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OPEN PEER REVIEW

A Lead Target Molecule for Excisional Wound Healing: Trypthantrin Compound

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 17 Jun 2022 – 28 Jun 2022

Referee 1 Reviewer

MINOR REVISION 17 Jun 2022

Subject
1-The above article was reviewed. This study of the compound as a lead compound for wound healing is sufficiently innovative in the field of wound healing therapy.
Title
2-In the title, “A Novel Target Molecule from Excisional Wound Healing: Trypthantrin Compound”, the compound is no longer novel. Please correct the sentence.
For example, you can use “an indoloquinazoline alkaloid for Excisional Wound Healing: Trypthantrin Compound”
Or “A Lead Target Molecule from Excisional Wound Healing: Trypthantrin Compound”.
3-In addition, please change the title so that it better reflects the methodology and the research content.

Abstract
4-In the abstract, please use keywords from MESH. You can use the following site:
https://www.ncbi.nlm.nih.gov/mesh/

Introduction

5-Explain the Trypthantrin compound in terms of its chemical structure as an indoloquinazoline alkaloid.
6-Studies related to this compound should be presented in relation to the relevant research.
7-Mention the natural source of Trypthantrin from the fungus and also the approach to its synthesis.
8-Give the reason and rationale for choosing this compound.

Materials And Methods
9- Please add the source of the compound. Was it purchased from sigma or elsewhere?

Discussion
10-The relationship between the observed effects and other studies on this compound should be mentioned.
11-In addition, given the antiangiogenic effects observed with this drug and the relevant cytotoxic effects, how are the wound healing effects explained?
12-Pharmacological research on this compound that agrees with or contradicts the observed effects should be discussed in the discussion section.

Referee 2 Reviewer

MINOR REVISION 28 Jun 2022

"A New Target Molecule from Excisional Wound Healing: Triptantrin
Compound "" has been designed quite nicely and has been studied experimentally in an appropriate way.
However, if a few points are addressed, it would be suitable for publication in your journal.
The expression of TGF-β, IL-1, and TNF-α, listed as the 1st keyword, was neither included in the study nor discussed. Therefore, it would be appropriate to remove this keyword.
In the description of the second experimental method, doses and group descriptions were not specified. It would be appropriate to specify the doses and describe the groups here.
3. It must be because it was uploaded twice: the figures and their descriptions seem to have gotten mixed up (especially fig 4.).

Muhammed Yayla Reviewer

MINOR REVISION 28 Jun 2022

Dear Editor,
Wound healing was an important health problem in the past and will be in the future. Therefore, experiments conducted to improve the wound healing process are very useful and informative for researchers. In this study, the author presents the information clearly and writes well.
However, some revisions are needed.
In the keywords, tnf or other parameters should be excluded.
In the methods: the groups should be explained clearly; there is no information about them.
What do you mean by control? Healthy, sham, or positive control?
Please add dosage information and a supporting reference.
Please clarify the statistical analysis and add this information to the legends as well.
Please add a scoring table for the pathology section.

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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;

Thank you very much for your kind interest on our manuscript Manuscript ID 127665 entitled " **A Novel Target Molecule for Excisional Wound Healing: Trypthantrin Compound**. We thank you and the referee's for constructive comments and recommendations which will help to improve quality of the paper. Following the referee's valuable comments, we have revised our manuscript. You can find our answers for referee listed below. Also you can see that the corrections made for referee's comments highlighted in green (Reviewer 1), yellow (Reviewer 2), blue (Reviewer 3) and pink (Reviewer 4).

Reviewer #1: Dear Editor wound healing was an important health problem in the past and be future. So experiments which conducted increased wound healing process is so effective and readable for researcher. In this study, author clearly stated and well writing.

Query 1: However some revisions need in the key words, TNF or other parameters should be excluded. In the methods: groups should be explain clearly, there is no information.
Response 1: It was made corrections that the reviewer suggested. That is to say, it was removed TNF-α from the keywords section.

