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OPEN PEER REVIEW

Tanshinone ⅡA Inhibits Alveolar Macrophage Polarization, Inflammation and Mitochondrial Damage by Regulating the PAPR-1 Signaling Pathway

Na Zhang, Xinjia Yang, Jiefei Liang, Chunyan Zhu, Guohua Shen, Chao Luo, Weibin Wu

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About this report

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

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1 Original submission

4 comments · 26 Sep 2025 – 30 Sep 2025

Referee 1 Reviewer

MINOR REVISION 26 Sep 2025

The manuscript presents a well-structured study with clear objectives and methodologies. It is written in an overall scientific and appropriate register. Nonetheless, some errors require correction, and certain data presentations are awkward and should be clarified.

• In the Introduction part, Lines 16-17:

"This supports the polarization of macrophages towards the pro-inflammatory phenotype (M1), thereby enhancing host defense against pathogens (7, 8)." This sentence seems to contradict the overall premise of the paper, which is that Tanshinone IIA inhibits M1 polarization due to its anti-inflammatory effects. While M1 macrophages are indeed important for host defense, the phrasing here could be misinterpreted as a positive effect of PARP-1 in the context of the study's anti-inflammatory focus. It would be preferable to rephrase it to clearly state that PARP-1 promotes M1 polarization, which is then targeted by Tanshinone IIA.

• In the Materials and Methods section, Line 54:

"0.45µM PVDF membrane was purchased from Merck Co. …." The unit for the PVDF membrane should likely be "µm" (micrometer) for pore size, not "µM" (micromolar), which is a concentration unit.

• In the Discussion part:

Several sentences start similarly or convey very similar information. For example, lines 213-214: "PARP-1 is implicated in the regulation of numerous inflammatory responses (6), which is intimately associated with the activation of immune cells…" and lines 216-217: "PARP1 enhances macrophage polarization towards the M1 phenotype by promoting the transcription and post." It is advisable to integrate these sentences more seamlessly.

The "In conclusion" paragraph (line 268) largely rephrases findings already presented in the abstract and earlier parts of the discussion. While a concise summary is good, it could be more impactful if it focuses on the broader implications of the findings and future research directions.

Referee 2 Reviewer

MAJOR REVISION 30 Sep 2025

The manuscript entitled " Tanshinone ⅡA inhibits alveolar macrophage polarization, inflammation and mitochondrial damage by regulating the PAPR-1 signaling pathway" presents data about the mechanism of tanshinone IIA in inhibiting macrophage polarization, mitigating the inflammatory response, and preventing mitochondrial damage.

Suggestions are as follows:

The manuscript contains some grammatical errors, and the language needs some improvement.

In the abstract, the results should be presented along with their statistical significance. This means that the authors must explain what percentage increase or reduction in each parameter was observed or at what levels these reductions or increases were statistically significant.

In the materials and method section, line 75, please specify the name and volume of the reagent and the brand of the spectrophotometer. The Griess assay should also be referenced.

In the materials and method section, line 83, please specify the brand of the microplate reader. In line 87, please specify the brand of the flow cytometer.

In the results section, the resolution of the western blot images should be improved.

In the discussion section, the authors should complete the discussion by referencing studies that investigated

tanshinone IIA or similar compounds in vitro or in vivo and reported similar or opposite results. This will help the authors support their results or discuss why their results differ from those of previous studies.
In the discussion section, the authors should explain the limitations of their research.
The last paragraph of the discussion should be revised to focus on the general conclusion of this study and recommendations for future work (do not repeat the results of the study).

