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 "**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.

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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.

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- 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
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

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Peer Review

International Journal of Cancer Management
Article DOI: https://doi.org/10.5812/ijcm-120224
Published in: International Journal of Cancer Management: 15(5) ; e120224

Peer Review Report for "Anti-proliferative and Apoptotic Effects of Valproic Acid on HeLa Cells"

Author(s): Nasser Hashemi, Mojtaba Yousefi zoshk , Amir Rashidian, Reza Laripour , Hossein Fasihi, Zahra Hami, Mohsen Chamanara

Review Timeline:

Submit Date:	3 Nov 2021
Revised Date:	8 May 2022
Accepted Date:	9 May 2022

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

11 Jan 2022

Dear Associate Editor,
Although there are some studies indicating the anti-tumor effects of Valproic acid on various cancer cell types, including HeLa cells, the novelty of the work of Hashemi et al. is associated with their investigating to clarify how valproic acid induces apoptosis in HeLa cells, and it is worthy. They conducted apoptosis and cell cycle assays, as well as real-time PCR, to confirm their findings. The paper is comprehensive. However, some minor revisions will improve the manuscript:
1. The advantages of using valproic acid were not fully clarified.
2. In the discussion section, the effects of other histone deacetylase inhibitors on the intrinsic pathway of apoptosis were not mentioned.
3. The authors also failed to clarify the limitations of their study.

REFEREE : Reviewer

12 Jan 2022

Dear AE,
The manuscript “Anti-proliferative and Apoptotic Effects of Valproic Acid on HeLa Cells” contains novel information regarding the potential anti-cancer effects of Valproic acid. The author tried to exhibit its effect on apoptosis and the cell cycle of HeLa cells. However, the manuscript needs minor revisions, as:
1. In the introduction section, add other histone deacetylase inhibitors with anti-cancer effects and explain how histone deacetylase inhibitors work.
2. Since you investigated the anti-cancer effects of Valproic acid on just HeLa cells, there is no need to add the cell type at the top of the charts.

REFEREE : Reviewer

18 Jan 2022

Dear AE,
In my opinion, this study is acceptable.
I have two comments for authors as follows:
1) Before using abbreviations, please write the complete form of some words in your sentences.
2) Please send your statistical equation, which was used in this study.

REFEREE : Associate Editor

24 Jan 2022

Dear EIC,
Based on the reviewers' comments, this manuscript needs some revisions.

REFEREE : EIC

24 Jan 2022

Dear author,
Please revise the manuscript according to the comments and resubmit. Thank you

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.

2022 ,26 ,01

Dear Editor-in-Chief;

Thank you very much for your letter enclosing the reviewer's comments on our manuscript. We found the comments very constructive which we are pleased to respond. Our detailed point-to-point response is attached. We did all our best to consider all comments raised by the reviewers, and revised our manuscript accordingly. All changes were indicated in the response section.

We hope that the revised manuscript meets the reviewer's comments, and facilitates consideration of our manuscript for publication in the **International Journal of Cancer Management.**

Yours Sincerely.

Comments and Responses:

Reviewer #1: In my opinion this study is acceptable.

I have two comments for authors as following below:

Comment #1: Before using abbreviations, please write the complete form of some words in your sentences.

Response #1: Thank you. We tried to use the complete form of all words in the main version of our manuscript. However, we added the missed word in the revised manuscript:

- "Valproic acid" was mentioned as "Valproic acid (VPA)": "Background section, Paragraph 2, Line 7

Comment #2: Please send your statistic equation which was used in this study.

Response #2: In the "Method" section and "Statistical analysis" subsection, the software (GraphPad Prism 8) and tests (one-way and two-way ANOVA tests followed by Tukey's multiple comparison test) that were used in the data analysis were mentioned.

Reviewer #2: Although there are some studies indicating the anti-tumor effects of Valproic acid on various cancer cell types, including HeLa cells, the novelty of the work of Hashemi et al. is associated with their investigating to clarify how valproic acid induces apoptosis in HeLa cells and it is worthy. They conducted apoptosis and cell cycle assays, as well as real-time PCR, to confirm their findings. The paper is comprehensive. However, some minor revisions will improve the manuscript:

Comment #1: The advantages of using valproic acid was not fully clarified.

Response #1: Thank you. In the “Background” section, we tried to clarify the anti-cancer effects of valproic acid with mention its effects on cell proliferation, autophagy, metastasis, angiogenesis, and apoptosis. Howere, we added its combinational advantage with other therapeutic agents. “Background” section, Paragraph 2, Lines 13-16

Comment #2: In the discussion section, the effects of other histone deacetylase inhibitors on the intrinsic pathway of apoptosis were not mentioned.

