

OPEN PEER REVIEW

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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.

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Jundishapur Journal of Natural Pharmaceutical Products

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Peer Review Report for "Anti-inflammatory and Antioxidant Effects of Ketotifen Against Gentamicin-Induced Hepatotoxicity Through NF- κ B Pathway Suppression"

Author(s): Mahdieh Sadat Badiie, Masoud Mahdavinia, Ali Hasan Rahmani, Ehsan Saburi, Fereshtesadat Fakhredini, Nooshin Ghadiri

Review Timeline:

Submit Date:	11 May 2025
Revised Date:	15 Jul 2025
Accepted Date:	15 Jul 2025

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

13 May 2025

with respect and value for the strengths of the study, following items require re evaluation.

total sample size of the five groups of study is thirty-seven.(6+10+7+14).

sample size calculation should be mentioned.

some conclusion appear overstated given the study"s limitations such as small sample size and short follow up.

conclusion could be structured into future research needs and be expanded to design similar research in animal and human .

limitation must be considered.

REFeree : Reviewer

16 May 2025

The manuscript titled "Ketotifen modulates the effects of gentamicin-induced hepatotoxicity in mice by suppressing inflammation, oxidative stress, and the NF- κ B signaling pathway" is interesting. I recommend its publication in the Jundishapur Journal of Natural Pharmaceutical Products but several minor revisions must be addressed before reconsideration.

1. The article contains numerous grammatical issues and requires significant editing and rewriting by a native English speaker. Many sentences are too long and confusing. The authors should rewrite them and break down large sentences into shorter, more understandable ones. For example this sentence "Due to the high volume of biological changes in the liver and the metabolism of substances and drugs and sometimes their conversion to active metabolites, if the detoxification capacity of the liver is reduced, complications such as fatty liver, ductal damage, vascular disorders, cholestasis, and cirrhosis occur ". The author may find many sentences in the manuscript that are confusing and need clarification. The author should consider rewriting the entire introduction, as it currently lacks coherence and uniformity.
2. In both the abstract and the Experimental Design section, the authors mention six groups; however, only five groups are described in the manuscript. Additionally, there is inconsistency in the number of mice used per group (n = 6–10). Could the authors clarify the reason for this discrepancy?
3. The group names used by the authors in the text and figures are not appropriate or sufficiently descriptive. The authors should revise the group names for clarity and consistency. For example, they could use names such as "Gen-Ket2" and "Gen-Ket3".
4. The authors should specify the dose of Gen used in the GEN-treated groups that received ketofol (KTF) at 2 and 3 mg/kg.
5. There is no need to include the CAS numbers in the Materials section.
6. The figure 1 is too confusing and should be redesigned to improve clarity and effectiveness.
7. There are many patterns available for columnar curves (Fig 2, 3, and others.), but the pattern used by the author is visually distracting and tires the eyes. It is recommended to choose a simpler, more reader-friendly pattern. The arrangement of the figures should be adjusted because placing one photo across two pages is inappropriate and disrupts the flow of the manuscript. The author should rearrange Figure 6 by placing three pictures in the top row and two pictures in the bottom row. This layout will create a more balanced and visually clear presentation, improving the figure's overall readability and flow.
8. The authors should remove the graphical abstract from the main text and avoid adding a description or caption for it there. According to standard journal guidelines, graphical abstracts are intended to be submitted as separate files and are usually placed at the beginning of the article or alongside the textual abstract, not embedded within the manuscript text itself. Including the graphical abstract within the text with a caption is not appropriate and goes against common publishing practices, which require it to be a standalone visual summary to quickly convey the main message without detailed explanation in the manuscript body

REFeree : Reviewer

22 May 2025

This manuscript investigates the potential protective role of ketotifen (KTF) in a mouse model of gentamicin (GEN)-induced hepatotoxicity, focusing on oxidative stress, inflammatory mediators, and NF- κ B signaling. The topic is relevant and of pharmacological significance. However, the manuscript in its current form requires major revision due to several issues related to scientific rigor, language clarity, methodological transparency, and data interpretation.

Below are detailed comments for the authors:

1. The manuscript contains numerous grammatical errors. Professional English language editing would be beneficial to ensure clarity and fluency.

