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Jundishapur Journal of Natural Pharmaceutical Products

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Peer Review Report for "Anti-inflammatory Effects of *Avicennia marina* on Carrageenan-Induced Paw Edema in Rats"

Author(s): Ali Asghar Hemmati, Mohammadamin Eslami Samarin, Mohammadreza Noveiri, Fatemeh Kiashi

Review Timeline:

Submit Date:	25 Dec 2024
Revised Date:	2 Aug 2025
Accepted Date:	2 Aug 2025

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

Zahra Shokati Eshkiki : Reviewer

29 Dec 2024

Dear Author,

Thank you for submitting your manuscript, "Anti-inflammatory Effects of *Avicennia marina* on CarrageenanInduced Paw Edema in Rats" to the Jundishapur Journal of Natural Pharmaceutical Products. Please find the comments below, which I hope will be constructive and helpful.

Methods

a) Kindly include a distinct section titled: Isolation Procedure- to provide a comprehensive explanation of the maceration method.

b) I believe that an additional step is necessary, specifically an In-vitro Anti-Inflammatory Assay. This assay should be conducted to determine the in vitro anti-inflammatory activity of the extracts.

c) I recommend creating a distinct section for Animal studies that includes:

Animal studies

- Lipid peroxidation study
- Measurement of IL-6
- In vivo anti-inflammatory assay

d) Kindly provide a comprehensive and precise list of the brands and kits utilized for the equipment and consumables in this study.

Discussion

I find the discussion section lacking in depth. In contrast to the extensive introduction, the discussion, which is crucial to the paper, is notably brief and offers minimal comparison with similar studies. A thorough comparison and presentation of your findings alongside relevant research is necessary. Benefits and constraints of your research in comparison to other studies.

References

It is advisable to incorporate more recent relevant studies, particularly in the discussion section, to enhance comparisons with your work.

Writing

The manuscript contains spelling and grammatical errors. Kindly conduct a thorough revision of the document for clarity and adherence to writing standards.

Thank you again for submitting your work.

REFeree : Reviewer

16 Jan 2025

Dear Editor in-chief

The following questions strongly requested to be answered to improve the quality of the present manuscript.

Introduction:

1. Line 28-58 of introduction is not well written. It explains the same topic repeatedly in different paragraphs. This part should be completely revised and summarized in 4-5 lines.
2. The authors try to highlight the aim of their study by mentioning that there is not information about the anti-inflammatory effects of Avicenna marina extract at the molecular and cellular levels, so why you did not focus on molecular mechanisms controlling the signalling pathways related to anti-inflammatory effects of Avicenna

marina extract and only measured blood concentration of IL6 and MDA which have been measured in several previous studies?

3. Based on previous studies, phenolic content, total flavonoid content and the anti-inflammatory effects and inhibitory effects of *Avicenna marina* extract has been established on IL6, so what is the novelty of present study in comparison to previous ones?

Materials and methods

4. what is the sensitivity of IL6 kit? Add the sensitivity and manufacturer country of using kit to the text.

5. How do you analyse the data? The manuscript has not statistical part. How do you understand there is a significant or non-significance difference between groups? What was your p- value levels? Do data were present as mean $\pm$ SEM or SE?

6. How was done blood sampling? try to give comprehensive information about the time, volume and methods of blood drawing.

7. How do you select the dose of extract for your study?

Results

8. in material parts you mentioned that Group 4, the 131 positive control, received 10 mg/kg of the non-steroidal anti-inflammatory drug, while in results part you present the data by intraperitoneal injection of indomethacin (300 mg/kg), try to give a clear information about the used dose of indomethacin. Also, try to give information and reference for selecting the dose of indomethacin.

9. In material parts, there is not any information about the method and kit to measure MDA, however, in results part you present some data about MDA, so, try to clearly discuss do you measure this factor or not?

10. results part should be revised completely. you present the data by using significant difference between groups. Try to present data by using the clear explanation such as decrease or increase.

11. using $p > 0.05$ is not common for presenting data, these part should be corrected in the text.

12. In the figure 1, is not clear. In the caption try to exactly explain which factors are measured in this figure. Also, to compare the groups, you should use symbols on curves which shows the significant difference between groups.

13. Captions of figures 2 and 3 has been writing as following: Mean Malondialdehyde Levels in Rat Paw Tissue and Evaluation of IL-6 Levels in Rat Paw Tissue. Based on material and method part you try to measure these factors in serum not tissue. So revised this part. or if you measure them in tissue samples try to exactly explain how do you do it in material and method part and delete serum measuring information from text.