Query 2: What do you mean control? Healthy or sham or positive control?
Response 2: It was used healthy control group in this study. It was made explained related to groups names and it was added in the material and methods section.

Query 3: Please add dosage information and reference supporting you. Please clarify statistical analysis and should be add legends also.
Response 3: We were given information about doses in the material and methods and we added new literature related to TRP doses. We added these information analysis sections and legends sections.

Query 4: Please add scoring table for pathology section.
Response 4: We added a scoring table in the pathology section.

Reviewer #2: "A New Target Molecule from Excisional Wound Healing: Triptantrin Compound "" has been designed quite nicely and has been studied experimentally in an appropriate way. But if a few points can be edited, they are suitable for publication in your

journal.

Query 1: TGF-β, IL-1, TNF-α expressions as the 1st keyword were neither included in the study nor discussed. Therefore, it would be appropriate to remove it from here.

Response 1: We removed parameters such as TGF-β, IL-1 and TNF-α from the keywords. (We colored it green, because the 1st reviewer gave the same suggestion.)

Query 2: In the description of the second experimental method, doses and group descriptions were not specified. It would be appropriate to specify and explain here.

Response 2: We were given information about doses in the material and methods and we added new literature related to TRP doses. (We colored it green, because the 1st reviewer gave the same suggestion)

Query 3: It must be because it was uploaded twice, as if the figures and their descriptions got mixed up. (especially fig 4.)

Response 3: It was made correction related to figures.

Reviewer # 3: The above article was reviewed. This research is sufficiently innovative in the field of wound healing therapy study on the composition as a lead compound for wound healing.

Query 1: In the title: A Novel Target Molecule from Excisional Wound Healing: Trypthantrin Compound", It is not yet a novel compound anymore. Please correct the sentence. For example, you can use "an indoloquinazoline alkaloid for Excisional Wound Healing: Trypthantrin Compound" Or "A Lead Target Molecule from Excisional Wound Healing: Trypthantrin Compound". In addition please change the title in such a way that it reflects more the methodolog and the research content.

Response 1: It was made correction that the reviewer suggested. That is to say, it was corrected the title of the article.

Query 2: In the abstract please uses Keywords from MESH? You can use the following site: https://www.ncbi.nlm.nih.gov/mesh/

Response 2: It was made that reviewer suggested.

Query 3: Explain the Trypthantrin compound in terms of its chemical structure as an indolquinazoline alkaloid.

Response 3: Section has been added to the introduction part of the article this paragraph ‘The natural product tryptanthrin (indolo[2,1-b]quinazoline-6,12-dione, Figure 1) is a weakly basic alkaloid. This bright yellow compound consists of a quinazoline ring fused to an indole moiety with carbonyl groups in the 6- and 12-positions. The name tryptanthrin is derived from the observation that this compound is produced by the yeast Candida lipolytica when grown in L-tryptophan-containing medium’.

Query 4: Studies related to this compound should be given in relation to the relevant research.

Response 4: It was added studies related to TRP.

Query 5: Mention the natural source of Trypthantrin from the fungus and also its synthesis approach.

Response 5: It added that information in the manuscript. **‘**The name TRP is derived from the observation that this compound is produced by the yeast Candida lipolytica when grown in an L-tryptophan-containing medium’. TRP derivatives which are natural as well as chemically synthesized has been observed and bear a different functional group at the sixth position of a common indolo[2,1-b]quinazoline core. It was first isolated from the culture of yeast Candida lipolytic and later on isolated from the Chinese medicinal plant Strobilanthes cusia Kuntze. It can be also obtained from other plant species (Isatis, Clanthe, Wrightia, Couroupota).

Query 6: Give the reason and rationale for choosing this compound?

Response 6: It was added these sentences in the manuscript. The therapeutic agent to be used in wound healing is necessary to have antimicrobial, cell proliferation and antioxidant properties. The related literature review has pointed out that TRP has antimicrobial, antioxidant and anti-inflammatory properties. Therefore it was chosen this compound for wound healing.

