OPEN PEER REVIEW

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- 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

Jundishapur Journal of Natural Pharmaceutical Products
Article DOI: 10.5812/jjnpp.112353
Published in: Jundishapur Journal of Natural Pharmaceutical Products: 16(4); e112353

Peer Review Report for "Red Ginger Oil Affects COX-2 and NMDAR Expression During Inflammatory- or Neuropathy-Induced Chronic Pain in Mice"

Author(s): Fifteen Aprila Fajrin, Elsa Dwi Hidayanti, Nila Lutfiatul Khoiroh, Gati Sulistyaningrum, Nidia Imandasari, Afifah Afifah, Sugi Hartono

Review Timeline:

Submit Date: 21 Dec 2020
Revised Date: 3 Feb 2021
Accepted Date: 4 Feb 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) — 22 Dec 2020

Dear AE,
The following points should be considered by the authors before making a final decision on the manuscript:
1- You should allude to the “all” methods that you performed in the study at the “Methods” sub-section of the “Abstract” section.
2- There is the main controversy regarding the statistical presentation of data in the article; you presented data as “mean ± SEM” while you evaluated the issues in the limited sample size!!! You should present data as “mean ± SD”. Please correct the issue.
3- You should explain the “limitations” of the study in the “Discussion” section.
4- You should allocate separate sections to “Availability of data” and “Ethics approval” [with related approval number(s)] after the “Conflicts of Interest” section and explain related issues in the sections.
Thanks.

REFEREE: Reviewer | **Revision** (0) — 1 Jan 2021

Dear AE,

The authors should revise the manuscript according to the note.
Note: Some expanded and porrect interpretations about the chronic pain model or induction of chronic pain for assessing the effect of Red Ginger Oil, by persisting on the issue in the study of other researchers.
Thanks.

REFEREE: Reviewer | **Revision** (0) 16 Jan 2021

Dear AE,
In this study, the authors examined the effect of Red Ginger Oil (RGO) on cyclooxygenase (COX)-2 and the N-methyl-D-aspartate receptor (NMDAR) using inflammatory- or neuropathy-induced chronic pain in mice. They concluded that RGO administration diminished hyperalgesia in chronic pain models through inhibition of COX-2 and NMDAR2B. This manuscript is well organized. Nevertheless, there are some issues that should be addressed by the authors before further processing:
1- Why are different doses used? What is the logic behind the dosage you picked?
2- In Figure 1, there is a spelling mistake that needs to be corrected ("spinal cord dan brain" should be "spinal cord and brain").
3- Explain the limitations of the procedure.
4- The conclusion should be clearly explained.
5- The English language needs correction and improvement; edited by a native English speaker.
Thanks.

REFEREE: Associate Editor | **Revision** (0) 22 Jan 2021

Dear EIC,
This article still needs major revision.
Thanks.

REFEREE: EIC | **Revision** (0) 22 Jan 2021

Dear Authors,
Review results of your manuscript are now completed. Please correct the manuscript according to their comments and upload the revised manuscript with a point-to-point answer to the reviewers' questions; highlight changes in the revised manuscript.
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.

January 27th, 2021

Dear Editor in Chief of Jundishapur Journal of Natural Pharmaceutical Products

I am re-submitting a manuscript for consideration of publication in Jundishapur Journal of Natural Pharmaceutical Products. The manuscript is ID. 112353 entitled “Red Ginger Oil Affects COX-2 and NMDAR Expression during Inflammatory- or Neuropathy-Induced Chronic Pain in Mice” I included the answers to the reviewer’s comments in a separate document. Thank you very much for your consideration.

Yours Sincerely,

Ref: 112353
Title: Red Ginger Oil Affects COX-2 and NMDAR Expression during Inflammatory- or Neuropathy-Induced Chronic Pain in Mice
Journal: Jundishapur Journal of Natural Pharmaceutical Products

Answers to Reviewers' comments

Reviewer No. 1

1. Comment 1.

Some expanded and porrect interpretations about the chronic pain model or induction of chronic pain for assessing the effect of Red Ginger Oil, by persisting on the issue in the study of other researchers.

Answer 1.

Thank you very much for your valuable comment. Our study was the first report of RGO in suppressing the expression of COX and NMDA in chronic pain after CFA and PSNL induction. The study of the RGO effect was very limited. Almost all research was conducted in ginger oil, not red ginger oil. We found that previously ginger oil could diminish hyperalgesia in arthritis pain (Funk et al., 2016). Other research also found the effectiveness of ginger oil in CFA-induced chronic pain (Jia et al., 2011). We have included the correction in our revised manuscript.

Reviewer No. 2

1. Comment 1.

You should allude to the "all" methods that you performed in the study at the "Methods" sub-section of the "Abstract" section.

Answer 1.

Thank you very much for your comment and kind response. We have included the correction in our revised manuscript.

2. Comment 2.

There is the main controversy regarding the statistical presentation of data in the article; you presented data as "mean ± SEM" while you evaluated the issues in the limited sample size!!! You should present data as "mean ± SD". Please correct the issue.

Answer 2.