Discussion

14. Discussion is very short and non- comprehensive. Most part of it repeats again the results part. Discussion part should be rewritten by comparing the present results by several previous studies which report the effects of *Avicenna marina* extract on inflammatory factors such IL6, TNF α and IL1 β in several inflammatory related condition.

15. you try discuss about the anti-inflammatory mechanisms of other plant. However, there are several studies about anti- inflammatory effects of *Avicenna marina* extract

in different experimental diseases models. So, try to rewrite the discussion part by using published manuscripts related to Avicenna marina extract medicinal potential for inhibit inflammatory responses.

16. In conclusion part you mentioned 'IL-6 expression', in the present study real time PCR and gene expression has not been done, you measure only the blood concentration of IL6. So, try to correct this sentence.

Sara Bahrainian : Associate Editor

18 Jan 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.

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

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 Reviewers,

We sincerely thank you for your thorough review and invaluable comments. We have carefully considered each point raised and revised the manuscript accordingly. Below, we provide detailed replies to all comments
reply to reviewer 1

a) *Kindly include a distinct section titled: Isolation Procedure- to provide a comprehensive explanation of the maceration method.* The text has been added.

b) *I believe that an additional step is necessary, specifically an In-vitro Anti-Inflammatory Assay. This assay should be conducted to determine the in vitro anti-inflammatory activity of the extracts.*

We sincerely thank the reviewer for this valuable suggestion. As noted, the present study was specifically designed to evaluate the anti-inflammatory activity of *Avicennia marina* using an in vivo carrageenan-induced paw edema model in rats. To our knowledge, no prior studies have comprehensively assessed the in vitro anti-inflammatory mechanisms of this plant, and our work aimed to provide foundational in vivo evidence. We fully agree that future studies should include in vitro assays, such as those involving macrophage cell lines to elucidate the molecular pathways and cellular targets involved. This will help to better characterize the extract's mechanism of action. Accordingly, we have mentioned this point in the *Discussion* section as a direction for future research.

c) *I recommend creating a distinct section for Animal studies that includes:*

Animal studies

- *Lipid peroxidation study*
- *Measurement of IL-6*
- *In vivo anti-inflammatory assay*

The content has been modified.

d) *Kindly provide a comprehensive and precise list of the brands and kits utilized for the equipment and consumables in this study.*

The change has been applied.

References

It is advisable to incorporate more recent relevant studies, particularly in the discussion section, to enhance comparisons with your work.

The section has been revised.

Writing

The manuscript contains spelling and grammatical errors. Kindly conduct a thorough revision of the document for clarity and adherence to writing standards.

The text has been edited.

Thank you again for submitting your work.

Reviewer 2

Line 28-58 of introduction is not well written. It explains the same topic repeatedly in different paragraphs. This part should be completely revised and summarized in 4-5 lines.

The section has been revised.

*The authors try to highlight the aim of their study by mentioning that there is not information about the anti-inflammatory effects of *Avicenna marina* extract at the molecular and cellular levels, so why you did not focus on molecular mechanisms controlling the signalling pathways related to anti-inflammatory effects of *Avicenna marina* extract and only measured blood concentration of IL6 and MDA which have been measured in several previous studies?*

Thank you for raising this important point. In this study, we aimed to evaluate the in vivo anti-inflammatory effects of *Avicennia marina* using the carrageenan-induced paw edema model, with a focus on establishing a dose-dependent response and quantifying both paw swelling and relevant biochemical markers such as IL-6 and MDA. We agree that examining intracellular signalling pathways like NF- κ B and MAPK would provide a deeper mechanistic understanding; however, due to resource limitations, this aspect was beyond the scope of the present work. We have now acknowledged this limitation in the revised Discussion and plan to address it in future studies. While previous investigations by Zamani Gandomani and Forouzandeh Malati (2014) (DOI: 10.22037/ijpr.2014.1574) and Bayat et al. (2012) (DOI: 10.22092/irjns.2012.100472) evaluated *Avicennia marina* extract, they differ fundamentally from our work. The former examined antinociceptive activity in a formalin test without assessing inflammation-related biomarkers, and the latter focused on adjuvant-induced arthritis, reporting only clinical findings without biochemical analysis or dose-response evaluation. Our study is the first to provide a comprehensive in vivo assessment of the extract's anti-inflammatory activity in an acute inflammation model with concurrent measurement of IL-6, MDA, and paw edema across three extract doses.

