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OPEN PEER REVIEW

Pomegranate Seed Oil Boosts Memory by Reducing Amyloid Plaques and Restoring Neuronal Density in Alzheimer's Model Rats

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1 Original submission

1 comment · 29 Dec 2024

Associate Editor

MAJOR REVISION 29 Dec 2024

Thank you for submitting your manuscript to JJNPP.
Please revise the manuscript and submit a point-by-point response to the reviewers' comments and concerns.

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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 of Jundishapur Journal of Natural Pharmaceutical Products

Thank you very much for your prompt attention to our manuscript. We are very pleased to receive your positive message and we appreciate the opportunity to be able to respond to the comments of your respectful reviewers. We hope that the respectful reviewers will be satisfied by our responses.

Response to respected Reviewer:

Reviewer 1:
1. The text has errors in terms of writing and grammar that need to be corrected.

Thank you for your feedback. The text has now been thoroughly reviewed and revised to address all grammatical and spelling issues.

2. The normal saline dosage is incorrect.

In our study, the dose of normal saline was used based on the following study:

Boroushaki MT, Asadpour E, Sadeghnia HR, et al. Effect of pomegranate seed oil against gentamicin -induced nephrotoxicity in rat. J Food Sci Technol. 2014;51(11):3510–3514.

3. Why have only two doses been used, while pharmacological studies should use three doses or more?

Our research was a study on the effect of pomegranate seed oil on memory and hippocampal tissue and was not a purely pharmacological study. The dose of pomegranate seed oil was determined based on the following study:

Boroushaki MT, Asadpour E, Sadeghnia HR, et al. Effect of pomegranate seed oil against gentamicin -induced nephrotoxicity in rat. J Food Sci Technol. 2014;51(11):3510–3514.

4. The comparisons in the graphs are not complete.

Comparisons that did not show significant differences were not included in the graphs, and only significant differences between groups were included in the graphs.

5. Why is 4% paraformaldehyde used for fixation? What advantages does it have over other fixatives?

4% paraformaldehyde is commonly used for fixation because it preserves the fine structure of neural tissues while maintaining antigenicity for immunostaining. It provides effective cross-linking of proteins, leading to clearer imaging, reduced background noise, and better morphological preservation of neuronal structures.

6. How is pomegranate seed oil prepared?

The pomegranate seed oil was purchased from Golnar Golestan Company (Gonbadkavos, Iran).

Reviewer 2:
Thanks to the authors,

1-The introduction justifies the use of natural products but could strengthen why pomegranate seed oil specifically was chosen over other polyphenol-rich oils.
Thank you for your feedback. We have revised the introduction to better justify the selection of pomegranate seed oil over other polyphenol-rich oils by highlighting its unique composition and established neuroprotective effects. The text has been updated accordingly.

2-The introduction mentions amyloid plaque reduction but doesn't cite specific pathways or mechanisms by which pomegranate achieves this. Could this be elaborated?

Thank you for your feedback. The Text has been changed accordingly.

3-Some references are older. Could the manuscript benefit from citing more recent reviews or primary studies from the last 5 years?

Thank you for your feedback. We have updated the manuscript to include more recent reviews and primary studies from the last five years as much as possible.

4-Why was scopolamine chosen as the model? It would be helpful to discuss briefly its relevance to Alzheimer's pathophysiology.

Thank you for your feedback. We have updated the introduction to include the role of scopolamine in Alzheimer's pathophysiology, highlighting its relevance as a model.

5- How does pomegranate seed oil compare to FDA-approved treatments for Alzheimer's disease regarding its potential mechanism?
Thank you for your insightful comment. While FDA-approved treatments for Alzheimer's disease, primarily focus on symptomatic relief, pomegranate seed oil (PSO) offers a

different therapeutic approach. As mentioned in introduction, Pomegranate extract has shown significant bioactive properties, including anti-inflammatory and antioxidant effects (1). These properties can mitigate oxidative stress and neuroinflammation, which are key contributors to AD pathogenesis (2).