Thank you very much for your comment and kind response. We have included the correction in our revised manuscript.

3. Comment 3.

You should explain the "limitations" of the study in the "Discussion" section.

Answer 3.

Thank you very much for your comment. In this study, we did not examine the exact mechanism associated with the RGO effect in improving the morphology of spinal cord's mice, as our limitation. Another limitation in our research was the expression of NMDAR2A not demonstrated in both models, inflammatory and neuropathy pain. Therefore, the relationship between NMDA subunit NR2A and NR2B in the context of chronic pain requires further study. We also have included the correction in our revised manuscript.

4. Comment 4.

You should allocate separate sections to "Availability of data" and "Ethics approval" [with related approval number(s)] after the "Conflicts of Interest" section and explain associated issues at the sections.

Answer 4.
Thank you very much for your comment and kind response. We have included the correction in our revised manuscript.

Reviewer 3

1. Comment 1.
Why are different doses used? What is the logic behind the dosage you picked?

Answer 1.
Thank you very much for your comment and kind response. We used different doses to observe the correlation between doses of RGO vs. the effect of RGO in inflammatory- or neuropathy-induced chronic pain, especially in inhibiting the COX and NMDA expression. The result of this correlation was shown in Fig 6 – 10. The dose's choice was because, in our previous study, these doses showed a gradual effect to minimize hyperalgesia in inflammatory- or neuropathy-induced chronic pain using a hot-plate test (Fajrin et al., 2019).

2. Comment 2.
In Figure 1, there is a spelling mistake that needs to be corrected ("spinal cord dan brain" should be "spinal cord and brain").

Answer 2.
Thank you very much for your careful reading. We have corrected the mistake in our revised manuscript.

3. Comment 3.
Explain the limitations of the procedure.

Answer 3.
Thank you very much for your comment and kind response. . In this study, we did not examine the exact mechanism associated with the RGO effect in improving the morphology of spinal cord’s mice, as our limitation. Another limitation in our research was the expression of NMDAR2A not demonstrated in both models, inflammatory and neuropathy pain. Therefore, the relationship between NMDA subunit NR2A and NR2B in the context of chronic pain requires further study. We also have included the correction in our revised manuscript.

4. Comment 3.
The conclusion should be clearly explained.

Answer 3.
Thank you very much for your comment and suggestion. We already changed the sentences and included the correction in our revised manuscript.

5. Comment 3.
The English language needs correction and improvement; edited by a native English speaker.

Answer 3.

Thank you very much for your comment and kind response. We have included the correction in our revised manuscript and proofread the manuscript before re-submission.



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CERTIFICATE OF EDITING

This is to certify that the paper titled **Red Ginger Oil Administration Changed The Expression of Cyclooxygenase (Affects COX)–2 and N-Methyl-D-Aspartate Receptor (NMDAR) after Expression during Inflammatory and- or Neuropathy-inducedInduced Chronic Pain in Mice.** commissioned to us by **Fifteen Aprila Fajrin** has been edited for English language, grammar, punctuation, and spelling by Enago, the editing brand of Crimson Interactive Inc. under Substantive Editing.

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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) 31 Jan 2021

Dear AE,
Comment for the author:
- According to my previous “comment number 4”, please allocate a separate section to “Data availability” after “Ethical Approval” section and explain related issues at the section.
Thanks.

REFEREE: Associate Editor | **Revision** (1) 31 Jan 2021

Dear EIC,
The authors should consider the reviewers' comments. They have raised points that require consideration and revision of the manuscript before it is suitable for publication.
THanks.

REFEREE: EIC | **Revision** (1) 31 Jan 2021

Dear Authors,
Please consider the final remarks of the reviewer's comment. Highlight the required changes in the revised manuscript.
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.

Feb 2nd, 2021

Dear Editor in Chief of Jundishapur Journal of Natural Pharmaceutical Products

I am re-submitting a manuscript for consideration of publication in Jundishapur Journal of Natural Pharmaceutical Products. The manuscript is ID. 112353 entitled “Red Ginger Oil Affects COX-2 and NMDAR Expression during Inflammatory- or Neuropathy-Induced Chronic Pain in Mice” I included the answers to the reviewer’s comments in a separate document. Thank you very much for your consideration.

Yours Sincerely,

Ref: 112353
Title: Red Ginger Oil Affects COX-2 and NMDAR Expression during Inflammatory- or Neuropathy-Induced Chronic Pain in Mice
Journal: Jundishapur Journal of Natural Pharmaceutical Products

Answers to Reviewers' comments
Reviewer No. 1

1. Comment 1.
According to my previous "comment number 4", please allocate a separate section to "Data availability" after "Ethical Approval" section and explain related issues at the section

Answer 1.
Thank you very much for your comment and kind response. We have included the correction in our revised manuscript.

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) 4 Feb 2021

Dear EIC,
The authors have made the minimum changes to render the paper accepted for publication.
Thanks.

REFEREE: EIC | **Revision** (2) 4 Feb 2021

Dear Authors,
I am glad to inform you of acceptance of your article in the current form.
Kind regards,