Manuscript title: 18β-glycyrrhetinic acid inhibits proliferation of gastric cancer cells through regulating the miR-345-5p/TGM2 signaling pathway

Manuscript ID: 84589

Reviewer#1:
Respected Reviewer (Number ID: 05754965):

First of all, I would like to express my sincere gratitude to the reviewer (Number ID: 05754965) for his/her detailed, pertinent and thoughtful comments as well as suggestions on our manuscript. Thank you for your valuable comments and the manuscript has been revised according to your recommendations. We have made point-by-point responses to the issues as follows:

**Issue 1: There are so many miRNAs with altered expression level. Why did the authors choose miR-345-5p to study but not others?**

**Response 1:** Thanks for the reviewer’ s professional review work on our manuscript. As for the selection of miR-345-5p, we add a detailed description in the manuscript. The miRBase website was used to predict the corresponding miRNAs of autophagy-related proteins, and then we intersected the miRNAs corresponding to autophagy-related proteins with the differentially expressed miRNAs screened by miRNA transcriptome. Among the obtained miRNAs, miR-345-5p was expressed most significantly. Please read page 15 of the revised manuscript, lines 12-15.

**Issue 2: miR-345-5p mimic and inhibitor should be used to determine the regulation of TGM2 by miR-345-5p.**

**Response 2:** Thanks for the reviewer’ s professional review work on our manuscript. The role of miR-345-5p in gastric cancer is still being further studied. We overexpressed miR-345-5p in gastric cancer cells by lentiviral transfection, and detected the expression of TGM2 and found that miR-345-5p overexpression could inhibit the expression of TGM2. This data has been added
to the manuscript. Please read Figure 9 of the revised manuscript. page 17, lines 1-7.

**Issue 3:** *Restoration assays are needed to demonstrate that the effect of 18β-GRA is through miR-345-5p/TGM2 axis.*

**Response 3:** We very much agree with your feedback. We overexpressed miR-345-5p in gastric cancer cells by lentivirus transfection technology, and then treated with 18β-GRA. During the experiment, we found that the cell state was very bad and could not carry out subsequent experiments. For this situation, we are improving the experimental program and looking forward to better experimental results. However, the effects of miR-345-5p overexpression on cell viability, cell cycle and apoptosis were examined in GC cells. We have added this part of the experimental results to the manuscript. Please read Figure 10 of the revised manuscript. page 17, lines 9-27.

**Issue 4:** *In your working model, miR-345-5p was mistakenly showed as miR-204-3p.*

**Response 4:** We are very sorry for our incorrect writing and we have corrected this problem. Please read Figure 10 of the revised manuscript.

**Issue 5:** *The reference #32 is not suitable for citing.*

**Response 5:** We are very sorry for our incorrect writing and we have corrected this problem. Please read reference of the revised manuscript.

Company editor-in-chief:

Respected Company editor-in-chief:

Thank you for your valuable comments and the manuscript has been revised according to your recommendations. We have made point-by-point responses to the issues as follows:

**Issue 1:** 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. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, “Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...”. Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is ‘original’, the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision.

Response 1: We have provided decomposing graphics and organized them into a PowerPoint file. All the graphics are original creations of the authors, with the exception of Figure 6A-F from a previous study by our research group, which has been published in the World Journal of Gastroenterology (Yuan L, Yang Y, Li X. et. 18β-glycyrrhetinic acid regulates mitochondrial ribosomal protein L35-associated apoptosis signaling pathways to inhibit proliferation of gastric carcinoma cells. World J Gastroenterol. 2022 Jun 14; 28(22): 2437-2456.DOI:
10.3748/wjg.v28.i22.2437. PMID: 35979263). The copyright information has been added in the lower right corner of the picture in the PowerPoint file. We have modified the Figure legends according to the requirements and added a highlight section. Please read the revised manuscript.