1. Ullah A, Khan A, Ahmed S, et al. A review of pomegranate supplementation: A promising remedial avenue for Alzheimer's disease. Heliyon. 2023;**9**(11):e22483. [PubMed ID: 38074891]. https://doi.org/10.1016/j.heliyon.2023.e22483.
2. Huang WJ, Zhang X, Chen WW. Role of oxidative stress in Alzheimer's disease. Biomed Rep. 2016;**4**(5):519-22. [PubMed ID: 27123241]. https://doi.org/10.3892/br.2016.630.

6-What is the rationale for choosing the doses (0.32 and 0.64 mg/kg)? Were pilot tests conducted to select these doses, or did the authors make this choice based on previous studies?

The aim of the study was to investigate the protective and therapeutic effects of two doses. Pilot tests were not done in this study and these doses were selected based on following study:

Boroushaki MT, Asadpour E, Sadeghnia HR, et al. Effect of pomegranate seed oil against gentamicin -induced nephrotoxicity in rat. J Food Sci Technol. 2014;51(11):3510–3514.

7-Could a more detailed discussion of the biochemical or molecular pathways involved in plaque reduction be included?
Thank you for your comment. We have expanded the discussion to include as much detail as possible on the biochemical and molecular pathways involved in plaque reduction, based on the current literature. However, we note that the accurate molecular mechanisms remain unclear and require further investigation.

8- The limitations are not explicitly discussed. For example, how do the rat findings translate to human Alzheimer’s disease?
Thank you for your comment. We agree that all model studies need clinical trials to confirm their findings. The study's limitations have been added to the text.
9- Concrete suggestions for future studies could benefit the discussion, including human trials or mechanistic explorations.

Many thanks, its mentioned in manuscript.
Reviewer 3:

This paper deals with " Pomegranate Seed Oil Improved Memory Through Reducing Amyloid Plaques and Enhancing Hippocampal neuronal density in Alzheimer’s Disease

Model Rats" I offer a minor revision and need a detailed clarification. This is an interesting paper and well revealed. I severely recommend accepting the recent paper in the “Jundishapur Journal of Natural Pharmaceutical Products”. If it is accepted, it will have an excellent role in increasing the citation and the Impact Factor of “Jundishapur Journal of Natural Pharmaceutical Products” in the future. A minor revision should be addressed by the researchers as follows:

1. Title must be presented in a good form, so that it attracts the reader’s attention.

Thanks a lot. This is revised as you kindly suggested.

2. Authorship contribution must be highlighted.

Many thanks, its highlighted at the end of the manuscript.

3. Suitable reference should be cited in therapeutic activity.

Thank you so much; it has been revised as suggested.

4. Bold the aim at the beginning of the Abstract.

The study aims are written as objectives in the abstract section.

5. More data must be presented.

Our data are only those included in this manuscript and there is no other data.

6. Aim of the introduction hasn’t been presented.

Thank you so much; it has been revised.

7. Methods and materials (Experimental) must be presented in details.

All details have been provided in the Methods section with references.

8. Statistical analysis must be presented in details.

The statistical analysis was modified as follows:

The data distribution was not normal, so the Kruskal-Wallis’s test was done followed by Dunn's multiple comparisons test.

9. Correct grammatical error and typo error.

Thank you for your feedback. The text has now been thoroughly reviewed and revised to address all grammatical and spelling issues.

10. Increase the resolution of Figures.

The resolution of Figures is 900 dpi.

11. Other therapeutic effects may be investigated.

Thank you for your suggestion. Our study was designed to achieve specific aims, as reported. We appreciate your input and recognize the potential for future investigations into other therapeutic effects.

12. The results are well presented, but no discussion and comparison with similar results has been done.

Thank you for your suggestion. In paragraphs 1, 5 and 8, comparison with similar results were done.

13. Conclusion is weak, please progress it.

Thank you so much; it has been revised.

14. Mention the limitation of the study before the References.

Thank you so much; it has been added.

15. Please check the references according to the journal format.

Thank you so much; it has been revised. PubMed ID and doi were added.

2 Revision 1

1 comment · 5 Mar 2025

Associate Editor

ACCEPT 5 Mar 2025

I am glad to inform you that your manuscript has been accepted for publication in this journal. We hope the authors will consider JJNPP as a journal for their future manuscripts.

I would also greatly appreciate the authors' contribution and the time they spend reviewing manuscripts for this journal. Without the dedication of reviewers like you, it would be impossible to manage an efficient peer review process and maintain the high standards necessary for a successful journal.