2. Title Revision:

The current title is descriptive but can be made more concise and scientific. I recommend revising the title to:

"Anti-Inflammatory and Antioxidant Effects of Ketotifen Against Gentamicin-Induced Hepatotoxicity Through NF- κ B Pathway Suppression."

3. Abstract Clarity:

o The objective sentence is vague. Please rephrase as:

"This study aimed to evaluate the hepatoprotective effects of ketotifen against gentamicin-induced toxicity in mice, focusing on inflammation, oxidative stress, and NF- κ B modulation."

o Avoid repeating the title in the abstract. Summarize the aim in a novel and concise manner.

o Statistical outcomes in the results section should include p-values to indicate significance.

4. Introduction Improvements:

o The introduction lacks logical flow. The background section is overly detailed and includes mechanisms not directly related to the current study.

o Please restructure the introduction to clearly state the research gap, rationale, and study hypothesis.

o Language issues are present throughout; editing for grammar, academic tone, and fluency is strongly advised.

5. Materials and Methods:

o Chemicals and Reagents Section: Follow standard formatting for companies, e.g., "Sigma-Aldrich (USA)". Separate chemical names from country names in parentheses for all chemicals.

o Animal Grouping: The number of animals and groups is inconsistently reported. There are five groups, not six as stated in some sections. Please clearly define each group and justify the differences in sample sizes.

o Reproducibility: Several procedures lack critical experimental details. Please ensure each method is described in sufficient detail to allow reproducibility (e.g., homogenization steps, ELISA procedure, Western blotting conditions).

- o Statistical Analysis: The type of post-hoc test is not specified. Also, indicate whether normality of data was checked before ANOVA.

2. Results Reporting:

- o Phrases such as “better effects” are non-scientific. Instead, use terms like “significantly more effective” or “greater reduction.”
- o Results should clearly differentiate which biomarkers increased or decreased in each group and significance values (e.g., $P < 0.05$, $P < 0.01$).
- o Ensure consistency between figure legends and textual descriptions. For example, Fig.1 significance levels in the text (e.g., \$\$) must match the figure legends.

3. Western Blotting Analysis:

- o Protein expression results should be presented as fold change relative to the control group.
- o Please revise figure titles to reflect this (e.g., “Fold Change of Control”).

4. Histopathology:

- o Quantification of histopathological scores should be described in the Methods section.

5. Discussion Quality:

- o The discussion is largely a repetition of results. A critical analysis is needed. Discuss how your findings compare or contrast with previously published studies.
- o The structure of the discussion should follow the order: biochemical results → oxidative stress → inflammation → molecular mechanism → histological findings .
- o Provide mechanistic insights and avoid overgeneralization.

6. Limitations and Future Directions:

- o No limitations are acknowledged in the manuscript. Please include a paragraph discussing possible limitations and propose directions for future research.

7. Conclusion:

- o The conclusion should be rephrased to reflect a synthesis of findings rather than a mere repetition of the abstract. Emphasize the potential clinical relevance and mechanistic contribution of the study.

REFeree : Associate Editor

22 May 2025

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 and highlight any changes in the text.

REFeree : EIC

23 May 2025

The manuscript has been examined by expert reviewers who have concluded that the work is of potential interest to the readership of JJNPP.

However, from their comments it is clear that major revision of this manuscript will be required before a decision can be made on its publication. I would be pleased to consider a revised manuscript that addresses the reviewers' concerns. Your revised

manuscript will be returned to one or more of the original reviewers for further consideration.

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.

Dear Manager of Jundishapur Journal of Natural Pharmaceutical Products Office: Dr. Masood Fereidoonnezhad

Thank you for sending me the manuscript for further edition. Here is my response to the comments of Editor and Reviewer.

Reviewer 1:

The manuscript titled "Ketotifen modulates the effects of gentamicin-induced hepatotoxicity in mice by suppressing inflammation, oxidative stress, and the NF- κ B signaling pathway" is interesting. I recommend its publication in the Jundishapur Journal of Natural Pharmaceutical Products but several minor revisions must be addressed before reconsideration.

