

OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "[Peer Review](#)". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

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.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- 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:

[Peer Review](#)



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Peer Review Report for "Quercetin and Catechin Modulate Alloxan-Induced Nephrotoxicity in Mice by Affecting Oxidative Stress, Inflammation and COX-2 Protein Expression"

Author(s): Amir Hossein Rastineh, Maryam Khamisi Pour, Ali Vadizadeh, Masoud Mahdavinia, Fereshtesadat Fakhredini, Mahdieh Sadat Badiie

Review Timeline:

Submit Date:	4 Nov 2025
Revised Date:	20 Dec 2025
Accepted Date:	20 Dec 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

4 Nov 2025

This research provides compelling evidence for the protective effects of quercetin and catechin against nephrotoxicity induced by alloxan. The combination therapy demonstrates enhanced efficacy, supporting the hypothesis that multi-antioxidant strategies could be beneficial in clinical settings. The study is well-structured, with clear methodologies and significant findings, contributing valuable insights into the management of nephrotoxicity. A few small notes to improve the quality of the article are mentioned below

1. In the introduction, there is no explanation regarding the relationship with COX-2. More explanation should be provided regarding the mechanisms.
2. In section 2.10, mention the names of the kits.
3. On what basis were the doses selected? Please provide the reference. It would have been better to test higher doses of each active ingredient. What is your reasoning?
4. The method for fasting blood sugar is not mentioned in the manuscript.
5. The arrangement of the graphs presented in the results should be aligned with the methods section. For example, TNF-alfa and ROS are mentioned together in the methods section, so the graphs should also be placed together in result section.
6. More explanation is needed about the toxicity and mechanism of renal toxicity of alloxan. The explanations are brief and incomplete.

REFeree : Reviewer

8 Nov 2025

The study explores the protective effects of quercetin (QCT) and catechin (CAT) against alloxan (ALLO)-induced nephrotoxicity in mice. While the topic is relevant and potentially impactful in the field of renal toxicology and natural antioxidants, the manuscript has major scientific weaknesses:

1. It is better to check the written language again with a native editor or relevant software.
2. In the abstract section, the introduction does not clearly define how the combined use of QCT and CAT is novel compared to existing studies. Many prior reports already describe antioxidant protection by polyphenols in nephrotoxicity.
3. The results mention an increase in COX-2 protein expression in treated groups compared to ALLO, but the conclusion claims reduced expression. This is a major contradiction.
4. ALLO is primarily a diabetogenic compound, not a classic nephrotoxin (like cisplatin, gentamicin, or adriamycin). The paper needs to clarify whether kidney injury is secondary to diabetes or a direct toxic effect.
5. The introduction repeats the antioxidant roles of quercetin (QCT), catechin (CAT), and green tea multiple times. The journals expect concise, non-repetitive background. The first half should establish the problem (nephrotoxicity or oxidative stress), the second half should justify the choice of compounds and the rationale for combining them.
6. The manuscript never explains why QCT and CAT were combined. Are they synergistic? Do they target different pathways?
7. You introduce COX-2 at the end abruptly. It needs a short bridge explaining that inflammation via COX-2 upregulation contributes to diabetic renal injury.
8. In experimental design section, "injection every other day for a duration of six days", lacks subject "Alloxan was administered...".
9. It is unclear whether QCT and CAT were administered together or separately in the

combined group (ALLO+QCT+CAT). The ratio or co-administration procedure (single gavage vs sequential) must be specified.

10. ALLO is given i.p. every other day for six days, but the timing of QCT and CAT relative to ALLO injection (simultaneous, after induction, or preventive?) is not clearly described.

11. Method for euthanasia (anesthetic type, dose).

12. In results section, you indicated, levels of total thiol, ROS, AOPP, SOD, and CAT in ALLO group were significantly below those found in control group.

But ROS and AOPP are oxidative damage markers, they should increase in nephrotoxicity, not decrease.

13. In the final sentence of histopathology section is contradictory, "the extent of these damages... was more pronounced in the cohort who received both QCT and CAT". This implies the combination worsened damage, contradicting earlier statements that combined therapy was most effective.

14. No numerical or percentage data, error bars, or statistical indicators (e.g., t values, mean $\pm$ SD) are presented.

15. In the line 190, capitalization mid-sentence, "The ALLO group".

16. You mention, total thiol, AOPP, SOD, and catalase exhibited a decrease in ALLO group... administration of QCT or CAT resulted in an increase in these oxidative markers. AOPP is not an antioxidant marker, it should decrease with treatment.

17. The discussion section cites many pathways (Nrf2, NF- κ B, COX-2, TNF- α , IKK α /p53, AKT/Raf/MEK/ERK) without a coherent hierarchy. Prioritize the most relevant ones for renal oxidative injury, Nrf2 (antioxidant defense) and NF- κ B/COX-2/TNF- α (inflammation).

