OPEN PEER REVIEW

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As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
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- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

Hepatitis Monthly
Article DOI: 10.5812/hepatmon.116875
Published in: Hepatitis Monthly: 21(6); e116875

Peer Review Report for "Effect of Quercetin on the Expression of NOXs and P-Smad3C in TGF-B-Activated Hepatic Stellate Cell Line LX-2"

Author(s): Narges Mohammadtaghvaei, Reza Afarin, Fatemeh Mavalizadeh, Elham Shakerian, Samaneh Salehipour Bavarsad, Ghorban Mohammadzadeh

Review Timeline:

Submit Date:	13 Jun 2021
Revised Date:	24 Jul 2021
Accepted Date:	8 Aug 2021

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (0)

15 Jun 2021

Dear AE,

1- In the first expression of abbreviations, It would be better that the complete form of abbreviation was Witten first and then the abbreviated form was presented in parenthesis; for example instead of “HBV and HCV viral(Hepatitis Band hepatitis C) “ , write “Hepatitis B and hepatitis C virus (HBV and HCV)”
2- “The results showed that the expression of NOX1, NOX2, and NOX4 138 genes was significantly decreased during 24 hours in the presence of quercetin compared to the 139 TGF-β group (Figure 2. A, B, and C).” this decrease is in all concentrations or in some of them? Was this effect concentration dependent?
3- Indicate the source of quercetin used in this study
4- “Behind 1 hour,…” did you mean before the test? It would be better to rewrite this.
5- Some sentences are not comprehensive and need revision; like:
“TGFβ-activated pathways stay the main aim for the medical remedy yet.”
“Our results prove formerly reported findings of the quercetin inhibitory effect on HSCs activation and proliferation.”
“All NOX 190 isoforms are membrane-bound enzymes that rely on NADPH for their activity

and the major source of ROS is generated when the flavin and haem-containing protein complex transfer electrons from cytosolic NADPH to molecular oxygen to produce O2 or H2O2."

6- The last paragraph of discussion is incomplete. It would be better the paragraph ends with the important finding of this study

7- There are some similar publications, which were not considered in the manuscript; such as:

• Hernández-Ortega LD, Alcántar-Díaz BE, Ruiz-Corro LA, Sandoval-Rodriguez A, Bueno-Topete M, Armendariz-Borunda J, Salazar-Montes AM. Quercetin improves hepatic fibrosis reducing hepatic stellate cells and regulating pro-fibrogenic/anti-fibrogenic molecules balance. J Gastroenterol Hepatol. 2012 Dec;27(12):1865-72. doi: 10.1111/j.1440-1746.2012.07262.x. PMID: 22989100.

• Li X, Jin Q, Yao Q, Xu B, Li Z, Tu C. Quercetin attenuates the activation of hepatic stellate cells and liver fibrosis in mice through modulation of HMGB1-TLR2/4-NF-κB signaling pathways. Toxicol Lett. 2016 Nov 2;261:1-12. doi: 10.1016/j.toxlet.2016.09.002. Epub 2016 Sep 4. PMID: 27601294.

• Eder Marcolin, Beatriz San-Miguel, Daniela Vallejo, Juliana Tieppo, Norma Marroni, Javier González-Gallego, María J. Tuñón, Quercetin Treatment Ameliorates Inflammation and Fibrosis in Mice with Nonalcoholic Steatohepatitis, The Journal of Nutrition, Volume 142, Issue 10, October 2012, Pages 1821–1828, https://doi.org/10.3945/jn.112.165274

REFEREE: Reviewer | **Revision** (0) 24 Jun 2021

Dear Editor

I have now completed the manuscript review process. In my opinion, this article can be re-evaluated after a profound revision. Here are some of the most important ones to consider. with the best wishes…

1. The text of the manuscript should be dramatically edited by a native speaker.
2. "Quercetin" should be written with capital word everywhere.
3. References have been carelessly written. e.g.: ([7,8), full stop before ␣ .(14). etc.
4. The manuscript structure should be exactly according to the guideline for authors.
5. The scientific writing should be observed: e.g.: (2 in CO2 should be subscript/ Units per milliliter (U/mL) NOT units/ml, 24hours ␣ 24 h, 37 ° C ␣ 37 °C, 1.5 hours ␣ 90 min. etc.
6. Where has Quercetin been purchased?
7. The code of "IR.AJUMS.MEDICINE.REC.1398.031" has been recorded for another project??