1. The article contains numerous grammatical issues and requires significant editing and rewriting by a native English speaker. Many sentences are too long and confusing. The authors should rewrite them and break down large sentences into shorter, more understandable ones. For example, this sentence "Due to the high volume of biological changes in the liver and the metabolism of substances and drugs and sometimes their conversion to active metabolites, if the detoxification capacity of the liver is reduced, complications such as fatty liver, ductal damage, vascular disorders, cholestasis, and cirrhosis occur ". The author may find many sentences in the manuscript that are confusing and need clarification. The author should consider rewriting the entire introduction, as it currently lacks coherence and uniformity.

Response: Thanks for your comment, the introduction was rewritten and grammatical errors were corrected.

2. In both the abstract and the Experimental Design section, the authors mention six groups; however, only five groups are described in the manuscript. Additionally, there is inconsistency in the number of mice used per group ($n = 6-10$). Could the authors clarify the reason for this discrepancy?

Response: Thanks for your comment, the number of groups was revised from 6 to 5. A larger number of animals were included in the groups where toxicity was induced, so that if

mortality occurred in these groups, the number of mice would be sufficient for statistical calculations.

3. The group names used by the authors in the text and figures are not appropriate or sufficiently descriptive. The authors should revise the group names for clarity and consistency. For example, they could use names such as "Gen-Ket2" and "Gen-Ket3".

Response: Thanks for your comment, the group names in the text and figures were revised.

4. The authors should specify the dose of Gen used in the GEN-treated groups that received ketofol (KTF) at 2 and 3 mg/kg.

Response: Thanks for your comment, GEN dose in KTF-treated groups was determined.

5. There is no need to include the CAS numbers in the Materials section.

Response: Thanks for your comment, CAS numbers were removed from the Materials section.

6. The figure 1 is too confusing and should be redesigned to improve clarity and effectiveness.

Response: Thanks for your comment, figure 1 was redesigned and revised.

7. There are many patterns available for columnar curves (Fig 2, 3, and others.), but the pattern used by the author is visually distracting and tires the eyes. It is recommended to choose a simpler, more reader-friendly pattern. The arrangement of the figures should be adjusted because placing one photo across two pages is inappropriate and disrupts the flow of the manuscript. The author should rearrange Figure 6 by placing three pictures in the top row and two pictures in the bottom row. This layout will create a more balanced and visually clear presentation, improving the figure's overall readability and flow.

Response: Thanks for your comment, column curves were corrected. Figure layout was adjusted. Figure 6 was arranged with three pictures in the top row and two in the bottom row.

8. The authors should remove the graphical abstract from the main text and avoid adding a description or caption for it there. According to standard journal guidelines, graphical abstracts are intended to be submitted as separate files and are usually placed at the beginning of the article or alongside the textual abstract, not embedded within the manuscript text itself. Including the graphical abstract within the text with a caption is not appropriate and goes against common publishing practices, which require it to be a standalone visual summary to quickly convey the main message without detailed explanation in the manuscript body.

Response: Thanks for your comment, the graphic abstract was removed from the main text and submitted as a separate file.

Reviewer 2:

This manuscript investigates the potential protective role of ketotifen (KTF) in a mouse model of gentamicin (GEN)-induced hepatotoxicity, focusing on oxidative stress, inflammatory mediators, and NF- κ B signaling. The topic is relevant and of pharmacological significance. However, the manuscript in its current form requires major revision due to several issues related to scientific rigor, language clarity, methodological transparency, and data interpretation.

Below are detailed comments for the authors:

1. The manuscript contains numerous grammatical errors. Professional English language editing would be beneficial to ensure clarity and fluency.

Response: Thanks for your comment, the grammatical errors in the manuscript was edited.

2. Title Revision: The current title is descriptive but can be made more concise and scientific. I recommend revising the title to: “Anti-Inflammatory and Antioxidant Effects of Ketotifen Against Gentamicin-Induced Hepatotoxicity Through NF- κ B Pathway Suppression.”

Response: Thanks for your comment, the title was revised.

3. Abstract Clarity:

The objective sentence is vague. Please rephrase as: This study aimed to evaluate the hepatoprotective effects of ketotifen against gentamicin-induced toxicity in mice, focusing on inflammation, oxidative stress, and NF- κ B modulation.” Avoid repeating the title in the abstract. Summarize the aim in a novel and concise manner.

Response: Thanks for your comment, the objective statement was rewritten.

