

Dear editor and reviewer,

Thank you very much for your letter and reviewer's comments on our manuscript "Inhibition of N-methyl-N-nitrosourea-induced gastric tumorigenesis by Liuwei Dihuang Pill in db/db mice" (ESPS manuscript NO: **33455**). Those comments are all valuable and helpful for revising and improving our manuscript. We have read the comments carefully and made corrections accordingly. In the revised manuscript, **all changes were marked with underline and strikethrough in red**. The point by point responses to reviewers are listed as below:

Reviewer's comments and authors' answers:

Comment 1: Fasting blood glucose values at baseline should be presented.

Answer: Thank you for your valuable advice. We have added fasting blood glucose at weeks 1 and 20 of the study as the values at baseline. This is because that we began to administer MNU at week 1 and to use Liuwei Dihuang Pill (LDP) at week 21. The fasting blood glucose at the two time points can indicate the values at baseline. We found that the fasting blood glucose at baseline did not differ among the four groups. These results were presented in Figure 3.

Comment 2: Figures 1A-D shows probably gastric dysplasia. However, photos of gastric dysplasia by higher magnification should be submitted. In addition, representative photos of gastric cancer should also be submitted. These photos should be clear enough for the readers to differentiate gastric dysplasia from gastric cancer.

Answer: According to the reviewer's thoughtful suggestion, we have submitted representative photos of gastric dysplasia and cancer with higher magnification (200×). In addition, we also marked the cells with dysplasia in black arrows and cancer cells in red arrows. This was presented in Figure 1A-1E.

Comment 3: In figure 2, it is not clear whether the submitted photos are histologically 'normal' or 'dysplastic' or 'cancer', since histological findings in figure

B seem gastric cancer. If so, it is possible that the differences of percent of Ki67 positive cells between 4 groups are caused by sampling bias, because it is easily imagine that gastric cancer shows increased percentage of Ki67 positive cells than gastric dysplasia. The percent of Ki67 positive cells should be compared between 4 groups by selecting 10 fields of ‘normal appearing’ area.

Answer: Thank you for your important and valuable suggestions. We checked the Figure 2B, indeed, it is a representative photo of gastric cancer. We are very sorry for our thoughtless and careless mistake. In revised manuscript, we selected only gastric dysplasia in each group for analyzing Ki67 positive cells. According to your suggestion, we counted 10 fields of ‘normal appearing’ area in each sample of gastric dysplasia. Our data suggest that gastric dysplasia in db/db diabetic mice had higher percentage of Ki67 positive cells compared with dysplasia in db/m non-diabetic mice. LDP and metformin significantly decreased percentage of Ki67 positive cells. The result was presented in Figure 2.

Responses to the editor

1. Please provide the format of doc, not the format of PDF.

According to your suggestion, we have submitted the revised manuscript in the format of doc.

2. Please provide a language certificate from a professional English language editing company.

Thank you for your valuable advice. We have provided a language certificate from **MedE Editing Group** which is one of professional English editing companies mentioned in “The Revision Policies in BPG for Article”. This manuscript has been carefully reviewed and revised by editors at MedE Editing Group.

3. Please read the core tip then provide the audio core tip.

We thank for editor’s suggestion. The audio core tip in the format of mp3 has been submitted as an attachment.

4. Please update the manuscript according to the Guidelines and Requirements for Manuscript Revision-Basic Study.

We thank for editor's comment. According to the Guidelines and Requirements for Manuscript Revision-Basic Study, the format has been updated.

5. Please provide the scientific research process.

We thank for editor's suggestion. We have added the part of "Scientific Research Process" and answered the following questions: 1) What did this study explore? 2) How did the authors perform all experiments? 3) How did the authors process all experimental data? 4) How did the authors deal with the pre-study hypothesis? 5) What are the novel findings of this study? This file was submitted as an attachment.

6. Please subject the final title of the manuscript to Google Scholar search, and store screenshot images of the results.

We thank for editor's suggestion. We searched the final title of our paper in Google Scholar, and we do not find the same title as ours. The screenshot image of the results has been submitted as an attachment.

7. Please provide the files related to academic rules and norms.

We thank for editor's advice. In our institution, the Institutional review board statement and the Institutional animal care and use committee statement are the same statement. We have submitted the files of **Institutional Animal Care and Use Committee statement**, **Animal care and use statement**, **Biostatistics statement**, **Conflict-of-interest statement**, and **Data sharing statement** in PDF format as the attachments.

8. Please provide the approved grant application form(s) or funding agency copy of any approval document(s)/letter(s).

We thank for editor's suggestion. However, I have to delete this part, because the grant application cannot be provided.

9. Please sign the Copyright Assignment form.

We thank for editor's suggestion. All authors have read the Copyright Assignment carefully, and approve the Copyright Assignment. The Copyright Assignment form has been signed by all authors and submitted in PDF format as an attachment.