*Based on previous studies, phenolic content, total flavonoid content and the anti-inflammatory effects and inhibitory effects of *Avicenna marina* extract has been established on IL6, so what is the novelty of present study in comparison to previous ones?*

We appreciate this thoughtful question. Although certain aspects such as phenolic and flavonoid content or IL-6 inhibition have been explored in earlier studies, our work is, to our knowledge, the first to integrate a dose-dependent in vivo analysis using a standardized carrageenan-induced paw edema model. This model enabled us to track inflammation progression over time while also assessing IL-6 and MDA levels alongside phytochemical profiling. Previous related studies, such as that by Zamani Gandomani and Forouzandeh Malati (2014) (DOI: 10.22037/ijpr.2014.1574), focused only on the analgesic effect in a pain model, and the study by Bayat et al. (2012) (DOI: 10.22092/irjns.2012.100472) was limited to clinical observations in a chronic arthritis model without examining inflammatory mediators or oxidative stress markers. Our study extends the findings of previous research by offering a more complete and practical evaluation of *A. marina*'s anti-inflammatory effects in an acute inflammation model, thus adding new and useful information to the existing literature.

what is the sensitivity of IL6 kit? Add the sensitivity and manufacturer country of using kit to the text.

Serum IL-6 levels were measured using a commercial ELISA kit (Catalogue No. SL0411Ra; SunLong Biotech Co., Ltd, China), according to the manufacturer's instructions. The sensitivity of the kit was 1.5 ng/L, and the assay range was 8–150 ng/L. Blood samples were collected after 5 hours of treatment, centrifuged at 3000 rpm for 20 minutes, and the serum was stored at –20 °C until analysis.

This part was added to the manuscript.

How do you analyse the data? The manuscript has not statistical part. How do you understand there is a significant or non-significance difference between groups? What was your p- value levels? Do data were present as mean $\pm$ SEM or SE?

For evaluating the statistical significance of differences between groups, one-way analysis of variance (ANOVA) with Tukey's post hoc test was performed. Data are expressed as mean $\pm$ SD.

How was done blood sampling? try to give comprehensive information about the time, volume and methods of blood drawing. Blood samples were collected 5 hours after carrageenan injection, immediately following the final paw volume measurement. Under deep ether anesthesia, approximately 1.0 mL of blood was obtained via cardiac puncture using a sterile syringe and needle. The blood was transferred into plain microtubes and allowed to clot at room temperature for 30 minutes. Samples were then centrifuged at 3000 rpm for 20 minutes at 4 °C (Hettich, Germany), and the serum was carefully separated and stored at -20 °C until biochemical analysis.

This part was added to the manuscript.

How do you select the dose of extract for your study?

The doses of 200 and 400 mg/kg were selected based on previous studies in which these concentrations demonstrated significant anti-inflammatory effects (DOI: 10.22037/ijpr.2014.1574; DOI: 10.22092/irjns.2012.100472). We also included a higher dose of 600 mg/kg to evaluate whether a greater therapeutic effect could be achieved. However, our findings indicated that the 400 mg/kg dose produced the most pronounced anti-inflammatory effect, and increasing the dose to 600 mg/kg did not result in any statistically significant additional improvement.

in material parts you mentioned that Group 4, the 131 positive control, received 10 mg/kg of the non-steroidal anti-inflammatory drug, while in results part you present the data by intraperitoneal injection of indomethacin (300 mg/kg), try to give a clear information about the used dose of indomethacin. Also, try to give information and reference for selecting the dose of indomethacin.

Correction has been made.

In material parts, there is not any information about the method and kit to measure MDA, however, in results part you present some data about MDA, so, try to clearly discuss do you measure this factor or not?

The section has been revised.

results part should be revised completely. you present the data by using significant difference between groups. Try to present data by using the clear explanation such as decrease or increase.

The section has been revised.

using $p > 0.05$ is not common for presenting data, these part should be corrected in the text.

The text has been edited.

In the figure 1, is not clear. In the caption try to exactly explain which factors are measured in this figure. Also, to compare the groups, you should use symbols on curves which shows the significant difference between groups .

Thank you for your observation. As the statistical comparisons and significance indicators (e.g., p -values and symbols) are presented separately in Table 1 and subsequent figures, we have clarified this in the revised caption of Figure 1 to avoid confusion. We appreciate your attention to clarity in data presentation.

Captions of figures 2 and 3 has been writing as following: Mean Malondialdehyde Levels in Rat Paw Tissue and Evaluation of IL-6 Levels in Rat Paw Tissue. Based on material and method part you try to measure these factors in serum not tissue. So revised this part. or if you measure them in tissue samples try to exactly explain how do you do it in material and method part and delete serum measuring information from text.

The change has been applied.

