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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 73907

Title: 18β-glycyrrhetinic acid regulates mitochondrial ribosomal protein 5-associated apoptosis signaling pathways to inhibit the proliferation of gastric carcinoma cells

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00036517
Position: Editorial Board
Academic degree: AGAF, MD, PhD
Professional title: Assistant Professor
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-05 06:19

Reviewer performed review: 2022-01-12 02:58

Review time: 6 Days and 20 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[ ] Yes [Y] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

Major points 1. The part of abstract is too long. 2. Also all part of the manuscript is long. I suggest that authors need to reduce the repeated data in discussion.

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Peer-review model: Single blind

Reviewer's code: 00039368
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Academic Research, Associate Professor
Reviewer's Country/Territory: Estonia
Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-05 09:17

Reviewer performed review: 2022-01-14 11:38

Review time: 9 Days and 2 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [Y] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This is a very well designed, performed and written experimental study for investigation of the mechanism by which 18 -glycyrrhetinic acid (18 .GRA) as an active compound of Glycyrrhizae radix, regulates Mitochondrial Ribosomal protein L35 (MIRPL35)-related signal proteins to inhibit the proliferation of gastric cancer (GC) cells. This study is an extension of a previous experimental study of the same authors group who showed that the expression of MRPL35 was significantly up-regulated in GC and was associated with poor survival rate in GC. For investigation of this aim the authors used normal gastric mucosal cell line GES-1 and GC cell lines as well as and animal model. The main and important finding of authors was that 18 -GRA could inhibit the proliferation of GC cells in dose and time-dependent manner, induce GC cell apoptosis and arrest the cell cycle in G0/G1 phase. Additionally, the migration and invasiveness of GC cells were inhibited. The noteworthy finding was that 18 -GRA inhibits proliferation and migration of GC and promotes their apoptosis by down-regulating MRPL35 expression, thereby affecting the expression of TP53, BCL2L1, COPS5, BAX and BAD proteins. This mechanism could be involved in inhibiting the proliferation of GC cells. The study is set up correctly. The paper is written well. Introduction gives a good overview of the study background and the authors raised clearly the aim of the study. The aim of the study is fulfilled. The authors used a large panel of methods, like cell proliferation assessment by Cell Counting Kit-8, flow cytometry for cell cycle and apoptosis analysis, transwell assays and cell scratch test for investigation of cell invasion and migration, tumor formation experiment in BALB/c nude mice, protein extraction, trypsin digestion and tandem mass tag (TMT) labeling,

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liquid chromatography-tandem mass spectrometry. The Table and Figures of high quality give a good overview about the results. This study makes a contribution to better understanding of the possible regulatory mechanisms participating in inhibition of GC cell proliferation.

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Peer-review model: Single blind

Reviewer's code: 04440035
Position: Peer Reviewer
Academic degree: MD, PhD
Professional title: Doctor
Reviewer's Country/Territory: Japan
Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-01-06 05:31

Reviewer performed review: 2022-01-18 12:41

Review time: 12 Days and 7 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The study by Yuan and colleagues investigates the role of 18β-GRA, a pentacyclic triterpene derivative extracted from the licorice, in the proliferation in gastric cancer. Application of this component effectively suppressed the growth of gastric cancer cell lines by induction of apoptosis and arrest of the cell cycle. 18β-GRA also impaired the migration and invasion ability of gastric cancer cells. They subsequently examined the biological activity of 18β-GRA in vivo model. 18β-GRA suppressed the growth of xenograft tumor volume. TMT technology showed that 18β-GRA is related with a variety of molecular biological process, including TP53 signaling pathway in gastric cancer cells. Utilizing the Retrieval of Interacting Genes/Proteins database, they found that COPS5, BAX, and BAD proteins were associated with MRPL35, TP53 and BCL2L1, which was confirmed by immunoblotting. 18β-GRA may open a new therapeutic avenue which will greatly impact the capacity to effectively treat gastric cancer patients. These findings will be of interest to clinicians involved in the treatment of gastric cancer, as well as researchers in the field. However, I regret to inform you that your manuscript could not be considered for publication in its present form. Several changes should be done to make it clearer and some additional data should be presented. My comments are as follows; Major comments; 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. 2. The results of proliferation of two different cell lines are so

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similar. The authors should explain why the differences between two cell lines are so small in most experiments. 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. 4. MRPL35 levels should be examined in the engrafted tumors in mice. 5. In vivo experiments need to be repeated at least twice for each experimental group. Did the authors report any toxic effect, as body weight loss, during the experiment? 6. The description of the number of the mice in the group may confuse readers. The text should be modified. 7. Clinical translation of these experiments is unclear and doubtful. Minor comments; 1. The wound healing assays, shown in Figure 6C 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. 2. Page 21 line 35-38: Appropriate literatures should be added to refer this sentence.