Reviewer#1:

Respected Reviewer (Number ID: 04440035):

First of all, I would like to express my sincere gratitude to the reviewer (Number ID: 04440035) 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: *Reviewer thinks the authors cannot rule out the possibility that MRPL35 is not involved in the 18β-GRA -induced suppression of the gastric cancer cell proliferation. To clarify this point, it would be preferable to examine the effect of down-regulated MRPL35 on the proliferation and apoptosis of gastric cancer cells, perhaps by testing a commercially available MRPL35 inhibitor in their assay or by RNA interference.*

Response 1: This is a very clear suggestion, and the same consideration as our team previously. So we conducted the experiments on the effects of down-regulated MRPL35 expression on the proliferation and apoptosis of gastric cancer cells first. This part has been published by us in 2021 and note in the revised manuscript (Page 12, line 9).

Please read the details in our paper: Yuan L, Li J, Yang Y, Chen Y, Ma T, Liang S, Bu Y, Yu L, Nan Y: Depletion of MRPL35 inhibits gastric carcinoma cell proliferation by regulating downstream signaling proteins. *World journal of gastroenterology* 2021; **27**:1785-1804.[PMID:33967557 DIO:10.3748/wjg.v27.i16.1785]

Issue 2: *The results of proliferation of two different cell lines are so similar. The authors should explain why the differences between two cell lines are so small in most experiments.*

Response 2: Some studies have shown that mitochondrial ribosomal proteins are related to tumorgenesis, and which are expected to be tumor markers. Our study is mainly based on MRPL35, a mitochondrial ribosomal protein closely related to gastric cancer, to explore the mechanism of 18β-GRA inhibiting gastric cancer. So, when selecting cell lines, we first detected the expression abundance of MRPL35 in gastric cancer cell lines, striving to select cell lines with similar MRPL35 expression, so as to investigate the mechanism of effects of 18β-GRA more significantly. Therefore, the results of proliferation of two different cell lines similarly may indicate that the anti-proliferation effect of 18β-GRA is related to MRPL35. We have included the results of *MRPL35*mRNA test in the supplementary materials (Supplementary Figure 1).

Issue 3: *Inhibitory effect of 18β-GRA on invasion looked similar compared to growth inhibition. It is likely that inhibitory invasion ability by 18β-GRA only results in impaired growth of cell lines.*

How the authors explain this question? To address this, authors should attempt to isolate factors involving in cancer invasion accelerated by 18β-GRA, by doing additional experiments.

Response 3: Cell invasion and proliferation represent different cellular functions. Cell invasion is a phenotype of malignant tumor, which is mainly a process in which tumor cells at the primary site detach from the primary lesion and infiltrate into the surrounding stroma through basement membrane. We tested the invasion ability of gastric cancer cells by Transwell and found that 18β-GRA could inhibit the invasion of gastric cancer cells through the Transwell membrane, which suggested that 18β-GRA could inhibit the invasion of gastric cancer cells. 18β-GRA could inhibit the proliferation and also inhibit the process of infiltrating into the surrounding stroma of gastric cancer cells. This view could be accepted. We are still working at the effects of 18β-GRA on the metastasis of gastric cancer cells, so we would like to make a few preparations in this paper to show some data related to metastasis.

Issue 4: *MRPL35 levels should be examined in the engrafted tumors in mice.*

Response 4: We supplemented this experiment using retained engrafted tumors of nude mice by qRT-PCR and add the result to the manuscript. 3 samples for each group were repeated testing for 3 times (Page 25, line 19).

Issue 5: *Did the authors report any toxic effect, as body weight loss, during the experiment?*

Response 5: As for toxicity, we detected and reported the effect of 18β-GRA on the survival rate of normal gastric mucosa cells GES-1(Page 22, line 15) in the manuscript before. When the concentration of 18β-GRA ranged from 12.5 μmol/L to 150 μmol/L, the drug had little effect on the survival rate of GES-1 cells. In the meantime, we also monitored the body weight, diet and water intake of mice at the laboratory animal center. The diet and water intake of mice in 18β-GRA group were slightly lower than that in control, but the body weight of mice in 18β–GRA group was higher than that in control, indicating low drug toxicity. We have uploaded this data to the supplementary materials (Supplementary Figure 2-4).

Issue 6: *The description of the number of the mice in the group may confuse readers. The text should be modified.*

Response 6: We are very sorry that we wrote the number of mice by mistake. The text has already been modified.