REFeree : Reviewer

9 Nov 2025

- Subject
 - 1) Is the article within the scope of the journal? yes
 - 2) Does the article have novelty? yes
- Title: Quercetin and catechin modulate alloxan-induced nephrotoxicity in mice by affecting oxidative stress, inflammation and COX-2 protein expression pathways
 - 3) Does the title reflect the content appropriately? yes
 - 4) Is there any abbreviation in the title? Yes, just in parentheses
- Abstract
 - 5) Is there a structured Abstract? yes
 - 6) Are Keywords (3-10) selected from MESH? yes
- Introduction
 - 7) Clarity of the objectives/hypotheses? (Are the objectives clearly stated?) yes
 - 8) Does the Introduction include: "What we know," "What we don't know," and "Aims"? yes , the introduction are written good but the properties and chemical structures of Quercetin and catechin must be given in this part.
- - Materials And Methods
 - 9) Clearly describe the selection of participants (patients or laboratory animals,

including controls). This research have not patients but the laboratory animals is used in this research work.

- 10) Study Design Described Sufficiently? The study design is cosidered sufficient and appropriate.
- Please identify and add the references of the Biochemical assay,Antioxidant enzymes activity assay parts, ROS and TNF- α assay and COX-2 protein expression assay.
- 11) Adequacy of the sample studied? The sample is appropriate according to the procedure.
- 12) Subjects Representative of the Target Population? yes
- 13) Provided sample size calculation or justification? -
- 14) Control Subjects Appropriate?-
- 15) Power of study declared? Power of study is proper quality.
- 16) Reported actual P values for primary analyses?-
- 17) Blinding of Investigators (if applicable)?
- 18) Blinding of subjects (if applicable)?
- 19) Identify the methods apparatus (give the manufacturer's name and address in parentheses). The name of companies are given for materials and apparatus.
- 20) Identify procedures in sufficient detail to allow other workers to reproduce the results. In experimental part, the procedures are clearly written and can be use for reproducing the results.
- 21) Identify precisely all drugs and chemicals used, including generic name(s), dose(s), and route(s) of administration. It is explained in no.19.
- 22) Inclusion/Exclusion Criteria Explained? -
- 23) Appropriate Statistical Analysis? -
- Results
- 24) Appropriateness, clarity, and adequacy of the Tables and Figures? The Figures are clearly prepared from the experimental part.
- 25) Present results in logical sequence in the text, tables, and illustrations, giving the main or most important findings. The results of all experiments are properly explained in text.
- 26) Duplicate data in graphs and tables? no
- 27) Use technical terms as non-technical in statistics, such as "random" (which implies a randomizing device), "normal," "significant," "correlations," and "sample."? -
- Discussion
- 28) Conclusion justified & substantiated?
- 29) Analysis supports the Conclusion? Conclusion is good written specially the results of reaserch article.
- References
- 30) Proper Writing of the References? yes
- 31) References for the last five years? yes

REFEREE : Reviewer

9 Nov 2025

This is a well-designed and comprehensively reported study that investigates the protective effects of quercetin (QCT) and catechin (CAT) against alloxan-induced

nephrotoxicity. The manuscript presents clear evidence of the synergistic effects of these polyphenols on oxidative stress, inflammation, and renal histopathology. The work is scientifically sound, ethically approved, and relevant to the field of natural product pharmacology and nephrotoxicity. However, several clarifications and minor revisions are required before it is suitable for publication.

Minor Concerns and Suggestions for Revision:

Clarification of Treatment Timeline:

The manuscript states that alloxan was administered every other day for 6 days, and then QCT/CAT were given for 14 days. However, it is unclear when the alloxan dosing ended relative to the start of the polyphenol treatment. A clear timeline or schematic would improve readability.

Justification of Doses:

While references are provided for the doses of alloxan, QCT, and CAT, a brief justification in the text for why these specific doses were chosen—especially the combination dose—would be helpful.

Figure and Legend Quality:

Some figures (e.g., Fig. 1–6) are included as text descriptions or placeholders. Ensure all figures are of high quality and clearly labeled.

The legend for Fig. 5 should more clearly describe the abbreviations used (e.g., Gm, Gd, EL, VD).

Language and Grammar:

Minor grammatical errors and awkward phrasings are present (e.g., "management of QCT and CAT", "effects of amalgamation therapy"). Professional language editing is recommended.

Discussion Section:

The discussion is thorough but somewhat repetitive. Consider condensing and focusing more on the novel aspects of the combination therapy.

The sentence on page 21: "The histological protection observed in the combination group corroborates reports..." – specify which studies or models are being referenced.

Limitations Acknowledgment:

The authors briefly mention limitations (e.g., no pharmacokinetics or long-term

safety data). This section could be expanded slightly to address the translational potential of the findings.

REFEREE : Associate Editor

10 Nov 2025

The Ms needs some major revisions before suitable for publication in JJNPP

REFEREE : EIC

10 Nov 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 Editor-in-Chief, Dr Masood Fereidoonnezhad

Thank you for submitting the manuscript for further editing. Here is my response to your comments.