"Investigation the effect of fibroblast growth factor 21 on smad3 carboxy region phosphorylation and gene expression of TGF-β in the cholesterol-treated LX2 cell line"

8. The method is quite vague and confusing. Groups are not specified. The treatments performed with Quercetin and TGF-β and their sequence were reported completely disrupted and incomprehensible.
9. Performed tests are not clear in regard of which groups and with what treatments
10. While clarifying and structuring the method and results, it is suggested to illustrate the working method.

11. I couldn't find any perspective in the discussion.
12. Figures and diagrams should be provided with higher quality and its description should be more complete.
13. The legends should be presented separately for different parts of the images.
14. The figures legend is not the place for discretion of statistical methods: e.g.: FIG 1: … Differences between means and significance of the treatments were analyzed using Prism 9 software and one-way ANOVA and Tukey test……

Mohammad Heiat: Associate Editor | **Revision** (0) 27 Jun 2021

Dear EIC,

Manuscript needs major revision.

Thanks

Seyed Moayed Alavian: EIC | **Revision** (0) 27 Jun 2021

Dear Authors,

Please follow the peer-review comments and submit a revision.

Regards,
EIC

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Dear Editor-in-Chief

We appreciate the valuable comments of reviewers. Based on the indicated comments of reviewers, we revised the manuscript entitled “Effect of Quercetin on the expression of NOXs and p-Smad3C in TGF-β activated hepatic stellate cell line LX-2” as below

Reviewer 1:

1- In the first expression of abbreviations, It would be better than the complete form of abbreviation was Witten first, and then the abbreviated form was presented in parenthesis; for example, instead of “HBV and HCV viral(Hepatitis Band hepatitis C), “write “Hepatitis B and hepatitis C virus (HBV and HCV).”

Answer: In-Page 2, Lines 2,3: The sentence was corrected.

2- The results showed that the expression of NOX1, NOX2, and NOX4 genes was significantly decreased during 24 hours in the presence of quercetin compared to the 139 TGF-β group (Figure 2. A, B, and C).” this decrease is in all concentrations or in some of them? Was this effect concentration dependent?

Answer: The effect observed in reducing gene expression depends on the concentration of quercetin. As you have seen, with increasing concentration, a more severe decrease in gene expression was observed, especially at a concentration of 100 µM of quercetin.

3- Indicate the source of quercetin used in this study

Answer: Quercetin was purchased from Sigma Aldrich

4- “Behind 1 hour,…” did you mean before the test? It would be better to rewrite this.

Answer: In-Page 5, Line 144: The sentence was corrected.

5- Some sentences are not comprehensive and need revision; like:

“TGFβ-activated pathways stay the main aim for the medical remedy yet.”

“Our results prove formerly reported findings of the quercetin inhibitory effect on HSCs activation and proliferation.”

“All NOX 190 isoforms are membrane-bound enzymes that rely on NADPH for their activity and the major source of ROS is generated when the flavin and haem-containing protein complex transfer electrons from cytosolic NADPH to molecular oxygen to produce O2 or H2O2.”

Answer: All of these sentences revised and highlighted based on reviewer suggestion

6- The last paragraph of discussion is incomplete. It would be better the paragraph ends with the important finding of this study.

Answer The last paragraph of the discussion revised and highlighted based on the reviewer suggestion

7- There are some similar publications, which were not considered in the manuscript; such as:

Hernández-Ortega LD, Alcántar-Díaz BE, Ruiz-Corro LA, Sandoval-Rodriguez A, Bueno-Topete M, Armendariz-Borunda J, Salazar-Montes AM. Quercetin improves hepatic fibrosis reducing hepatic stellate cells and regulating pro-fibrogenic/anti-fibrogenic molecules balance. J Gastroenterol Hepatol. 2012 Dec;27(12):1865-72. doi: 10.1111/j.1440-1746.2012.07262.x. PMID: 22989100.