Response #2: Thank you. We added some studies according to your comment. “Disscusion” section, Paragraph 4, Lines 23-29

Comment #3: The authors also failed to clarify the limitations of their study.

Response #3: Thank you for your precise consideration. The limitations of our study were mentioned. “Disscusion” section, Paragraph 5, Lines 1-6

Reviewer #3: The manuscript “Anti-proliferative and Apoptotic Effects of Valproic Acid on HeLa Cells” contains novel information regarding the potential anti-cancer effects of Valproic acid. The author tried to exhibit its effect on apoptosis and cell cycle of HeLa cells. However, the manuscript needs minor revisions, as:

Comment #1: In the introduction section, add other histone deacetylase inhibitors with anti-cancer effects and how histone deacetylase inhibitors work?

Response #1: Thank you. We added some examples of histone deacetylase inhibitors and their mechanism of action. “Background” section, Paragraph 2, Lines 1-7

Comment #2: Since you investigated the anti-cancer effects of Valproic acid on just HeLa cells, there is no need to add cell type at the top of the charts.

Response #2: Thank you for your precise consideration. The cell type (“HeLa cells”) at the top of charts were deleted. Figures 2, 3E, and 4E.

OPEN PEER REVIEW

Revision (1)

REFEREE : Reviewer — 15 Feb 2022

Dear Associate Editor,
The requested comments have been addressed completely.

REFEREE : Reviewer — 4 Mar 2022

Dear AE,
I found that this manuscript is acceptable, because in my view, the results are accurate.
Sincerely

REFEREE : Reviewer — 10 Mar 2022

Dear Associate Editor,
The authors completely applied the comments.

REFEREE : Associate Editor — 15 Mar 2022

To EIC,
In my opinion, this manuscript is appropriate for publishing

REFEREE : EIC — 15 Mar 2022

Dear author,
The conclusion of your study is not obvious, please explain the conclusion more clear in the manuscript.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

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

2022 ,15 ,03

Dear Editor-in-Chief;

Thank you very much for your letter enclosing the reviewer's comments on our manuscript. We found that our previous responses to the reviewer's comments addressed completely. However, based on the "EIC Decision", the conclusion requires to be more clear. Our point-to-point response is attached. We did all our best to consider the comment raised by the EIC, and revised our manuscript accordingly. All changes were indicated in the response section.

We hope that the revised manuscript meets the EIC comment, and facilitates consideration of our manuscript for publication in the **International Journal of Cancer Management.**

Yours Sincerely.

Comments and Responses:

EIC Decision:

Dear author,

The conclusion of your study is not obvious, please explain the conclusion more clear in the manuscript.

Response: Thank you for your precise consideration. The conclusion of the study was changed to obviously explain the concluded results. The changes were marked with red. Discussion section, Paragraph 6.

OPEN PEER REVIEW

Revision (2)

REFEREE : EIC

22 Apr 2022

Dear authors,
For access to the review, please download the attached file and see the comments.
Also, all abbreviations used in the table should be introduced separately in the footnote table.

OPEN PEER REVIEW

Revision (3)

Reply to Reviewers

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

Dear Editor-in-Chief;

Thank you very much for your letter enclosing the reviewer's comments on our manuscript. We found that our previous responses to the reviewer's comments addressed completely. However, based on the "EIC Decision", the conclusion requires to be more clear. Our point-to-point response is attached. We did all our best to consider the comment raised by the EIC, and revised our manuscript accordingly. All changes were indicated in the response section.

We hope that the revised manuscript meets the EIC comment, and facilitates consideration of our manuscript for publication in the **International Journal of Cancer Management.**

Yours Sincerely.

Comments and Responses:

EIC Decision:

Dear authors,

For access to the review, please download the attached file and see the comments.

Also, all abbreviations used in the table should be introduced separately in the footnote table.

Response: Thank you. Regarding the comment in the manuscript about the statistical test, because the nature of the sample was different at different times, the use of one-way ANOVA method was preferred to repeated measure method. In fact, the cells were treated for 24 hours and analyzed at the end of time and were discarded, and new cells were cultured for 48 hours as well as for 72 hours and analyzed at the end of each time and were discarded.

Regarding table abbereviations, our manuscript has one table related to the primers of the genes. Since the genes are very familiar to biologists and medical science field experts, they do not require abbreviations.

OPEN PEER REVIEW

Revision (3)

REFEREE : EIC

9 May 2022

Dear Author,

This is my pleasure to announce you that your article has been accepted by the editorial committee after peer review in the International Journal of Cancer Management (IJCM). Hopefully, it will be published in future issues.