Query 7: Please add the source of the compound? It is purchased from sigma or elsewhere?

Answer 7: It was purchased from BLDpharma company.

Query 8: The relationship between the observed effects and other studies on this compound should be mentioned.

Response 8: It has been added discussion section of in the manuscript these senteneces ‘Many studies have revealed that TRP has many biological and pharmacological activities such as antimicrobial, anti-inflammatory, anti-allergic, anti-cancer, anti-protozoal, and antiallergic ones. Also, in the studies that were done, compound coated with the TRP has been shown that has anti-inflammatory, antimicrobial, wound healing, anti-tumor, anti-allergic, and other biological activities. In addition, according to other a study, indigo promotes wound closure in human keratinocyte HaCaT cells.’

Query 9: In addition, according to the antiangiogenic effects seen from this drug and according to the relevant cytotoxic effects, how the wound healing effects are explained?

Response 9: Dear reviewer thank you very much about show this point of this drug. As we know endothelial cells senescence and antiangiogenic are associated with the onset and progression of impaired wound healing. Some antiangiogenic drugs used in cancer may use the wound healing process. At the onset of wound healing, insufficient angiogenesis should stop or control. The antiangiogenic effect may useful to control insufficient angiogenesis.

Query 10: Pharmacological research which is done on this compound in the agreement or against observed effects should be discussed in the discussion section.

Response 10: It was added pharmacological research in the discussion of the manuscript.

Reviewer 4:I have reviewed your manuscript entitled “A Novel Target Molecule from Excisional Wound Healing: Triptantrin Compound”. Considering the known antimicrobial and anti-inflammatory effects of Trypthantrin (TRP), an indole quinazoline alkaloid, you tested the different doses of TRP on the excisional wound (EW) model. You found that TRP increased wound healing and did not leave a scar after the 14th day. I see that your results are important for the literature. However, there are some minor issues that you need to revise for this paper.

Query 1: The title “A Novel Target Molecule from Excisional Wound Healing: Triptantrin Compound” needs to be revised; I suggest authors use “for” instead of the “from” in the title.

Response 1: It was made correction that the reviewer suggested. That is to say, it was corrected the title of the article. (We colored it blue, because the 3th reviewer gave the same suggestion)

Query 2: In the material and method section, the doses used for TRP were not given. Then please provide those details and give the reference of the studies in which the selected doses were determined.
Response 2: We were given information about doses in the material and methods and we added new literature related to TRP doses. But we couldn't find doi number of some literature. (We colored it green, because the 1st reviewer gave the same suggestion)

Query 3: The study groups should be specified in the material-method section, and detailed information about each group should be given.
Response 3: It has been added this sentence in the material-method section 'It were divided 5 groups as healthy, excisional wound (EW), EW+ 1 mg/kg, EW+2.5 mg/kg, EW+5 mg/kg'.

Query 4: Abbreviations need to be written long when it was reported the first time in the manuscript. Check the manuscript for acronyms and be consistent in use.
Response 4: It was made correction related to abbreviations that the reviewer suggested.

Query 5: Figure 4, the figure legend does not provide what means "#" . Then please also provide the meaning of that in the legend.
Response 5: The meaning of the # symbol is compared to the control group. (# $p<0.05$, ## $p<0.01$, ### $p<0.001$). This explanation was added to the legend section.

Query 6: I see there are some minor problems with the references. Please double-check the references and edit them in accordance with the journal guidelines.
Response 6: It was made correction related to references that the reviewer suggested.

2 Revision 1

2 comments · 13 Jul 2022 – 17 Jul 2022

Referee 3 Reviewer

ACCEPT 13 Jul 2022

Necessary revisions have been done.
Acceptable

Irfan Cinar Reviewer

ACCEPT 17 Jul 2022

The author and his team have made the desired corrections in an appropriate format. Therefore, the relevant study can be published in your journal.