Revision: 0

Based on the abstract provided, the study design appears to be an experimental study involving animal subjects (mice). The appropriate checklist for reviewing this type of study would be the CONSORT checklist for Randomized Trial Studies, as it involves intervention and control groups.

I will now use the CONSORT checklist to perform the peer review of the abstract. Let's proceed with the review:

1. Question of the checklist: Title and Abstract

- o **Peer Review:** The title and abstract clearly describe the study's purpose, methods, results, and conclusion. The abstract provides a concise summary of the study, including the background, methods, results, and conclusion.

Response: Thanks for your comment.

2. Question of the checklist: Introduction (Background and Objectives)

- o **Peer Review:** The background provides a clear rationale for the study, explaining the issue of nephrotoxicity and the potential role of QCT and CAT. The objective of the study is clearly stated as evaluating the combined effects of QCT and CAT on ALLO-induced nephrotoxicity in mice.

Response: Thanks for your comment.

3. Question of the checklist: Methods (Participants)

- o **Peer Review:** The abstract specifies that thirty male mice were used, divided into five groups. However, it does not provide details on the randomization process or criteria for inclusion/exclusion of the mice.

Response: Thanks for your comment. Details of the randomization process and inclusion/exclusion criteria for mice were mentioned in the abstract.

4. Question of the checklist: Methods (Interventions)

- o **Peer Review:** The interventions are clearly described, including the dosages and administration methods for ALLO, QCT, and CAT. The duration of treatment and the procedure for administration are also specified.

Response: Thanks for your comment.

5. Question of the checklist: Methods (Outcomes)

- o **Peer Review:** The outcomes measured include biochemical markers, oxidative stress, inflammation factors, and protein expression of COX-2. However, the abstract does not specify the primary and secondary outcomes.

Response: Thanks for your comment. Primary and secondary outcomes were described in the abstract.

6. Question of the checklist: Results (Participant Flow)

- o **Peer Review:** The abstract does not provide information on the flow of participants through the study, such as the number of mice that completed the study or any dropouts.

Response: Thanks for your comment. In this study, thirty male mice, each weighing 25 ± 2 g, were randomly divided into five groups of six. The number of mice was constant and no mortality was observed.

7. **Question of the checklist: Results (Outcomes and Estimation)**

- o **Peer Review:** The results are presented with specific findings on the reduction and increase of various biochemical markers and oxidative stress indicators. However, the abstract does not provide statistical measures or estimates of effect size.

Response: Thanks for your comment. P-values were stated in the results.

8. **Question of the checklist: Discussion (Interpretation)**

- o **Peer Review:** The conclusion interprets the findings, suggesting that QCT and CAT may influence ALLO-induced nephrotoxicity by reducing oxidative stress and inflammation. The implications of the findings are briefly mentioned.

Response: Thanks for your comment.

9. **Question of the checklist: Other Information (Funding)**

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

Response: Thanks for your comment. The funding sources and conflicts of interest are stated in the abstract.

Major Comments:

- The abstract lacks details on the randomization process and criteria for inclusion/exclusion of the mice.
- The primary and secondary outcomes are not specified.
- Statistical measures or estimates of effect size are not provided in the results.
- **Response:** Thanks for your comment. Details of the randomization process and inclusion/exclusion criteria for mice were mentioned in the abstract. Primary and secondary outcomes were described in the abstract. P-values were stated in the results.

Minor Comments:

- The abstract does not mention the flow of participants through the study or any dropouts.
- There is no information on funding sources or potential conflicts of interest.
- **Response:** Thanks for your comment. In this study, thirty male mice, each weighing 25 ± 2 g, were randomly divided into five groups of six. The number of mice was constant and no mortality was observed. The funding sources and conflicts of interest are stated in the abstract.

OPEN PEER REVIEW

Revision (1)

Kobra Shirani : Reviewer

15 Nov 2025

Dear Editor-in-Chief,

I have completed my review of the manuscript entitled "Quercetin and catechin modulate alloxan-induced nephrotoxicity in mice by affecting oxidative stress, inflammation and COX-2 protein expression pathways" (Manuscript ID: 167250, Revision [1]).

Thank you for giving me the opportunity to evaluate this work. I have assessed the manuscript thoroughly and find it to be a valuable contribution to the field. The study is well-designed, the data are robust and clearly presented, and the conclusions are supported by the experimental results.

The manuscript addresses a relevant topic and provides significant insights into the protective mechanisms of quercetin and catechin against drug-induced nephrotoxicity.

Therefore, I am pleased to recommend that the manuscript be accepted for publication in its present form.

REFEREE : Reviewer

15 Nov 2025

Dear editor in chief

The manuscript that my colleagues and I reviewed has been completely disregarded by the authors, and unfortunately, they have not provided any response to our feedback. This lack of engagement is quite disappointing, especially considering the effort and time we invested in our review.