Statistical outcomes in the results section should include p-values to indicate significance.

Response: Thanks for your comment, the p-values were mentioned in the statistical results section.

4. Introduction Improvements:

The introduction lacks logical flow. The background section is overly detailed and includes mechanisms not directly related to the current study. Please restructure the introduction to clearly state the research gap, rationale, and study hypothesis.

Response: Thanks for your comment, introduction has been rewritten.

Language issues are present throughout; editing for grammar, academic tone, and fluency is strongly advised.

Response: Thanks for your comment, the language problems of the manuscript were corrected.

5. Materials and Methods:

o Chemicals and Reagents Section: Follow standard formatting for companies, e.g., "Sigma-Aldrich (USA)". Separate chemical names from country names in parentheses for all chemicals.

Response: Thanks for your comment, standard formatting for companies has been used. Chemical names have been separated from country names in parentheses.

Animal Grouping: The number of animals and groups is inconsistently reported. There are five groups, not six as stated in some sections. Please clearly define each group and justify the differences in sample sizes.

Response: Thanks for your comment, the number of groups was revised from 6 to 5. A larger number of animals were included in the groups where toxicity was induced, so that if mortality occurred in these groups, the number of mice would be sufficient for statistical calculations.

Reproducibility: Several procedures lack critical experimental details. Please ensure each method is described in sufficient detail to allow reproducibility (e.g., homogenization steps, ELISA procedure, Western blotting conditions).

Response: Thanks for your comment, homogenization steps, ELISA procedure, and Western blot conditions were described in sufficient detail.

Statistical Analysis: The type of post-hoc test is not specified. Also, indicate whether normality of data was checked before ANOVA.

Response: Thanks for your comment, the type of post hoc test and normality check of data were specified before ANOVA.

2. Results Reporting:

Phrases such as “better effects” are non-scientific. Instead, use terms like “significantly more effective” or “greater reduction.”

Response: Thanks for your comment, the phrases “significantly more effective” or “greater reduction” have been replaced with the phrase “better effects.”

Results should clearly differentiate which biomarkers increased or decreased in each group and significance values (e.g., $P < 0.05$, $P < 0.01$).

Response: Thanks for your comment, significant P values were specified in the results.

Ensure consistency between figure legends and textual descriptions. For example, Fig.1 significance levels in the text (e.g., \$\$) must match the figure legends.

Response: Thanks for your comment, consistency between figure captions and textual descriptions was considered.

3. Western Blotting Analysis:

Protein expression results should be presented as fold change relative to the control group. Please revise figure titles to reflect this (e.g., “Fold Change of Control”).

Response: Thanks for your comment, Western blot figure title has been revised to “Fold Change of Control”.

4. Histopathology:

Quantification of histopathological scores should be described in the Methods section.

Response: Thanks for your comment, quantification of histopathological scores was described in the Methods section.

5. Discussion Quality:

The discussion is largely a repetition of results. A critical analysis is needed. Discuss how your findings compare or contrast with previously published studies. The structure of the discussion should follow the order: biochemical results → oxidative stress → inflammation → molecular mechanism → histological findings. Provide mechanistic insights and avoid overgeneralization.

Response: Thanks for your comment, the structure of the discussion was modified as requested.

6. Limitations and Future Directions:

No limitations are acknowledged in the manuscript. Please include a paragraph discussing possible limitations and propose directions for future research.

Response: Thanks for your comment, study limitations were noted and future research directions were suggested.

7. Conclusion:

The conclusion should be rephrased to reflect a synthesis of findings rather than a mere repetition of the abstract. Emphasize the potential clinical relevance and mechanistic contribution of the study.

Response: Thanks for your comment, the conclusion was rewritten and revised.

Reviewer 3:

with respect and value for the strengths of the study, following items require re evaluation. total sample size of the five groups of study is thirty-seven.(6+10+7+14). sample size calculation should be mentioned.

Response: Thanks for your comment, a larger number of animals were included in the groups where toxicity was induced, so that if mortality occurred in these groups, the number of mice would be sufficient for statistical calculations. Thirty-seven male NMRI mice were randomly divided into 5 groups (n=6-10). Including: Control (normal saline 80 ml/kg, ip, n=6), GEN (80 mg/kg, ip, n=10), KTF (3 mg/kg, ip, n=7), and groups treated with GEN 80 mg/kg + KTF 2 mg/kg (n=7) and GEN 80 mg/kg + KTF 3 mg/kg (n=7).