Associate Editor

MAJOR REVISION 30 Sep 2025

Dear authors,
Below, please see the comments made by 2 expert reviewers on your submission. As seen in the comments, both reviewers requested some revisions to your initial submission. I will therefore ask you to please carefully read all the comments and provide thoughtful, reference-based answers to each concern raised by the 2 reviewers, point by point. Finally, revise your manuscript accordingly.
With kind regards,
Jalal Pourahmad
Associate Editor

Reviewer 1:
The manuscript presents a well-structured study with clear objectives and methodologies. It is written in an overall scientific and appropriate register. Nonetheless, some errors require correction, and certain data presentations are awkward and should be clarified.
• In the Introduction part, Line 16-17:
"This supports the polarization of macrophages towards the pro-inflammatory phenotype (M1), thereby enhancing host defense against pathogens (7, 8)." This sentence seems to contradict the overall premise of the paper, which is that Tanshinone IIA inhibits M1 polarization due to its anti-inflammatory effects. While M1 macrophages are indeed important for host defense, the phrasing here could be misinterpreted as a positive effect of PARP-1 in the context of the study's anti-inflammatory focus. It would be preferable to rephrase it to clearly state that PARP-1 promotes M1 polarization, which is then targeted by Tanshinone IIA.
• In the Materials and Methods section, Line 54:
"0.45µM PVDF membrane was purchased from Merck Co.…." The unit for the PVDF membrane should likely be "µm" (micrometer) for pore size, not "µM" (micromolar), which is a concentration unit.
• In the Discussion part:
Several sentences start similarly or convey very similar information. For example, lines 213-214: "PARP-1 is implicated in the regulation of numerous inflammatory responses (6), which is intimately associated with the activation of immune cells..." and line 216-217: "PARP1 enhances macrophage polarization towards the M1 phenotype by promoting the transcription and post." It is advisable to integrate these sentences more seamlessly.
The "In conclusion" paragraph (lines 268) largely rephrases findings already presented in the abstract and earlier parts of the discussion. While a concise summary is good, it could be more impactful if it focuses on the broader implications of the findings and future research directions.
Decision:
Minor revision

Reviewer 2:
The manuscript entitled " Tanshinone ⅡA inhibits alveolar macrophage polarization, inflammation and mitochondrial damage by regulating the PAPR-1 signaling pathway" presents data about the mechanism of tanshinone IIA in the inhibition of macrophage polarization, mitigation of the inflammatory response, and prevention of mitochondrial damage.

Suggestions are as follows:
The manuscript contains some grammatical errors, and the language needs some improvement.
In the abstract, the results should be presented along with statistical significance. This means that the authors must explain what percentage increase or reduction was observed in each parameter or at which statistical significance levels the reduction or increase in each parameter occurred.
In the materials and methods section, line 75, please specify the name and volume of the reagent and the brand of the spectrophotometer. The Griess assay should also be referenced.
In the materials and methods section, line 83, please specify the brand of the microplate reader. Line 87, please specify the brand of the flow cytometer.
In the results section, the resolution of western blot images should be improved.
In the discussion section, the authors should complete the discussion by referencing studies that investigated tanshinone IIA or similar compounds in vitro or in vivo and reported similar or opposite results. This will help the authors prove their results or discuss why their results differ from those of previous studies.
In the discussion section, the authors should explain the limitations of their research.
The last paragraph of the discussion should be revised to focus on the general conclusion of this study and recommendations for future work (do not repeat the results of the study).
Decision:
Major revision

Editor-in-Chief MAJOR REVISION 30 Sep 2025

Major Revision

2

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.

October 03, 2025

IJPR-166272

Dear Dr. Elham Rezaee,

We sincerely appreciate the comments and suggestions from you and the reviewers on our manuscript. After careful revision, we are now pleased to submit our revised version of manuscript back to you. We believe the revision has well addressed the comments and enhanced the overall quality of our work. Here are the point-to-point responses (highlighted in blue) refer to each of the reviewers' comments (in *italics*):

Reviewer #1

The manuscript presents a well-structured study with clear objectives and methodologies. It is written in an overall scientific and appropriate register. Nonetheless, some errors require correction, and certain data presentations are awkward and should be clarified.

Response: We are deeply thankful for your comprehensive review and the constructive guidance you provided, which have helped us to enhance critical elements of the manuscript. We sincerely appreciate your contribution to this work.

