language editing company (MedE: <http://www.meditorexpert.com/IcmskooV1/Index.aspx>) as Company editor-in-chief's suggestion.

21. Science editor: 1 Scientific quality: The manuscript describes a basic study of the protective effect and mechanisms of Traditional Mongolian medicine Sulongga-4 on pyloric-ligation induced gastric-duodenal ulcer in rats by microarray analysis. The topic is within the scope of the WJG. (1) Classification: Grade B and two Grades C; (2) Summary of the Peer-Review Report: Authors studied the expression of cytokines. The questions raised by the reviewers should be answered; and (3) Format: There are 4 tables and 5 figures. A total of 56 references are cited, including 4 references published in the last 3 years. There are no self-citations. 2 Language evaluation: Classification: Grade A and two

Grades B. A language editing certificate issued by JWEDIT was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, the Institutional Review Board Approval Form No academic misconduct was found in the CrossCheck detection and Bing search. 4 Supplementary comments: This is an unsolicited manuscript. The study was supported by China National Natural Science Foundation Project, Inner Mongolia Autonomous Region Talent Development Fund project. The topic has not previously been published in the WJG. 5 Issues raised: (1) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s); (2) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; (3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout; and (4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text. 6 Re-Review: Required. 7 Recommendation: Conditional acceptance.

Answer 21: Thanks very much for the advice! (1) The approved grant application form and funding agency copy of the approval documents were attached with manuscript resubmission. (2) The editable all figures were prepared in PPT and attached with the resubmission. (3) PMID and DOI numbers were added in the reference list as advised. (4) Article highlights was added in the end of the main text.