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OPEN PEER REVIEW

Malleatin A and B: New Premyrsine-Type Diterpenes from *Euphorbia malleata* with Cytotoxic Effects Against A2780 Wild and A2780 R-CIS Ovarian Cancer Cell Lines in Mono or Combination Treatment with Cisplatin

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About this report

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1 Original submission

2 comments · 24 Jun 2024 – 26 Jun 2024

Referee 1 Reviewer

MAJOR REVISION 24 Jun 2024

Dear authors,
1. As per the study's stated purpose and the Chou-Talalay formula, it is essential to maintain a constant concentration of cisplatin while incrementally increasing the Malleatin concentration. The calculation of the CI without this step remains unclear. Please provide further details on how you derived the CI values under these conditions.
2. The figures representing cell cytotoxicity results exhibit suboptimal quality. I recommend replacing them with higher-quality figures. Ensure that the new figures are well-labeled, clear, and accurately depict your experimental data.
3. The decision to use Malleatin at 50 micromolar for combination therapy warrants clarification. Please justify your choice despite this dose being lower than the IC50 in both cell lines. Consider factors such as toxicity, efficacy, and potential synergistic effects. Refer to existing literature or experimental evidence to support your rationale.
4. It is advisable to review the text for grammatical errors and unify the spelling of terms, such as "Malleatin A," throughout the document.

Associate Editor

MAJOR REVISION 26 Jun 2024

According to the reviewers' comments, in its current state, the manuscript is not acceptable for publication in IJPR and requires major revisions.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor

Regards for useful comments, the manuscript was revised, as well as its English and grammar improvement.

Reviewers' Comments:

Reviewer 1:
Unfortunately, the manuscript suffers from poor methodology, design, and writing. The manuscript in its current form does not reach a high-priority index for publication in IJPR. Therefore, it is not suitable for publication.

Response:

We tried to revise the manuscript. I think it is OK in its current form.

Reviewer 2:
1- The whole manuscript needs revision in English.

Response: The English grammar was corrected, and revised.
2- Scientific names should write in italic.

Response: The scientific names made italic.

3- Based on the title, the story of the introduction can be better and more fully rewritten.
4- Malleatin A, and B are isolated in this study, so their structures should be drawn in the results, not the introduction.

Response: The structure transferred to result section.

5- in the Plant Material, should be mentioned which part of plant was collected and used.

Response: It was aerial part which was added.

6-The separation process is written briefly and is not clear in some parts.

Response: Separation part was rewritten

Response:
7- Conclusion need so me revision, What did the authors conclude from the results of this work?
-

Reviewer 3:
Dear authors,
1. As per the study's stated purpose and the Chou-Talalay formula, it is essential to maintain a constant concentration of cisplatin while incrementally increasing the Malleatin concentration. The calculation of the CI without this step remains unclear. Please provide further details on how you derived the CI values under these conditions.

Response: we did again cytotoxicity assay of combination treatment of a fixed concentration of Cisplatin(IC50) while incrementally increasing the concentration of Malleatin A. as well as Combination treatment of a fixed concentration of Malleatin A (IC50) while incrementally increasing the concentration of Cisplatin in addition to single therapies. Then we calculate the CI and DRI according to Chou Talalay equations as follows:

$$CI = \frac{\text{IC50 of Cisplatin in combination}}{\text{IC50 of Cisplatin alone}} + \frac{\text{IC50 of maleatin in combination}}{\text{IC50 of maleatin alone}}$$

$$DRI = \frac{\text{IC50 of drug alone}}{\text{IC50 of drug in combination}}$$

I have deleted all the data processed by Compusyn software and calculated the CI and DRI from the above equations as per the recommendation of the referee. I have added only the data of combination therapies for cisplatin-resistant cells and deleted the ones for wild type.

2. The figures representing cell cytotoxicity results exhibit suboptimal quality. I recommend replacing them with higher-quality figures. Ensure that the new figures are well-labeled, clear, and accurately depict your experimental data.

Response: It was corrected.
3.1 The decision to use 50 micromolar of Malleatin for combination therapy warrants clarification. Please justify your choice despite this dose being lower than the IC50 in both cell lines..

Response: We did again the experiments with IC50 value Maleatine which is 62.5 micromolar in A2780 R-CIS cell lines, and replaced data. I have deleted the combination t3.2 herapy data for the wild cell line.

3.2 *Consider factors such as toxicity, efficacy, and potential synergistic effects. Refer to existing literature or experimental evidence to support your rationale.*

Response: I have added existing literature for toxicity, efficacy, and potential synergistic effects as recommended by referee at the end of discussion as follows:

"The cytotoxic effects of Malleatin A were consistent with previous findings on the cytotoxic properties of other myrsinane compounds. In a study by Abdolmohammadi et al, 13(17)-Epoxy-8,10(18)-Myrsinadiene polyester compounds demonstrated cytotoxicity against OVCAR-3 (HTB-161) and Caov-4 (CVCL_0202) ovarian cancer cells, with IC50 values ranging from 35 to 40 µM(15). Proliferin A, featuring a 13(17)-Epoxy-8-myrsinene structure isolated from *E. prolifera*, exhibited cytotoxicity against A2780 wild cells with an IC50 of 7.7 µM(16). Previous research has reported MDR activity in Myrsinane-type compounds. Some myrsinanes displayed MDR activity by inhibiting the rhodamine 123 efflux pump in mice lymphoma cells (15). Additionally, a study by Vasas et al. explored the synergistic activity of myrsinanes in combination therapy with doxorubicin(17).

"

4. It is advisable to review the text for grammatical errors and unify the spelling of terms, such as "Malleatin A," throughout the document.

Response: It was done.

Associate Editor's Comments:

Associate Editor 1:
According to the reviewers' comments, In current status, the manuscript is not acceptable for publication in IJPR and requires major revisions.

Response: The manuscript was revised completely according to the referee`s recommendations

2 Revision 1

2 comments · 6 Oct 2024 – 6 Oct 2024

Referee 1 Reviewer

MINOR REVISION 6 Oct 2024

In the text, it is stated that the research was conducted on the resistant cell line, as also depicted in Figure 2. However, the subtitle and the discussion section erroneously refer to the non-resistant cell line, which was not tested. This discrepancy needs to be corrected to maintain consistency and accuracy throughout the document.

Associate Editor

MINOR REVISION 6 Oct 2024

Thanks to the respected authors for the corrections to the manuscript. It needs very minor corrections and will be acceptable for publication.

3

Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor
Regards for useful comments, the manuscript was corrected as follows:

Reviewer 1:
In the text, it is stated that the research was conducted on the resistant cell line, as also depicted in Figure 2. However, the subtitle and the discussion section erroneously refer to the non-resistant cell line, which was not tested. This discrepancy needs to be corrected to maintain consistency and accuracy throughout the document.

Associate Editor's Comments:

Associate Editor 1:
Thanks to the respected authors for the corrections of the manuscript, it needs very minor corrections and will be acceptable for publication.

Response:

Wild cells were trated only as single therapy which are illustrated in figure 2. While combination therapy was done only on resistance cells (A2780 R-CIS cell lines). However according to reviewer's suggestion, we did following correction, and highlighted the text in yellow collor:

1-We checked and corrected "Combination Effect Analysis" section in material and method.

2- We checked and corrected discussion to increase emphasis on resistant cells.

3- We checked and corrected caption of Figure 2.

- All the correction were highlighted in the text.

3 Revision 2

0 comments

No public comments in this round.