Comment 1: In the Introduction part, Line 16-17:

"This supports the polarization of macrophages towards the pro-inflammatory phenotype (M1), thereby enhancing host defense against pathogens (7, 8)." This sentence seems to contradict the overall premise of the paper, which is that Tanshinone IIA inhibits M1 polarization due to its anti-inflammatory effects. While M1 macrophages are indeed important for host defense, the phrasing here could be misinterpreted as a positive effect of PARP-1 in the context of the study's anti-inflammatory focus. It would be preferable to rephrase it to clearly state that PARP-1 promotes M1 polarization, which is then targeted by Tanshinone IIA.

Response 1: Thank you for your suggestion. We have refined the expression in the manuscript to emphasize the role of PARP-1 in amplifying inflammatory reactions subsequent to macrophage polarization.

Comment 2: In the Materials and Methods section, Line 54:

"0.45μM PVDF membrane was purchased from Merck Co….The unit for the PVDF membrane should likely be "μm" (micrometer) for pore size, not "μM" (micromolar), which is a concentration unit.

Response 2: We are sorry for the mistake. And the corrected version has been revised in the manuscript.

Comment 3: In the Discussion part:

several sentences start similarly or convey very similar information. For example, lines 213-214: "PARP-1 is implicated in the regulation of numerous inflammatory responses (6), which is intimately associated with the activation of immune cells..." and line 216-217: "PARP1 enhances macrophage polarization towards the M1 phenotype by promoting the transcription and post. It is advisable to integrate these sentences more seamlessly.

Response 3: Thank you for your comment. We have refined the presentation of this component within the manuscript.

Comment 4: In the Discussion part:

The "In conclusion" paragraph (lines 268) largely rephrases findings already presented in the abstract and earlier parts of the discussion. While a concise summary is good, it could be more impactful if it focuses on the broader implications of the findings and future research directions.

Response 4: Thanks a lot for your suggestion. We have improved the conclusion expression of the discussion section, focusing on highlighting the significance and shortcomings of the research.

Reviewer #2

The manuscript entitled " Tanshinone ⅡA inhibits alveolar macrophage polarization, inflammation and mitochondrial damage by regulating the PAPR-1 signaling pathway" presents data about the mechanism of tanshinone IIA in inhibition of macrophage polarization,

mitigation of inflammatory response, and prevention of mitochondrial damage.

Response: We sincerely appreciate your recognition of the research significance and the rigor of our methodology. Your insightful comments have not only affirmed the value of our work but also provided us with valuable perspectives for further improvement.

Comment 1: The manuscript contains some grammatical errors and the language needs some improvements.

Response 1: We apologize for the language issue and have now carefully revised the manuscript accordingly.

Comment 2: In abstract, the results should be presented along with statistical significance. It means that the authors must explain how percent increase or reduction in each parameter was observed or the reduction or increase in each parameter was at which statistical levels.

Response 2: Thanks for your comment. We have refined the expression of the results section in the abstract.

Comment 3: In materials and method section, line 75, please determine the name and the volume of reagent and the brand of spectrophotometer. The Griess assay also should be referenced.

Response 3: We appreciate for your suggestion. The manuscript has been updated to include detailed information on reagent names, dosages, and equipment brands.

Comment 4: In materials and method section, line 83, please determine the brand of microplate reader. Line 87, please determine the brand of flow cytometer.

Response 4: Thank you for your comment. And the details have now been added in the manuscript.

Comment 5: In results section, the resolution of western blot images should be improved.

Response 5: We appreciate for your comment. We have refined the resolution of the western blot images, without altering the presentation of the results. However, due to the size restrictions

on uploaded images in the submission system, the improvement in image quality may not be very noticeable.

Comment 6: In discussion section, the authors should complete the discussion by referencing to studies which performed about tanshinone IIA or similar compounds invitro or invivo and reported similar or opposite results. This contributes to authors to prove their results or to discuss why their results are different with previous studies.

Response 6: We appreciate for your comment. We have added comments and comparisons of existing anti-inflammatory studies on tanshinone IIA in the discussion

Comment 7: In discussion section, the authors should explain the limitation of their research.