I had anticipated that the authors would take our concerns seriously and address each of the points we raised individually. It is standard practice for authors to provide detailed explanations in their response letters, clarifying how they have revised the manuscript in light of the feedback received. This process not only enhances the quality of the article but also fosters a constructive dialogue between reviewers and authors.

In my opinion, the manuscript, as it currently stands, is not acceptable for publication. The failure to respond to our critiques raises concerns about the authors' commitment to improving their work and adhering to the standards expected in academic publishing.

REFEREE : Reviewer

17 Nov 2025

The revised manuscript and the authors' rebuttal have fully addressed all concerns. The paper is now accepted for publication.

REFEREE : Associate Editor

18 Nov 2025

Key Problems with the Authors' Response:

1-Dismissive and Template-Driven: The repeated phrase "Thanks for your comment" without substantive engagement is disrespectful and unprofessional. It signals that the authors either don't understand or don't value the reviewer's expertise.

2-False Claims of Compliance: The authors repeatedly state that requested information is "mentioned in the abstract" when it's not actually there:

Randomization: Abstract only says "randomly divided"—no method, allocation concealment, or timeline.

Inclusion/exclusion criteria: Completely absent.

Primary/secondary outcomes: All outcomes are lumped together without hierarchical distinction.

Effect sizes: Only P-values are reported; no confidence intervals, standard errors, or effect size metrics.

3-No Evidence of Revision: A proper response should specify exactly where changes were made (e.g., "We have added this to the Methods section, page X, lines Y-Z"). The authors provide no manuscript locations, suggesting no actual revisions occurred.

4- Scientific Checklist Misalignment: The reviewer incorrectly applied the CONSORT checklist (for human trials) instead of the ARRIVE guidelines (for animal studies). This is a legitimate error, but the authors failed to politely point this out—a missed opportunity to demonstrate expertise while acknowledging the valid underlying concerns.

Critical gaps include:

No sample size justification

No blinding of outcome assessors (essential for histopathology)

Humane endpoints not described

AOPP and ROS results are biologically questionable: AOPP typically rises with oxidative damage, yet the abstract claims it increased with treatment—opposite to expectations.

COX-2 expression: The abstract's wording is ambiguous about whether treatment increased or decreased COX-2.

REFEREE : EIC

18 Nov 2025

I am writing to express serious concerns regarding your recent response to peer review, which has been brought to my attention by the reviewer. Their complaint that

you have "completely disregarded" their feedback is unfortunately accurate. Your response letter consists of generic, template-driven acknowledgments that fail to address the substantive scientific issues raised and, in several instances, falsely claim that requested information is present in the manuscript when it clearly is not. This approach is unacceptable in scholarly publishing. Peer review is a collaborative process designed to ensure scientific rigor, and it requires authors to engage thoughtfully and transparently with critiques. A proper response must be point-by-point, specifying exactly where each revision was made (including page and line numbers), what changes were implemented, and providing scientific justification when a suggestion was not adopted.

Please provide a completely revised submission accompanied by a detailed, good-faith response letter that directly and thoroughly addresses every reviewer comment with specific evidence of change.

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 JJNPP Office

Thank you for sending me the manuscript for further edition. Here is my response to the comments of reviewers and Editor-in-Chief.

Reviewers' Comments:

Reviewer 0:

Dear Editor-in-Chief,

I have completed my review of the manuscript entitled "Quercetin and catechin modulate alloxan-induced nephrotoxicity in mice by affecting oxidative stress, inflammation and COX-2 protein expression pathways" (Manuscript ID: 167250, Revision [1]).

Thank you for giving me the opportunity to evaluate this work. I have assessed the manuscript thoroughly and find it to be a valuable contribution to the field. The study is well-designed, the data are robust and clearly presented, and the conclusions are supported by the experimental results. The manuscript addresses a relevant topic and provides significant insights into the protective mechanisms of quercetin and catechin against drug-induced nephrotoxicity. Therefore, I am pleased to recommend that the manuscript be accepted for publication in its present form.

Response: Thank you for your comment Dear Reviewer.

Reviewer 1:

The revised manuscript and the authors' rebuttal have fully addressed all concerns. The paper is now accepted for publication.

Response: Thank you for your comment Dear Reviewer.

Reviewer 2:

Dear editro in chief

The manuscript that my colleagues and I reviewed has been completely disregarded by the authors, and unfortunately, they have not provided any response to our feedback. This lack of engagement is quite disappointing, especially considering the effort and time we invested in our review.

I had anticipated that the authors would take our concerns seriously and address each of the points we raised individually. It is standard practice for authors to provide detailed explanations in their response letters, clarifying how they have revised the manuscript in light of the feedback received. This process not only enhances the quality of the article but also fosters a constructive dialogue between reviewers and authors.

In my opinion, the manuscript, as it currently stands, is not acceptable for publication. The failure to respond to our critiques raises concerns about the authors' commitment to improving their work and adhering to the standards expected in academic publishing.