Some conclusion appear overstated given the study's limitations such as small sample size and short follow up. Conclusion could be structured into future research needs and be expanded to design similar research in animal and human .limitation must be considered.

Response: Thanks for your comment, conclusion revised. Limitations were considered.

Reviewer Assistant Comments:

These comments were generated by AI based on your manuscript. Please review them and consider incorporating the suggestions to enhance your article.

Based on the abstract provided, the study appears to be an experimental study involving animal subjects (mice) to investigate the effects of ketotifen on gentamicin-induced hepatotoxicity. This type of study is often categorized under experimental or laboratory research rather than clinical trials or observational studies like cohort, case-control, or cross-sectional studies. However, since it involves testing interventions in a controlled environment, it aligns most closely with the CONSORT checklist for Randomized Trial Studies, even though it's not a human clinical trial. Let's proceed with the peer review using the CONSORT checklist for Randomized Trial Studies:

Question of the checklist: Title and Abstract

Peer Review: The title is not provided in the abstract, but the abstract is structured with sections such as Background, Objectives, Methods, Results, and Conclusion, which is consistent with standard reporting practices.

Response: Thanks for your comment, the title was provided in the abstract.

Question of the checklist: Introduction - Background and Objectives

Peer Review: The background provides a rationale for the study, explaining the known effects of gentamicin and the potential protective effects of ketotifen. The objectives are clearly stated, focusing on the protective effect of ketotifen on gentamicin-induced hepatotoxicity.

Response: Thanks for your comment.

Question of the checklist: Methods - Participants

Peer Review: The abstract mentions the use of thirty-six male NMRI mice, divided into six groups. However, details on the selection criteria for the mice are not provided.

Response: Thanks for your comment, the number of groups was revised from 6 to 5. A larger number of animals were included in the groups where toxicity was induced, so that if

mortality occurred in these groups, the number of mice would be sufficient for statistical calculations.

Question of the checklist: Methods - Interventions

Peer Review: The interventions are described, including the dosages of gentamicin and ketotifen administered to the mice.

Response: Thanks for your comment.

Question of the checklist: Methods - Outcomes

Peer Review: The outcomes measured include levels of various enzymes and proteins related to liver function and oxidative stress, as well as histological examinations.

Response: Thanks for your comment.

Question of the checklist: Methods - Randomization

Peer Review: The abstract does not mention the randomization process for assigning mice to different groups.

Response: Thanks for your comment, the randomization process for assigning mice to different groups was mentioned in the abstract.

Question of the checklist: Results - Participant Flow

Peer Review: The abstract does not provide detailed information on the flow of participants (mice) through the study.

Response: Thanks for your comment, the information on the mice during the study was described in the abstract.

Question of the checklist: Results - Outcomes and Estimation

Peer Review: The results are presented with specific findings on the effects of ketotifen on various biochemical markers and histopathological results.

Response: Thanks for your comment.

Question of the checklist: Discussion - Interpretation

Peer Review: The conclusion interprets the findings, suggesting that ketotifen is effective in mitigating gentamicin-induced hepatotoxicity.

Response: Thanks for your comment.

Question of the checklist: Other Information - Funding

Peer Review: The abstract does not mention any funding sources or conflicts of interest.

Response: Thanks for your comment, funding sources and conflicts of interest are listed at the end of the study.

Major Comments:

The abstract lacks details on the randomization process and participant flow, which are crucial for assessing the validity of the study's findings.

Response: Thanks for your comment, details about the randomization process and participant flow were disclosed.

There is no mention of the study's title or funding sources, which are important for transparency and context.

Response: Thanks for your comment, funding sources and conflicts of interest were disclosed.

Minor Comments:

The abstract could benefit from a brief mention of the criteria for selecting the mice to provide more context on the study population. Including the study's title would help in identifying the research focus at a glance.