Response 7: Thank you for your comment. We have revised the discussion by adding a description of the limitations of the research.

Comment 8: The last paragraph of discussion should revise with focus on general conclusion of this study and recommendation for future work (do not repeat the results of study).

Response 8: Thank you for your suggestion. We have improved the expression of the last paragraph, focusing on highlighting the significance and shortcomings of the research.

Again, we appreciate a lot for the valuable comments and constructive suggestions from the editor and the reviewers. We hope the revised format of manuscript responds clearly to address all the questions.

With best regards and sincerely,

2 Revision 1

3 comments · 12 Oct 2025 – 13 Oct 2025

Referee 2 Reviewer

MINOR REVISION 12 Oct 2025

In the discussion section, the authors should complete the discussion by referring to studies that were performed on tanshinone IIA or similar compounds in vitro or in vivo and reported similar or opposite results. This helps the authors prove their results or discuss why their results differ from those of previous studies.

In the discussion section, line 221, the sentences in this paragraph need references. Please add references for these sentences.

Associate Editor

MINOR REVISION 12 Oct 2025

Dear authors,
Please see below the comments made by one of your former reviewers on your revised manuscript. As seen in his comments, he still feels that your manuscript needs some necessary corrections. I will therefore ask you again to read carefully the remaining comments and once again revise your manuscript accordingly.
With kind regards,
Jalal Pourahmad
Associate Editor

Reviewer's Comment:
In the discussion section, the authors should complete the discussion by referring to studies that were performed on tanshinone IIA or similar compounds in vitro or in vivo and reported similar or opposite results. This helps the authors prove their results or discuss why their results differ from those of previous studies.
In the discussion section, line 221, the sentences in this paragraph need references. Please add references for these sentences.
Decision:
Minor revision

Editor-in-Chief

MINOR REVISION 13 Oct 2025

Minor Revision

3

Revision 2

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.

October 13, 2025

IJPR-166272

Dear Dr. Elham Rezaee,

We sincerely appreciate the comments and suggestions from you and the reviewers on our manuscript. After careful revision, we are now pleased to submit our revised version of manuscript back to you. We believe the revision has well addressed the comments and enhanced the overall quality of our work. Here are the point-to-point responses (highlighted in blue) refer to each of the reviewers' comments (in *italics*):

Reviewer #1

Comment 1: In discussion section, the authors should complete the discussion by referencing to studies which performed about tanshinone IIA or similar compounds invitro or invivo and reported similar or opposite results. This contributes to authors to prove their results or to discuss why their results are different with previous studies.

Response 1: Thank you for your suggestion. In the revised manuscript of R1 version, we have already discussed the anti-inflammatory effect of tanshinone IIA and its associated mechanism in the discussion section, and supplemented it in lines 242-250. And now, we have further refined the discussion of this part.

Comment 2: In discussion section, line 221, the sentences in this paragraph need references. Please add references for these sentences.

Response 2: We appreciate for your suggestion. The reference has been marked in the manuscript.

Again, we appreciate a lot for the valuable comments and constructive suggestions from the editor and the reviewers. We hope the revised format of manuscript responds clearly to address all the questions.

With best regards and sincerely,

3 Revision 2

3 comments · 31 Oct 2025 – 1 Nov 2025

Referee 1 Reviewer

ACCEPT 31 Oct 2025

The authors have carefully and clearly addressed the reviewers' concerns. The revisions improve both the interpretive depth and citation accuracy of the work. The manuscript now fulfills the requirements for publication.

Associate Editor

ACCEPT 1 Nov 2025

Dear authors,
I am pleased to inform you that your 2nd revised manuscript was accepted by the final reviewer. Please see her comment below.
With kind regards,
Jalal Pourahmad
Associate Editor

Final review comment:
The authors have carefully and clearly addressed the reviewers' concerns. The revisions improve both the interpretive depth and citation accuracy of the work. The manuscript now fulfills the requirements for publication.
Decision:
Accept

Editor-in-Chief

ACCEPT 1 Nov 2025

Accept