Response: Thank you for your comment Dear Reviewer. Due to the conversion of the tracked file to non-tracked, the corrections made have been reverted. Please accept our apologies for this problem. The changes have been re-applied.

Associate Editor's Comments:

Associate Editor 0:

Key Problems with the Authors' Response:

1-Dismissive and Template-Driven: The repeated phrase "Thanks for your comment" without substantive engagement is disrespectful and unprofessional. It signals that the authors either don't understand or don't value the reviewer's expertise.

Response: Please accept our apologies for using this phrase.

2-False Claims of Compliance: The authors repeatedly state that requested information is "mentioned in the abstract" when it's not actually there:

Response: Due to the conversion of the tracked file to non-tracked, the corrections made have been reverted. Please accept our apologies for this problem.

Randomization: Abstract only says "randomly divided"—no method, allocation concealment, or timeline.

Response: The method of randomization of animals was described in the Methods section of the abstract.

Inclusion/exclusion criteria: Completely absent.

Response: Since the study was an animal study and all mice were healthy and in a similar weight range, there were no inclusion or exclusion criteria.

Primary/secondary outcomes: All outcomes are lumped together without hierarchical distinction.

Response: The results section first lists the effect of QCT and CAT on the serum factors, then oxidant, antioxidant, and inflammatory tissue factors, and finally COX-2 protein expression compared to the ALLO group.

Effect sizes: Only P-values are reported; no confidence intervals, standard errors, or effect size metrics.

Response: Due to the length of the abstract, these criteria are listed in the figure captions.

3-No Evidence of Revision: A proper response should specify exactly where changes were made (e.g., "We have added this to the Methods section, page X, lines Y-Z"). The authors provide no manuscript locations, suggesting no actual revisions occurred.

Response: Modifications were mostly to the abstract, which are highlighted in yellow in the text.

4- Scientific Checklist Misalignment: The reviewer incorrectly applied the CONSORT checklist (for human trials) instead of the ARRIVE guidelines (for animal studies). This is a legitimate error, but the authors failed to politely point this out—a missed opportunity to demonstrate expertise while acknowledging the valid underlying concerns.

Response: The authors were aware of this error and responded to the questions by considering the animal studies guidelines. Perhaps this is why the reviewers were not held accountable for the authors' responses.

Critical gaps include:

No sample size justification

Response: Thirty male mice were divided into cages based on weight, then randomization was performed within each cage and the animals were divided into five groups of six.

No blinding of outcome assessors (essential for histopathology)

Response: Interpretation of histopathology slides was performed in a randomized and blinded manner according to Section 2–12.

Humane endpoints not described

Response: As this is an animal study, it is not possible to describe human endpoints in this study.

AOPP and ROS results are biologically questionable: AOPP typically rises with oxidative damage, yet the abstract claims it increased with treatment—opposite to expectations.

Response: The increase in AOPP in the treatment groups was a typographical error that was corrected in the abstract. The results section in Figure 2F confirms this.

COX-2 expression: The abstract's wording is ambiguous about whether treatment increased or decreased COX-2.

Response: This sentence has been corrected as follows: COX-2 protein expression decreased in the QCT and CAT groups compared with the ALLO group ($P<0.001$).

EIC Decision:

EIC 0:

I am writing to express serious concerns regarding your recent response to peer review, which has been brought to my attention by the reviewer. Their complaint that you have "completely disregarded" their feedback is unfortunately accurate. Your response letter consists of generic, template-driven acknowledgments that fail to address the substantive scientific issues raised and, in several instances, falsely claim that requested information is present in the manuscript when it clearly is not. This approach is unacceptable in scholarly publishing. Peer review is a collaborative process designed to ensure scientific rigor, and it requires authors to engage thoughtfully and transparently with critiques. A proper response must be point-by-point, specifying exactly where each revision was made (including page and line numbers), what changes were implemented, and providing scientific justification when a suggestion was not adopted.

Please provide a completely revised submission accompanied by a detailed, good-faith response letter that directly and thoroughly addresses every reviewer comment with specific evidence of change.

Response: Due to the conversion of the tracked file to non-tracked, the corrections made have been reverted. Please accept our apologies for this problem. The changes have been re-applied.

OPEN PEER REVIEW

Revision (2)

REFEREE : Reviewer

25 Nov 2025

Dear editor in chief

This manuscript is still not acceptable. I wonder why the authors do not answer the previous referee questions point by point ?

You should answer all the previous referee questions point by point. I request the editor to pay attention to this issue. As a referee, I did not receive any of your answers and if this manuscript is published in this way, I do not think it is acceptable.

REFEREE : Associate Editor

7 Dec 2025

As the final reviewer, I cannot recommend acceptance of this manuscript. Despite positive feedback from Reviewers 0 and 1, the submission suffers from fundamental deficiencies in scientific conduct and reporting that undermine its credibility. The authors' response to peer review is unacceptable and violates core principles of academic publishing.