Response: Thanks for your comment, the criteria for selecting mice were described. A larger number of animals were included in the groups where toxicity was induced, so that if mortality occurred in these groups, the number of mice would be sufficient for statistical calculations. Thirty-seven male NMRI mice were randomly divided into 5 groups (n=6-10). Including: Control (normal saline 80 ml/kg, ip, n=6), GEN (80 mg/kg, ip, n=10), KTF (3 mg/kg, ip, n=7), and groups treated with GEN 80 mg/kg + KTF 2 mg/kg (n=7) and GEN 80 mg/kg + KTF 3 mg/kg (n=7).

OPEN PEER REVIEW

Revision (1)

REFeree : Reviewer

7 Jul 2025

The revised manuscript demonstrates significant improvements in addressing reviewers' concerns, though minor refinements could further strengthen its scientific rigor. Key methodological issues such as group inconsistencies (revised from 6 to 5 groups) and sample size justification ($n=6-10$ to account for mortality risk) have been clarified, while standardized statistical reporting now includes explicit p-values (e.g., $P<0.001$) and post-hoc test specifications (Tukey's test for ANOVA). Structural enhancements include redesigned figures with simplified patterns (Figs. 2–6), revised group labels (e.g., "GEN+KTF3"), and a reorganized discussion that logically progresses from biochemical outcomes to molecular mechanisms. Transparency measures, such as disclosing funding sources and ethical approval (IR.AJUMS.AEC.1403.057), align with journal guidelines. However, power calculations for sample sizes remain absent, weakening statistical validity, and the discussion, while improved, still underutilizes comparative analysis with established hepatoprotective agents (e.g., NAC or silymarin). Residual phrasing issues (e.g., "better effects" in Fig. 2 legend) and inconsistent abbreviation usage ("ip" vs. "i.p.") require polishing. With minor adjustments to address these gaps—particularly mechanistic details on NF- κ B upstream regulators (e.g., I κ B kinase) and a final proofread for language precision—this work meets publication standards, offering novel insights into ketotifen's therapeutic potential against drug-induced hepatotoxicity.

REFeree : Reviewer

12 Jul 2025

With respect and value for the strengths of the study, following minor revisions require.

- 1- In line 153, the Kruskal-Wallis test is not used for multiple comparisons; rather, it is equivalent to a non-parametric ANOVA. Please specify in the descriptions of each comparison which test was employed—either ANOVA or Kruskal-Wallis.
- 2- In line 205, the use of "more significant" is incorrect, as the p-value only indicates significance and does not imply the strength of the relationship.

REFeree : Associate Editor

12 Jul 2025

The Ms still needs some minor revisions before suitable for publication in JJNPP

REFeree : EIC

12 Jul 2025

Our impression is that the above-mentioned manuscript could become suitable for publication in JJNPP. However, the criticism from the referees requires that we defer a final decision until you have considered their remarks and revised your manuscript accordingly.

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 Manager of Jundishapur Journal of Natural Pharmaceutical Products Office: Dr. Masood Fereidoonnezhad

Thank you for sending me the manuscript for further edition. Here is my response to the comments of Editor and Reviewer.

:Reviewer 0

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Response: Thank you for your comments, dear reviewer. G-Power software was used to determine sample size and power. Comparative analysis with known hepatoprotective agents (e.g. NAC or silymarin) was applied in the discussion. The term “better effects” was amended in the Figure 2 guide. “ip” was amended to “i.p.”. Mechanistic details regarding upstream regulators of NF- κ B (e.g. I κ B kinase) were applied in the discussion. Final editing was performed for accuracy of language in accordance with publication standards.

Reviewer 1:

With respect and value for the strengths of the study, following minor revisions require.

1-In line 153, the Kruskal-Wallis test is not used for multiple comparisons; rather, it is equivalent to a non-parametric ANOVA. Please specify in the descriptions of each comparison which test was employed—either ANOVA or Kruskal-Wallis.

Response: Thank you for your comments, The tests used are specified.

2-In line 205, the use of "more significant" is incorrect, as the p-value only indicates significance and does not imply the strength of the relationship.

Response: Thank you for your comments, The phrase more significant has been corrected.

:Associate Editor 1

The Ms still needs some minor revisions before suitable for publication in JJNPP.

Response: Thank you for your comments, The corrections have been made to the manuscript.

OPEN PEER REVIEW

Revision (2)

REFEREE : EIC

15 Jul 2025

I am pleased to inform you that your manuscript has been accepted for publication.