Discussion

discussion is very short and non- comprehensive. Most part of it repeats again the results part. Discussion part should be rewritten by comparing the present results by several previous studies which report the effects of Avicenna marina extract on inflammatory factors such IL6, TNF α and IL1 β in several inflammatory related condition.

The section has been revised.

you try discuss about the anti-inflammatory mechanisms of other plant. However, there are several studies about anti- inflammatory effects of Avicenna marina extract in different experimental diseases models. So, try to rewrite the discussion part by using published manuscripts related to Avicenna marina extract medicinal potential for inhibit inflammatory responses.

Thank you for your valuable comment. We fully agree that the discussion should be based on published studies specifically related to *Avicennia marina* and its anti-inflammatory effects. In response, we carefully reviewed the available literature and incorporated the two most relevant and directly related studies, which examined the effects of *A. marina* extract on pro-inflammatory cytokines (IL-6, TNF- α , IL-1 β) in disease models such as arthritis and diabetic liver injury. These references have been clearly discussed and compared with our findings in the revised Discussion section.

We acknowledge that although *A. marina* has been traditionally used for inflammatory conditions, there is currently limited experimental research available that specifically addresses its anti-inflammatory mechanisms. Therefore, this study helps to expand the existing knowledge by demonstrating its efficacy in an acute inflammation model (carrageenan-induced paw edema), and we believe it provides a valuable addition to the limited but growing body of literature on this plant.

In conclusion part you mentioned 'IL-6 expression', in the present study real time PCR and gene expression has not been done, you measure only the blood concentration of IL6. So, try to correct this sentence.

The change has been applied.

OPEN PEER REVIEW

Revision (1)

Zahra Shokati Eshkiki : Reviewer

8 Jun 2025

Dear Author,

Thank you for submitting your manuscript entitled "Anti-inflammatory Effects of *Avicenna marina* on Carrageenan Induced Paw Edema in Rats" to Jundishapur Journal of Natural Pharmaceutical Products. Below, please find the comments, which I hope will be constructive and helpful.

1. Title:

- The title is accurate; however, there is a mistake in it: "*Avicenna marina*" should be changed to "*Avicennia marina*" (throughout the document).

2. Introduction:

- Cut down on the general background and put greater emphasis on the current in vivo or in vitro data for *A. marina*.

- Stress the shortcomings of previous models or data, such as the absence of acute inflammatory studies with dose-response curves.

3. Methods:

- Provide a more strong justification for dosage selection with citations that go beyond just citing previous effectiveness.

4. Conclusion:

- It's worth mentioning that *A. marina* has promise for chronic inflammatory models as well as acute ones.

Thank you again for submitting your work.

REFEREE : Associate Editor

14 Jul 2025

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

REFEREE : EIC

14 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 Reviewer,

We sincerely thank you for your thorough review and invaluable comments. We have carefully considered each point raised and revised the manuscript accordingly. All edits have been highlighted in green for your convenience.

Reply to reviewer

1. Title:

- The title is accurate; however, there is a mistake in it: "Avicenna marina" should be changed to "Avicennia marina" (throughout the document).

The change has been applied.

2. Introduction:

- Cut down on the general background and put greater emphasis on the current in vivo or in vitro data for *A. marina*.

- Stress the shortcomings of previous models or data, such as the absence of acute inflammatory studies with dose-response curves.

The section has been revised.

3. Methods:

- Provide a more strong justification for dosage selection with citations that go beyond just citing previous effectiveness.

This part was added to the manuscript.

4. Conclusion:

- It's worth mentioning that *A. marina* has promise for chronic inflammatory models as well as acute ones.

This section has been edited.

OPEN PEER REVIEW

Revision (2)

Zahra Shokati Eshkiki : Reviewer

23 Jul 2025

Dear Author,

Thank you for submitting your manuscript entitled "Anti-Inflammatory Effects of *Avicennia marina* on Carrageenan-Induced Paw Edema in Rats" to Jundishapur Journal of Natural Pharmaceutical Products. Please, find the comments, which I hope will be constructive and helpful.

