Author's response to reviews

Title: Gastroduodenal cytoprotective and anti-Helicobacter pylori herbal formula HZJW: safety and efficacy assessment

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Author’s response to reviews: see over
Dear Editors and Reviewers:

On behalf of my co-authors, we thank you very much for giving us an opportunity to revise our manuscript. We appreciate editor and reviewers very much for their careful considerations and valuable comments on our manuscript entitled “Gastroduodenal cytoprotective and anti-\textit{Helicobacter pylori} herbal formula HZJW: safety and efficacy assessment” (ID: 3271484358732221). Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. According to your email on 19 Feb., 2013, we have taken into consideration of your suggestions and the reviewer’s comments in preparing the revised manuscript. We are very sorry for our negligence of some detailed information and relevant references and incorrect writing of certain spelling and grammatical expressions. We revised the manuscript in accordance with the reviewers’ comments, and carefully proof-read the manuscript to minimize typographical mistakes and grammatical errors. The revised portion has been highlighted with yellow color for indication. The main corrections in the paper and the responses to the reviewer’s comments are as following:

\textbf{Reviewer #1:}

\textbf{Major Compulsory Revisions}

1. Comment: The figures and tables do not correspond to those mentioned in the text, and they need to be corrected.

Response: The figures and tables were corrected in correspondence with those mentioned in the revised MS.

2. Some paragraphs are difficult to understand and/or can be shortened.

Response: The section “On week 26, significant decreases in hemoglobin in the mid-dose \((P < 0.01 \text{ vs. control group})\) and high-dose males \((P < 0.05 \text{ vs. control group})\) were observed. A significant decrease in mean corpuscular hemoglobin \((P < 0.05 \text{ vs. control group})\) was observed in high-dose males on Week 26. Lower levels of
mean corpuscular hemoglobin concentration were noted in males of three treatment
group on Week 26 and high-dose group after 4-week recovery. A significant increase
of mean platelet volume ($P < 0.01$ vs. control group) was noted in high-dose males
after 4-week recovery. A significant elevation of white blood cell and lymphocytes in
mid-dose and high-dose males ($P < 0.01$ vs. control group) was observed on Week 13
and low-dose male ($P < 0.01$ vs. control group) on Week 26. A significant increase of
neutrophils in mid-dose and high-dose males ($P < 0.01$ vs. control group) was noted
on Week 13 and all the treated males ($P < 0.01$ vs. control group) on Week 26.
lymphocytes (%) was decreased among all the treated males ($P < 0.01$ vs. control
group) on Week 26 and after recovery. A significant increase of mean corpuscular
hemoglobin and mean corpuscular hemoglobin concentration in all the treated female
on Week 26, declined lymphocytes (%) in mid-dose female ($P < 0.05$ vs. control
group) on Week 26 and all the treated female on Week 31.” was shorted as “Despite a
significant change was observed in some parameters (hemoglobin, mean corpuscular
hemoglobin, mean corpuscular hemoglobin concentration, mean platelet volume,
white blood cell, lymphocytes, neutrophils), the above parameters remained within
the range of normal physiological variation and there was no dose response
relationship.

The paragraph “A statistically significant increase in aspartate aminotransferase
activity ($P < 0.05$ vs. control group) in males of three treatment group appeared on
Week 13. While the level of glucose was affected only at the high-dose group on
Week 26. Triglycerides in high-dose male decreased on Week 13 ($P < 0.01$ vs. control
group) while increased on Week 26 (P < 0.05 vs. control group). Meanwhile, total protein and total bilirubin were elevated noticeably in mid-dose and high-dose males on Week 26 (P < 0.01 vs. control group). For the liver function tests, the plasma level of alanine aminotransferase activity and aspartate aminotransferase activity were significantly decreased in low-dose (P < 0.05 vs. control group) and high-dose (P < 0.01 vs. control group) females on Week 13 but was not significantly changed on Week 26 and after the recovery. The alkaline phosphatase activity level in females did not vary significantly during the whole experimental period. A statistically significant increase in total protein was also detected in mid-dose (P < 0.05 vs. control group) and high-dose females (P < 0.01 vs. control group) on Week 13. Albumin in high-dose female increased on Week 13. Other changes in females included: significantly decreased total bilirubin (P < 0.05 vs. control group) and direct bilirubin (P < 0.01 vs. control group) in mid-dose group on Week 26, elevated Urea level in high-dose group on Week 26. Once again, there were no dose response relationships and all of above parameters remained within the physiological range.” was revised as “Despite some parameters experienced significant variation (glucose, triglycerides, aspartate aminotransferase activity, alanine aminotransferase activity, total protein, total bilirubin, direct bilirubin, alkaline phosphatase activity, albumin and urea), there were no dose response relationships and all of above parameters remained within the physiological range.”