• Li X, Jin Q, Yao Q, Xu B, Li Z, Tu C. Quercetin attenuates the activation of hepatic stellate cells and liver fibrosis in mice through modulation of HMGB1-TLR2/4-NF-κB signaling pathways. Toxicol Lett. 2016 Nov 2;261:1-12. doi: 10.1016/j.toxlet.2016.09.002. Epub 2016 Sep 4. PMID: 27601294.

• Eder Marcolin, Beatriz San-Miguel, Daniela Vallejo, Juliana Tieppo, Norma Marroni, Javier González-Gallego, María J. Tuñón, Quercetin Treatment Ameliorates Inflammation and Fibrosis in Mice with Nonalcoholic Steatohepatitis, The Journal of Nutrition, Volume 142, Issue 10, October 2012, Pages 1821–1828,

Answer: In Page 3, Lines 60-62: All of these articles were used in the introduction section and listed of references

Reviewer 2:

1- The text of the manuscript should be dramatically edited by a native speaker.

Answer: The whole text was reviewed and revised based on the reviewer's suggestion.

2- “Quercetin” should be written with capital word everywhere.

Answer: The word Quercetin. corrected in the whole text.

3- References have been carelessly written. e.g.: ([7,8), full stop before ≺ .(14). etc.

Answer: All references corrected in the whole text and reference list.

4- The manuscript structure should be exactly according to the guideline for authors.

Answer: Corrected based on the reviewer suggestion.

5- The scientific writing should be observed: e.g.: (2 in CO2 should be subscript/ Units per milliliter (U/mL) NOT units/ml, 24hours ≺ 24 h, 37 ° C ≺ 37 °C, 1.5 hours ≺ 90 min. etc.

Answer: This point corrected based on reviewer suggestion

6- Where has Quercetin been purchased?

Answer: Quercetin was purchased from Sigma Aldrich

7- The code of “IR.AJUMS.MEDICINE.REC.1398.031” has been recorded for another project??

“Investigation the effect of fibroblast growth factor 21 on smad3 carboxy region phosphorylation and gene expression of TGF-β in the cholesterol-treated LX2 cell line”

Answer: this point corrected based on the reviewer suggestion

8- The method is quite vague and confusing. Groups are not specified. The treatments performed with Quercetin and TGF-β and their sequence were reported completely disrupted and incomprehensible.

Answer: This point corrected based on the reviewer suggestion

9- Performed tests are not clear in regard of which groups and with what treatments.

Answer: This point corrected based on the reviewer suggestion

10- While clarifying and structuring the method and results, it is suggested to illustrate the working method.

Answer: This point corrected based on the reviewer suggestion

11- I couldn’t find any perspective in the discussion.

Answer: This point corrected based on the reviewer suggestion

12- Figures and diagrams should be provided with higher quality and its description should be more complete.

Answer:The figures have been replaced with the highest quality, and the description has been corrected.

13- The legends should be presented separately for different parts of the images.

Answer:Due to the limitation of sending images, we have merged them as much as possible.

14- The figures legend is not the place for discretion of statistical methods: e.g.: FIG 1: … Differences between means and significance of the treatments were analyzed using Prism 9 software and one-way ANOVA and Tukey test……

Answer: This point corrected based on the reviewer suggestion

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) — 7 Aug 2021

Dear editor,

Authors should use the same shape of “mL” and “µL“ all over the text

Regards

Mohammad Heiat: Reviewer | **Revision** (1) — 7 Aug 2021

Dear AE,

Manuscript can be published.

Regards

Mohammad Heiat: Associate Editor | **Revision** (1) — 7 Aug 2021

Dear EIC,

Please consider the revised manuscript for publication.

Regards,
AE

Seyed Moayed Alavian: EIC | **Revision** (1) — 8 Aug 2021

Dear Authors,

I am delighted to inform that your manuscript is accepted for publication.

Regards,
EIC