Rewrite the response letter entirely: Provide a genuine, point-by-point rebuttal with exact page/line numbers for every change

Critical Issues:

1. Unprofessional & Dishonest Response to Peer Review

The authors' response letter is a template-driven evasion that demonstrates either profound incompetence or deliberate disregard for the review process:

- Dismissive pattern: 14 instances of "Thank you for your comment" without substantive engagement
- Factually false claims: Repeatedly stating information was "added to the abstract" when the Associate Editor (AE) confirmed it was absent
- "File conversion" excuse: Blaming technical problems is not credible when combined with a pattern of non-compliance. Even if true, authors must verify final submissions
- No accountability: No acknowledgment that their approach was inappropriate

2. Failure to Meet ARRIVE Guidelines (Animal Research Standards)

Despite the AE explicitly flagging this, critical omissions remain:

- No sample size justification: $n=6/\text{group}$ is stated without power analysis or citation
- Inadequate randomization: "Randomly divided" is insufficient. No method described, no allocation concealment, no timeline
- Blinding inadequately described: While "histopathological interpretations were performed in a randomized and blinded manner" is mentioned, who was blinded, to what, and how is not specified—essential for histopathology scoring

- No humane endpoints: Claiming "not possible" for animal studies is factually incorrect and violates ethical standards. ARRIVE 2.0 requires this
- No inclusion/exclusion criteria: The response "all mice were healthy" is scientifically invalid. All studies must state explicit criteria

3. Data Transparency & Interpretation Problems

- Effect sizes missing: Only P-values reported. No confidence intervals, standard errors, or effect size metrics. The excuse "abstract length" is irrelevant—these belong in main text/figure legends
- Primary/secondary outcomes: Not hierarchically distinguished as requested
- Biologically questionable data: The AOPP issue (initially reported as increasing with treatment) suggests either a serious typographical error or lack of understanding. While corrected in the provided manuscript, the fact this reached review is concerning

Specific Manuscript Deficiencies (As Currently Submitted):

- Abstract (Lines 12-13): "randomization was performed within each cage"—still no method details
- Methods 2.3 (Lines 114-115): Duplicate text from abstract; no additional experimental design details
- Methods 2.12 (Lines 170-174): "randomized and blinded manner"—insufficient detail for reproducibility
- Results: All figures report $*P < 0.001$ but no effect sizes. This is not acceptable for modern scientific publishing
- Discussion: Overstates conclusions ("may influence" in abstract vs. definitive statements in discussion)

REFeree : EIC

7 Dec 2025

Your manuscript requires fundamental rewriting to address critical deficiencies in scientific conduct and reporting. You have one opportunity to submit a revised version that fully complies with academic standards; incomplete or evasive responses will result in immediate rejection without further review. First, you must completely rewrite your response letter, not the manuscript itself, to provide a genuine, point-by-point rebuttal with exact page/line numbers for every change. Unacceptable patterns in your previous response included fourteen instances of dismissive "Thank you for your comment" without substantive engagement; factually false claims of revisions that the Associate Editor confirmed absent; and an unverifiable "file conversion" excuse that demonstrates disregard for the review process. No template language is permitted; each reviewer comment must be answered with specific, trackable modifications. Second, you must achieve full ARRIVE 2.0 compliance despite prior warnings. Your submission remains non-compliant in several critical areas: you must provide explicit power analysis calculations or cite validated precedent for $n=6/\text{group}$ in Methods 2.3 (Lines 114-115), where "randomly divided" is currently insufficient specify the randomization method (e.g., computer-generated sequences), allocation concealment mechanism, and timeline. In Methods 2.12 (Lines 170-174), your blinding protocol description must clarify who was blinded (e.g., pathologist, statistician), to what (treatment groups,

animal IDs), and how (coded samples, third-party allocation). Your claim that humane endpoints are "not possible" is factually incorrect and violates ethical standards; ARRIVE 2.0 mandates explicit criteria, which you must provide or justify their absence with institutional approval documentation. Additionally, "All mice were healthy" is scientifically invalid as inclusion/exclusion criteria; you must state explicit, pre-specified criteria for animal exclusion or data censoring. Third, your data transparency and statistical reporting require complete overhaul: throughout the Results, replace lone $*P<0.001$ statements with confidence intervals, standard errors, and effect size metrics (e.g., Cohen's d , partial η^2), as "abstract length" is not an excuse—this belongs in main text and figure legends. You must explicitly designate primary versus secondary outcomes with pre-specified analysis plans. While the AOPP data correction is noted, you must provide a verification statement confirming the error was typographical, not analytical, and describe steps taken to prevent future occurrences. Specific manuscript deficiencies remain: the abstract (Lines 12-13) must not duplicate text from Methods and must expand randomization description beyond "within each cage"; Methods 2.3 (Lines 114-115) must remove verbatim repetition from the abstract and insert comprehensive experimental design details; all figure legends must immediately add effect size and variability information; and the Discussion must align conclusion strength with abstract language to remove overstatement. This is your sole opportunity for revision; any pattern of deflection, omission, or non-compliance will result in rejection and may affect future submissions to this journal. Submit your revised manuscript and a properly constructed response letter within 20 days.