- The research talks about IL-1 β and TNF- α ; however, it doesn't provide any real outcomes or data for these cytokines. This is wrong and needs to be fixed or explained.
- The route of administration for *A. marina* extract with indomethacin is intraperitoneal, which may not be the same as conventional or clinical methods (such as oral). This makes it less useful for translation.
- There is no mention of blinding or randomization during treatment or analysis, which is necessary to minimize bias.
- We don't know whether vehicle control was employed for the ethanol extract (for example, diluting ethanol without the extract). If leftover ethanol had any effects, it could compromise the findings.
- The number of samples (n=6) per group is fine for an exploratory study; however, it may not be statistically strong enough to find smaller variations, particularly across extract dosages.
- It was said that statistical comparisons between extract dosages were not significant; however, 400 mg/kg is said to be the "most effective." This requires more numbers or clarification.
- The IL-6 ELISA kit range (8–150 ng/L) doesn't seem to match the claimed sensitivity (1.5 ng/L). This may need to be explained or fixed.
- Please ensure the findings are aligned with the discussion, and avoid mentioning cytokines that were not quantified.
- Fix or explain any differences in methods (for example, TNF- α /IL-1 β or the dosage strategy).

Best Regards

REFeree : Associate Editor

23 Jul 2025

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

REFeree : EIC

23 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 (3)

Reply to Reviewers

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You can read the authors' responses to the reviewers' comments in the next page.

Dear Reviewer,

We sincerely thank you for your thorough review and invaluable comments. We have carefully considered each point raised and revised the manuscript accordingly. All edits have been highlighted in yellow for your convenience.

Reply to the reviewer

- The research talks about IL-1 β and TNF- α ; however, it doesn't provide any real outcomes or data for these cytokines. This is wrong and needs to be fixed or explained.

Thank you for your observation. We have revised the manuscript to clarify that IL-1 β and TNF- α were not directly measured in this study. Their mention now refers only to prior research findings. All discussions regarding these cytokines have been limited to literature-based context and removed from the results and conclusion sections of the present study.

- The route of administration for A. marina extract with indomethacin is intraperitoneal, which may not be the same as conventional or clinical methods (such as oral). This makes it less useful for translation.

We appreciate this point. A clarifying sentence has been added to the Discussion to explain that the intraperitoneal route was used to ensure consistent bioavailability and experimental control in this animal model. We have also acknowledged that future studies should consider oral administration for better clinical translation.

- There is no mention of blinding or randomization during treatment or analysis, which is necessary to minimize bias.

Thank you for pointing this out. We have now included details in the Methods section confirming that animals were randomly assigned to groups and that the investigator performing the measurements was blinded to group allocation to reduce bias.

- We don't know whether vehicle control was employed for the ethanol extract (for example, diluting ethanol without the extract). If leftover ethanol had any effects, it could compromise the findings.

We have added a sentence to the extraction section clarifying that the extract was fully dried to eliminate residual ethanol before administration. Therefore, a separate vehicle control group was not used. Nevertheless, we acknowledge this as a limitation and recommend including a vehicle control group in future studies.

- The number of samples (n=6) per group is fine for an exploratory study; however, it may not be statistically strong enough to find smaller variations, particularly across extract dosages.

We agree with this important point. A sentence has been added to the Discussion acknowledging that the sample size, while suitable for preliminary investigation, may limit the detection of subtle differences between dosage groups.

- It was said that statistical comparisons between extract dosages were not significant; however, 400 mg/kg is said to be the "most effective." This requires more numbers or clarification.

This has been clarified in both the Abstract and Results sections. Instead of using the term "most effective," we now refer to the 400 mg/kg dose as showing "the most consistent reduction across all markers," which better reflects the statistical outcomes.

- The IL-6 ELISA kit range (8–150 ng/L) doesn't seem to match the claimed sensitivity (1.5 ng/L). This may need to be explained or fixed.

We have revised the Methods section to report only the assay range (8–150 ng/L) as provided by the manufacturer. The statement regarding sensitivity (1.5 ng/L) has been removed to avoid confusion.

- Please ensure the findings are aligned with the discussion, and avoid mentioning cytokines that were not quantified.

Thank you for the reminder. We carefully reviewed the Discussion and Conclusion sections to ensure that only IL-6 and MDA (which were measured) are discussed in terms of our findings. TNF- α and IL-1 β are now referenced only in the context of previous studies.

- Fix or explain any differences in methods (for example, TNF- α /IL-1 β or the dosage strategy).

We have clarified that TNF- α and IL-1 β were not part of the experimental measurements in this study and are only included for literature comparison. Additionally, the justification for dosage selection has been expanded with supporting references to previous efficacy and safety data.

OPEN PEER REVIEW

Revision (3)

REFEREE : EIC

2 Aug 2025

I am pleased to inform you that your manuscript has been accepted for publication. Please pay more attention in proof of your article that, All values of Table 1 should be presented with three significant digits after the decimal point for consistency. for example 0.36 ± 0.068 change to 0.360 ± 0.068 or 0.728 ± 0.0475 to 0.728 ± 0.047 .