Issue 7: *Clinical translation of these experiments is unclear and doubtful.*

Response 7: Currently, gastric cancer is mainly treated by surgery, combined with radiotherapy and chemotherapy, but the therapeutic effect is still not good. The 5-year survival rate for patients with advanced gastric cancer is less than 20% and the prognosis is poor. The drug resistance, toxicity and side effects of chemotherapy drugs, the low compliance of patients during chemotherapy, the low survival rate after surgery and the inadaptability for surgery, which are all suggest that it is urgent to find a natural, effective and low toxic active substance to resist the proliferation of gastric cancer, as well as improve the survival rate and survival treatment of gastric cancer patients. Glycyrrhetinic acid is already used in clinical trials for liver disease. A number of researchers, including us, have been confirming its effect on gastric cancer. We believe that 18β-GRA or the derivatives could have clinical transformation potential.

Issue 8: *The wound healing assays, shown in Figure 7C and D, need to be compared when the control wound is completely closed. The photographs do not show the clear significance by 18β-GRA treatments.*

Response 8: After we typeset all the images, Figure 6 in the original manuscript is changed to Figure 7 in the current manuscript. Wound healing test is a simple method to measure cell migration ability. The photographs in the first row show the state of each group of cells at the beginning (0 h) of the experiment, and the ones in the second row shows the state of each group of cells at 24 h after drug intervention. I added 0 h and 24 h labels in the Figure 7A-D. After 24 h of culture, the peripheral cells grew to the central area of the scratch, which could show the significance.

Issue 9: *Page 21 line 35-38: Appropriate literatures should be added to refer this sentence.*

Response 9: References are added in that section (Page 35, line 1).

Reviewer#2:

We have read this reviewer's comment, and the conclusion is to accept our manuscript without specific modification requirements.

Reviewer#3:

Respected Reviewer (Number ID: 00036517):

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: *The part of abstract is too long.*

Response 1: We have shortened the abstract part of the article

Issue 2: *Also all part of the manuscript is long. I suggest that authors need to reduce the repeated data in discussion.*

Response 2: The repeated data in discussion has been deleted, and some parts have been shortened in the manuscript.

Science editor:

Respected Science editor:

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: *Please supplement the effect of down-regulated MRPL35 on the proliferation and apoptosis of gastric cancer cells.*

Response 1: Our previous experiments have proved that down-regulation of MRPL35 expression can inhibit proliferation and promote apoptosis of gastric cancer cells, and it was published by us in 2021. Please read the details in our paper: Yuan L, Li J, Yang Y, Chen Y, Ma T, Liang S, Bu Y, Yu L, Nan Y: Depletion of MRPL35 inhibits gastric carcinoma cell proliferation by regulating downstream signaling proteins. *World journal of gastroenterology* 2021; **27**:1785-1804. [PMID:33967557 DIO:10.3748/wjg.v27.i16.1785]

Issue 2: *Supplementary explanation for so little difference between the two cell lines in most experiments.*

Response 2: Before screening cell lines, we detected the expression abundance of MRPL35 in gastric cancer cell lines and found that the expression abundance of MRPL35 in BGC-823 and MGC80-3 cells was similar, which helped us to study more mechanisms of 18β-GRA. Therefore, many results of the two cells were similar, which may indicate that the anti-proliferative effect of 18β-GRA is related to MRPL35. And the results of MRPL35 expression abundance in gastric cancer cells into supplementary materials (Supplementary Figure 1).

Issue 3: *Supplementary suggestion to isolate factors associated with 18β-GRA-accelerated cancer invasion by doing additional experiments.*

Response 3: Cell proliferation and invasion abilities were detected in this paper, which represent different cell functions. Cell invasion is a phenotype of malignant tumor, mainly a process in which tumor cells at the primary site break away from the primary lesion and infiltrate into the surrounding stroma through the basement membrane. The results of our cell invasion assay suggested that 18β-GRA could inhibit the invasion of gastric cancer cells by inhibiting the invasion of peripheral stroma of cancer cells, which was acceptable.

Issue 4: *Supplementation in mouse xenograft tumors Check MRPL35 levels.*

Response 4: We supplemented this experiment using retained engrafted tumors of BABL/C nude mice by qRT-PCR and add the result to the manuscript. 3 samples for each group were repeated testing for 3 times (Page 25, line 19).

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: *Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. 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.*

Response 1: We have provided decomposing graphics and organized them into a PowerPoint file. All graphics in the article are original, and the copyright information has been added in the lower right corner of the picture in the PPT.