**Minor Essential Revisions**

3. The results section is not indicated in the text.
Response: “Results” was added as in the results section.

4. There are some spelling and grammatical errors in the text.

Response:

a. Page 5, line 6: “oriented” was corrected as “oriental”; line 9: “,” was changed to “;”;
b. “Scientific names” in the text was all revised to italics form in revised MS;
c. Page 8, line 4: The sentence “Chemical profile of HZJW was analyzed by HPLC (see Additional file 1)” was added;
d. Page 9, line 5: “to” was revised as “an”; “by” was deleted;
e. Page 10, line 10: “was ” was corrected as “were”; line 11: “the” was deleted; line 16: “1mL” was revised as “1 mL”;
f. Page 11, line 1: “stomach” was deleted; line 13: “1mL” was revised as “1 mL”;
g. Page 13, line 21: “3min” was revised as “3 min”;
h. Page 14, line 1: “rest stomach” was revised as “rest of the stomach”;
i. Page 17, line 14: “chlorideion” was corrected as “chloride ion”;
j. Page 19, line 10: “in the form of hemorrhagic streaks” was revised as “(in the form of hemorrhagic streaks)”; “with” was changed to “of”; line 12: “inhibited” was changed to “reduced”; line 13: “)” between “0.01” and “at” was replaced behind “respectively”;
k. Page 20, line 3: “index(” was corrected as “index (”; line 8: “assay” was revised as “assay”; line 19“animals” was removed; “of” was corrected as “with”;
l. Page 21, line 8: “rate 11.76 %” was corrected as “rate of 11.76 %”;
m. Page 26, line 14: “.” behind “[23,24]” was revised as “,”; Page 27, line 5: “of inducing gastric lesions” was deleted; line 9: “provokes” was corrected as “causes”; “the solubilization of components of the mucus of the stomach production and bicarbonate secretion” was revised as “solubilization of mucus”;
n. Page 28, line 6: “most” was corrected as “main”;
o. Page 29, line 13: “the survival of H. pylori in the highly acidic environment of the
stomach” was revised as “the colonization of H. pylori in the stomach”;

p. Page 30, line 2: “suggested” was corrected as “suggests”; line 6: “stomachs” was revised as “stomach”; line 7: “level of the” was deleted.

q. Reviewer also advised to add “standard deviation brackets” in ulcer inhibition (Figure 2). The inhibition percentage was calculated by the following formula: ulcer index (UI)

\[
\text{Inhibition (\%) = } \left\{ \frac{\text{UI}_{\text{control}} - \text{UI}_{\text{treat}}}{\text{UI}_{\text{control}}} \right\} \times 100\%
\]

And there is no standard deviation in ulcer inhibition (%), as suggested by other references, such as

Anti-ulcer activity of Swietenia mahagoni leaf extract in ethanol-induced gastric mucosal damage in rats (Al-Radahe S et al., 2012);

Antiulcer principle from Zingiber montanum (Al-Amin M et al., 2012);

Gastric antisecretory and antiulcer activities of Cedrus deodara (Roxb.) Loud. In Wistar rats” (Kumar A et al., 2011);

Anti-ulcer activity of the 9alpha-bromo analogue of Beclomethasone dipropionate against ethanol-induced gastric mucosal injury in rats (Ketuly KA et al., 2011).

Therefore, the standard deviation had not been added to ulcer inhibition in revised MS.

Discretionary Revisions

5. The tables are somehow difficult to follow... It might help if there are horizontal dotted lines between sections.

Response: The three-line table adopted in the text was a normalized type for data-processing and table-setting, hence this fashion was maintained in the revised MS although somehow complexed.

Reviewer #2:

1. Comment: The title could be changed to accurately convey what was found.
Response: The title “Gastroduodenal cytoprotective and anti-*Helicobacter pylori* herbal formula HZJW: safety and efficacy assessment” was changed to “Gastroprotective and anti-*Helicobacter pylori* potential of herbal formula HZJW: safety and efficacy assessment” according to the suggestion of reviewer.

2. Comment: the discussions could have been more extended, as it is a very vast paper with a lot of methods and parameters being evaluated, to only discuss 5 pages out of 30 approx. There are some references missing and the limitations of the work are not clearly stated. Something important I found, is the disorganization on the Figure’s section, as in the text one figure is referred to one designated number and in the section correspondent to “Figures” has another designation; also, there are results not discussed or mentioned, and footnotes are missing in some figures. The section of results should be re-arranged in a way that permits an easier digestion of all the info being generated.

Response:

The following references were supplemented to the corresponding citations and the sequence was rearranged in the revised MS:


e. Wallace JL: Pathogenesis of NSAID-induced gastroduodenal mucosal injury.
“In view of the doses of the components consumed in traditional medicine, HZJW was extrapolated to offer a wide margin of safety by oral route and was not likely to cause hepatic and rental dysfunction in future therapeutic use. In addition to further toxicity assessment in other species, such as dogs, careful observation should be also conducted in clinical practice.” was revised as “In view of the doses of the components consumed, HZJW was extrapolated to offer a wide margin of safety by oral route. However, since toxicity in animals and humans is genetically diverse and may respond differently, especially with respect to conditions of gastrointestinal disorders, additional toxicological assessment in other species, such as dogs, needs to be performed to evaluate the safety of HZJM, and careful observation should be also conducted in clinical practice.”

The disorganization on the Figure’s section was revised, and the section of results was shortened as suggested by both reviewers.

We tried our best to improve the manuscript and made some variations accordingly. These changes will not influence the content and framework of the paper. I hope you will find that this revised manuscript has been satisfactorily improved, and worthy of publication in the *BMC Complementary and Alternative Medicine*.

We appreciate for Editors/Reviewers’ warm work earnestly, and hope that the correction will meet with approval. Should you have any questions, please don’t hesitate to contact us at the address below. Once again, thank you very much for your comments and suggestions.

Best regards.

Yours sincerely,

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