OPEN PEER REVIEW

Revision (3)

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 Editor-in-Chief, Dr Masood Fereidoonnezhad

We sincerely thank you and the reviewers for the valuable feedback on our manuscript titled ***“Quercetin and catechin modulate alloxan-induced nephrotoxicity in mice by affecting oxidative stress, inflammation and COX-2 protein expression pathways.”*** We acknowledge the concerns raised and have made significant revisions to address each point. Below is our detailed, point-by-point response, including page and line numbers for all changes made.

Reviewer 0:

Dear editor in chief

This manuscript is still not acceptable. I wonder why the authors do not answer the previous referee questions point by point? You should answer all the previous referee questions point by point. I request the editor to pay attention to this issue. As a referee, I did not receive any of your answers and if this manuscript is published in this way, I do not think it is acceptable.

Response: We appreciate the reviewer's insistence on addressing all previous comments. We have thoroughly revised our response to ensure that each comment is answered directly and in detail.

Associate Editor's Comments:

Associate Editor 0:

As the final reviewer, I cannot recommend acceptance of this manuscript. Despite positive feedback from Reviewers 0 and 1, the submission suffers from fundamental deficiencies in scientific conduct and reporting that undermine its credibility. The authors' response to peer review is unacceptable and violates core principles of academic publishing.

Rewrite the response letter entirely: Provide a genuine, point-by-point rebuttal with exact page/line numbers for every change

Critical Issues:

1. Unprofessional & Dishonest Response to Peer Review

The authors' response letter is a template-driven evasion that demonstrates either profound incompetence or deliberate disregard for the review process:

Response: We apologize for the previous response's shortcomings. We have corrected our approach and now provide detailed, substantive responses below.

- Dismissive pattern: 14 instances of "Thank you for your comment" without substantive engagement.

Response: We acknowledge the repetitive use of "Thank you for your comment" and have replaced these phrases with specific responses to each comment.

- Factually false claims: Repeatedly stating information was "added to the abstract" when the Associate Editor (AE) confirmed it was absent.

Response: We have revised the abstract to include the necessary details as confirmed by the AE. (See Abstract, Lines [12-14 and 24-31]).

- "File conversion" excuse: Blaming technical problems is not credible when combined with a pattern of non-compliance. Even if true, authors must verify final submissions.

Response: We recognize this was an inadequate explanation. We take full responsibility for the oversight and have ensured all files were properly checked and verified before submission.

- No accountability: No acknowledgment that their approach was inappropriate.

Response: We accept the criticism regarding our previous response and have made a conscious effort to engage fully with the review process.

2. Failure to Meet ARRIVE Guidelines (Animal Research Standards).

Response: We have made extensive revisions to ensure compliance with ARRIVE 2.0.

Despite the AE explicitly flagging this, critical omissions remain:

- No sample size justification: $n=6/\text{group}$ is stated without power analysis or citation.

Response: We have included a power analysis justifying our sample size of $n=6/\text{group}$. (See Methods 2.3, Lines 115-117).

- Inadequate randomization: "Randomly divided" is insufficient. No method described, no allocation concealment, no timeline.

Response: We have clarified our randomization methods, including the use of computer-generated sequences and allocation concealment. (See Methods 2.3, Lines [116-117]).

- Blinding inadequately described: While "histopathological interpretations were performed in a randomized and blinded manner" is mentioned, who was blinded, to what, and how is not specified—essential for histopathology scoring.

Response: We have specified who was blinded (e.g., pathologist) and how blinding was implemented. (See Methods 2.12, Lines 179-188).

- No humane endpoints: Claiming "not possible" for animal studies is factually incorrect and violates ethical standards. ARRIVE 2.0 requires this.

Response: We have revised our statements to align with ethical standards and included explicit humane endpoints. (See Animals and ethical statement, Lines [112-113]).

- No inclusion/exclusion criteria: The response "all mice were healthy" is scientifically invalid. All studies must state explicit criteria.

Response: We have specified the inclusion/exclusion criteria for animal studies in accordance with ARRIVE guidelines. (See Experimental Design, Lines [117-120]).

3. Data Transparency & Interpretation Problems

- Effect sizes missing: Only P-values reported. No confidence intervals, standard errors, or effect size metrics. The excuse "abstract length" is irrelevant—these belong in main text/figure legends.

Response: We have added confidence intervals, standard errors, and effect size metrics to all relevant results sections. (See Results).

- Primary/secondary outcomes: Not hierarchically distinguished as requested.

Response: We have clearly distinguished primary and secondary outcomes as requested. (See Experimental Design, Lines [130-132]).

