OPEN PEER REVIEW

Open Peer Review (OPR)

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
- 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

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

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Peer Review Report for "Synergistic Effects of Metformin-Lapatinib Combination on the Expression of Bax in SK-BR3 Cells"

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Review Timeline:

Submit Date: 3 Nov 2020
Revised Date: 2 Dec 2020
Accepted Date: 5 Dec 2020

Revision (0)

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

Seyyed Ali Mard: EIC | **Revision** (0) 3 Nov 2020

Dear Author,
Thanks for considering JJCMB to publish this valuable manuscript. You should mention the Ethical approval in it. It is mandatory for all research studies to mention ethical approval.
Thanks.

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.

Reply to Reviewers

Dear Editor

. Please mention the Ethical approval in it. It is mandatory for all research studies to mention ethical approval.

Ethical approval was obtained from the Ethics Committee at Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran. (grant number 97s51).

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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) 6 Nov 2020

Dear AE,
There are some comments which should be addressed by the author:
1- Please mention the list of groups exactly in the materials and methods instead of phrase different concentrations of metformin and lapatinib...
2- Please correct the value of 10 ml DMSO to 100µl DMSO in materials and methods.
3- In western blotting assay Is concentration of metformin and lapatinib for bax according to IC50 or not.please explain.
4- Similarity index is 37%.
Thanks.

REFEREE: Reviewer | **Revision** (1) 7 Nov 2020

Dear AE,
The methods are insufficient to conclude that: Metformin-Lapatinib combination induced apoptosis in SK-BR3 cell line. In fact, the ratio of Bax /Bcl2 expression must be determined to conclude the possible advantage of metformin-lapatinib combination for intervention in the breast cancer patients with overexpressing of HER2.
- Keywords: SR-BR3 must be written as SR-BR3 cell line.
- The Methods were not included enough for choosing the time and the dose of Met and Lap. The references must be mentioned.
- Figure 3: The units of Met and Lap concentrations are not defined.
- Figure 3,4: The differences between Met or Lap application alone or in combination is not determined. The significant difference between different groups must be shown by different letters (eg: *, **, ***).
With best wishes

REFEREE: Reviewer | **Revision** (1) 7 Nov 2020

Dear AE,
This manuscript needs to be revised in Methods and results
Method:
1. Mention the name, city, and country of companies provided/purchased antibodies and .....in methods
2. Mention ethical approval of the study in methods and a section in the last part of the

manuscript entitled "ethical approval" as a number/code . Actually, you got that number from your University/institute Ethical committee

Results, Figure

1. There is a discrepancy between the effect of Metformin at dose 20 in figure 2 (cell viability is about 60%) and 3 (cell viability is about 70%) . Did the study repeat it at a new experiment or not? Make it clear, please.
2. Figure 3 is confusing due to using "L" and "M" on X-axis. Please change it appropriately to avoid being confusing.
3. Why did the study used metformin at doses 20 and 40 and Lapatinib at doses 200 and 400 to evaluate their combination effect? Please define it in Method.
4. Mention reference for the dose and time of exposure of the studied variables, met and lap if possible?

Thanks.

Seyyed Ali Mard: Associate Editor | **Revision** (**1**) 7 Nov 2020

Dear EIC,

The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs minor revision.

Kind regards,

Seyyed Ali Mard: EIC | **Revision** (**1**) 7 Nov 2020

Dear Author,

Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (2)

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 indicted comments of reviewers, we revised the manuscript entitled “Synergistic Effects of Metformin-Lapatinib Combination on the expression of Bax in SK-BR3 Cells” as below

Reviewer 1:
dear author
1- please mention the list of group exactly in the materials and methods instead of phrase different concentration of metformin and lapatinib..

-This point corrected and highlighted based on the reviewer suggestion

.
2- please correct value of 10 ml DMSO to 100µl DMSO in materials and methods.

- Corrected and highlighted based on reviewer suggestion

3- In western blotting assay Is concentration of metformin and lapatinib for bax according to IC50 or not.please explain.

-For western blotting, the lower concentration of its related IC_{50} of each drug was used. The dose-dependent inhibitory effect of lapatinib and metformin on the cell viability was evaluated based on their IC_{50} and the results can be observed briefly in Figures 1 and 2, respectively. In the current study, the lowest effective concentrations of the two drugs were used for the measurement of BAX expression in order to reduce of their harmful side effects.

4- similarity index is 37%.

-The similarity was reduced approximately to < % 22 based on the iThenticate report

Reviewer 2:
Dear Authors

The methods are insufficient to conclude that: Metformin-Lapatinib combination induced apoptosis in SK-BR3 cell line. In fact the ratio of Bax /Bcl2 expresion must be determined to conclude the possible advantage of metformin-lapatinib combination for intervention in the breast cancer patients with overexpressing of HER2.

- Considering that the total cost of this student project was 40000000 rials, and considering that the price of each antibody is at least 80000000 rials, we didn't measure both proteins based on these limitations.

Keywords: SR-BR3 must be written as: SR-BR3 cell line.

-Corrected and highlighted based on reviewer suggestion

The Methods were not included enough for choosing the time and the dose of Met and Lap. The references must be mentioned.

--The references for the selection of dose and time of treatment are presented and highlighted in the text

Fig3: The units of Met and Lap concentrations are not defined.
-Corrected and highlighted based on reviewer suggestion

*Fig3,4: The differences between Met or Lap application alone or in combination is not determined. The significant difference between different groups must be shown by different letters (eg: *, **, ***).*

-Corrected and highlighted based on reviewer suggestion
With best wishes

Reviewer 3:
This manuscript needs to be revised in Methods and results
Method:
1. Mention the name, city, and country of companies provided/purchased antibodies and .....in methods

-Corrected and highlighted based on reviewer suggestion

2. Mention ethical approval of the study in methods and a section in the last part of manuscript entitled "ethical approval" as a number/code . Actually, you got that number from your University/institute Ethical committee

-Corrected and highlighted based on reviewer suggestion

Results, Figure
1. There is a discrepancy between the effect of Metformin at dose 20 in figure 2 (cell viability is about 60%) and 3 (cell viability is about 70%) . Did the study repeat it at a new experiment or not? Make it clear please

-I would like to inform you that these two experiments were performed completely separately with the same conditions.

2. Figure 3 is confusing due to using "L" and "M" in X-axis. Please change it appropriately to avoid being confusing.

- Unfortunately we can only use Lapatinib = L & Metformin = M in the caption. Because there is not enough space for it in the figure.

3. Why did the study used metformin at doses 20 and 40 and Lapatinab at doses 200 and 400 to evaluate their combination effect? Please define it in Method.

-These concentrations were selected based on their IC_{50} obtained from the MTT assay of each drug. This point was presented in the method section

4. Mention reference for the dose and time of exposure of the studied variables, met and lap if possible?

-The references for the selection of dose and time of treatment are presented and highlighted in the text

Yours Sincerely

Fatemeh Ahmapour

OPEN PEER REVIEW

Revision (2)

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

REFEREE: Associate Editor | **Revision** (2) 5 Dec 2020

Dear EIC,
I am satisfied with the corrections made, so it is acceptable.
Thanks.

Seyyed Ali Mard: EIC | **Revision** (2) 5 Dec 2020

Dear Author,
The correction was made by you are acceptable. Therefore, I am agreed to accept.
Thanks.