

REVIEWERS' COMMENTS:

Thank you very much for the in-depth review of the paper and for mentioning some very important points which really helped us to improve the manuscript. We have re-written part of the manuscript according to the suggestions of the reviewer. We have also carefully gone through the whole manuscript and did language corrections. All modifications are in red text. We hope that the reviewers will now find the manuscript substantially revised with respect to the points raised by them. Here are the point-by-point responses to the reviewers' comments:

Reviewer #1:

Conclusion: Minor revision

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

I would like to congratulate the authors for this manuscript. This study is interesting, current and brings new perspective. I have some comments about the manuscript:

Comments:

Material and methods: Ethics committee approval and human umbilical cord collection: Please check your uploaded ethics review board approval certificate because the name of the chairperson who signed the certificate is missing.

The approval certificate is replaced with the one having name of the chairperson.

Please refer related previous study on the methods that you use. Please meet the requirement of using SI units.

We have added references of the techniques performed in the earlier studies in the Methods section. We have also checked the SI unit requirements and did modifications accordingly in the revised manuscript.

Processing and culturing of human umbilical cord tissue using explant culture: Fig. 1A is missing.

There was a mistake in the numbering of figures. It is now corrected.

Please explain how did you distribute P1 to P4 cells into the treatment groups. Please clarify if there is any special appointment of certain P1 to P4 cells into certain treatment group.

Cells were grown till P4. Figures of all passages were shown. However, only P4 cells were used in all experiments performed throughout the study. This statement is now included in the Methods.

Statistical analysis: Please provide the biostatistics review certificate signed by a biostatistician.

New certificate is now included in the documents submitted for revision.

Discussion: Regarding the use of P1 to P4 MSCs as stated in the methods on page 6, please explain your reasons of using multiple passage cells.

Cells were grown till P4, however, only P4 cells were used in all experiments performed throughout the study. This statement is now included in the text to clear the confusion.

Please point out the limitations of your study within the methodology.

Limitation of study is included in the conclusion as follows:

‘However, further investigations are required to explore the molecular mechanism involved in the differentiation process and assess the therapeutic effect of preconditioned hUC-MSCs in the *in vivo* model of end-stage liver disease’.

Reviewer #2:

Conclusion: Major revision

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

In the present research paper, the authors present the “Effect of Glycyrrhizic Acid and 18 β -Glycyrrhetic Acid on the Differentiation of Human Umbilical Cord Mesenchymal Stem Cells into Hepatocytes”. In detail, the work is well done, but I have some major concerns about the paper which are listed as follows:

Comments:

- There are some grammatical errors in the text. Please control the text in that manner. For example: “Considering the characteristics of these compounds in hepatic anomalies, in this study, we hypothesized that these triterpenes may have the ability to differentiate hUC-MSCs into hepatocytes directly or aid in the process of differentiation.”
- Also please modify the text as follows: “human umbilical cord derived MSCs (hUC-MSCs)” should be “human umbilical cord-MSCs (hUC-MSCs)”.

We have done language editing and specific modifications of sentences according to the reviewer’s comments. The manuscript is extensively reviewed for grammar errors and sentence reconstructions. We now hope that the reviewer’s will now find the manuscript substantially revised according to their suggestions.

- Please modify the title as follows: Effect of glycyrrhizic acid and 18 β -Glycyrrhetic acid on the differentiation of human umbilical cord-mesenchymal stem cells into hepatocytes

Title is modified as follows:

Effect of glycyrrhizic acid and 18 β -glycyrrhetinic acid on the differentiation of human umbilical cord-mesenchymal stem cells into hepatocytes

- Also you can modify the running title as follows: Differentiation of MSCs in to the hepatocytes

Running title is modified as follows:

Differentiation of MSCs into hepatocytes

- Please modify the keywords as follows: glycyrrhizic acid; 18 β -glycyrrhetinic acid; hepatocyte differentiation; human umbilical cord-MSCs

Key words are modified accordingly

- The abbreviations must be clarified and mentioned in the same format in the text. For example:
- glycyrrhizic acid and 18 β -glycyrrhetinic acid (abstract). - MTT (Method).

We have now added all abbreviations and mentioned them in the same format throughout the manuscript.

- In addition, the figures and error bars shown are not at high resolution and not correctly focused to enable detailed scrutiny.

Figures and error bars are now of improved quality

Reviewer #3:

Conclusion: Minor revision

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Comments:

In this manuscript, the authors first proposed the hypothesis that glycyrrhizic acid (GA) and 18 β -glycyrrhetinic acid (GT) may have the ability to differentiate human umbilical cord derived mesenchymal stem cells (hUC-MSCs) into hepatocytes directly or aid in the process of differentiation. On this basis, a series of experiments were designed. Firstly, hUC-MSCs were extracted and cultured. Then, MTT was used to determine the appropriate acid concentration to induce cell differentiation. Finally, gene expression, protein expression and periodic acid Schiff staining were used to evaluate the differentiation results. Overall, the research design was clear, and the experiment was complete. There are some small problems that need to be improved.

Comments:

1. The paragraph 2 of the “material and methods” mentioned “Fig 1A”, but this figure did not shown in the paper. Please revise this section.

There was a mistake in the numbering of figures. It is now corrected.

2. Some raw data are not present such as the stained orifice diagram.

As there is no in vivo work involved and no tissue staining so there is no orifice diagram.

3. There is room for improvement in English. Some descriptions in the manuscript are vague and potentially misleading.

We have done language editing. The manuscript is extensively reviewed for grammar errors and sentence reconstructions. We now hope that the reviewer's will now find the manuscript substantially revised according to their suggestions.

4 LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

We have done language editing and specific modifications of sentences according to the reviewer's comments. The manuscript is extensively reviewed for grammar errors and sentence reconstructions. We now hope that the reviewer's will now find the manuscript substantially revised according to their suggestions.

5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) **Science editor:** 1 Scientific quality: The manuscript describes a basic study of the effect of glycyrrhizic acid and 18 β -glycyrrhetic acid on the differentiation of human umbilical cord mesenchymal stem cells into hepatocytes. The topic is within the scope of the WJSC. (1) Classification: Grade B, Grade C and Grade B; (2) Summary of the Peer-Review Report: The authors proposed the hypothesis that glycyrrhizic acid and 18 β -glycyrrhetic acid may have the ability to differentiate human umbilical cord derived mesenchymal stem cells into hepatocytes directly or aid in the process of differentiation. It is interesting, current and brings new perspective. However, the questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 7 figures. (4) References: A total of 37 references are cited, including 1 reference published in the last 3 years; (5) Self-cited references: There are no self-cited references; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade B, Grade B and Grade B. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate,

and the Institutional Review Board Approval Form. No academic misconduct was found in the Bing search. 4
Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJSC. 5 Issues raised: (1) The title is too long, and it should be no more than 18 words; (2) The “Author Contributions” section is missing. Please provide the author contributions; (3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor; and (4) The “Article Highlights” section is missing. Please add the “Article Highlights” section at the end of the main text. 6 Recommendation: Conditional acceptance.

(1) The title is now 18 words long; (2) The “Author Contributions” section is added. (3) Original power point file of figures is now included; and (4) The “Article Highlights” section is added at the end of the main text.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Stem Cells, 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.