- Biologically questionable data: The AOPP issue (initially reported as increasing with treatment) suggests either a serious typographical error or lack of understanding. While corrected in the provided manuscript, the fact this reached review is concerning.

Response: The AOPP issue has been corrected, and we have clarified the correction in the abstract. We confirm that the error was typographical. (See Abstract, Lines [29-30]).

Specific Manuscript Deficiencies (As Currently Submitted):

- Abstract (Lines 12-13): "randomization was performed within each cage"—still no method details.

Response: Abstract revised to provide a detailed description of the randomization process. (See Abstract, Lines [12-14]).

- Methods 2.3 (Lines 114-115): Duplicate text from abstract; no additional experimental design details.

Response: Comprehensive details of the experimental design have been updated. (See Methods 2.3, Lines [115-120]).

- Methods 2.12 (Lines 170-174): "randomized and blinded manner"—insufficient detail for reproducibility.

Response: Enhanced with sufficient detail for reproducibility. (See Methods 2.12, Lines [179-188]).

- Results: All figures report $*P < 0.001$ but no effect sizes. This is not acceptable for modern scientific publishing.

Response: We have added confidence intervals, standard errors, and effect size metrics to all relevant results sections. (See Results).

- Discussion: Overstates conclusions ("may influence" in abstract vs. definitive statements in discussion).

Response: Discussion has been revised and parts have been removed to ensure consistency in the strength of the conclusions.

EIC Decision:

Your manuscript requires fundamental rewriting to address critical deficiencies in scientific conduct and reporting. You have one opportunity to submit a revised version that fully complies with academic standards; incomplete or evasive responses will result in immediate rejection without further review. First, you must completely rewrite your response letter, not the manuscript itself, to provide a genuine, point-by-point rebuttal with exact page/line numbers for every change. Unacceptable patterns in your previous response included fourteen instances of dismissive "Thank you for your comment" without substantive engagement; factually false claims of revisions that the Associate Editor confirmed absent; and an unverifiable "file conversion" excuse that demonstrates disregard for the review process. No template language is permitted; each reviewer comment must be answered with specific, trackable modifications. Second, you must achieve full ARRIVE 2.0 compliance despite prior warnings. Your submission remains non-compliant in several critical areas: you must provide explicit power analysis calculations or cite validated precedent for $n=6/\text{group}$ in Methods 2.3 (Lines 114-115), where "randomly divided" is currently insufficient specify the randomization method (e.g., computer-generated sequences), allocation concealment mechanism, and timeline. In Methods 2.12 (Lines 170-174), your blinding protocol description must clarify who was blinded (e.g., pathologist, statistician), to what (treatment groups, animal IDs), and how (coded samples, third-party allocation). Your claim that humane endpoints are "not possible" is factually incorrect and violates ethical standards; ARRIVE 2.0 mandates explicit criteria, which you must provide or justify their absence with institutional approval documentation. Additionally, "All mice were healthy" is scientifically invalid as inclusion/exclusion criteria;

you must state explicit, pre-specified criteria for animal exclusion or data censoring. Third, your data transparency and statistical reporting require complete overhaul: throughout the Results, replace lone $*P<0.001$ statements with confidence intervals, standard errors, and effect size metrics (e.g., Cohen's d , partial η^2), as "abstract length" is not an excuse—this belongs in main text and figure legends. You must explicitly designate primary versus secondary outcomes with pre-specified analysis plans. While the AOPP data correction is noted, you must provide a verification statement confirming the error was typographical, not analytical, and describe steps taken to prevent future occurrences. Specific manuscript deficiencies remain: the abstract (Lines 12-13) must not duplicate text from Methods and must expand randomization description beyond "within each cage"; Methods 2.3 (Lines 114-115) must remove verbatim repetition from the abstract and insert comprehensive experimental design details; all figure legends must immediately add effect size and variability information; and the Discussion must align conclusion strength with abstract language to remove overstatement. This is your sole opportunity for revision; any pattern of deflection, omission, or non-compliance will result in rejection and may affect future submissions to this journal. Submit your revised manuscript and a properly constructed response letter within 20 days.

Response: We appreciate the opportunity to revise our manuscript. We believe that the changes made significantly improve the quality and integrity of our work. We are committed to adhering to the highest standards of academic publishing and hope that our revisions meet the expectations of the editorial team and reviewers.

OPEN PEER REVIEW

Revision (3)

REFEREE : EIC

20 Dec 2025

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

Your work underwent a rigorous peer-review process, and the reviewers and editorial board were impressed by the originality, scientific rigor, and relevance of your findings. We believe your contribution will be of significant interest to our readership and will advance the field of natural pharmaceutical products.

Before publication, our production team will contact you regarding final formatting, proofs, and any necessary administrative steps. Please ensure that all authors have approved the final version of the manuscript and that any required ethical or copyright documentation is in order.

On behalf of the editorial board, I congratulate you and your co-authors on this excellent work and thank you for choosing to publish in JJNPP.