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OPEN PEER REVIEW

Role of *Arctium lappa* L. Root (Burdock) Extract in CFA-induced Arthritis Rat Model: Impact on Antioxidant Activity and Inflammation

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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

3 comments · 19 May 2025 – 21 May 2025

Referee 1 Reviewer

MAJOR REVISION 19 May 2025

- Explain how the doses of A. lappa were selected and justified.
- Prednisolone dose seems extremely high. 250 mg/kg/day orally for 30 days is unrealistically high and likely toxic. Check and correct this dose. If it's a typo, clarify. If accurate, explain the rationale and cite relevant toxicological tolerance data.
- Only n=5 per group was used. This small sample size may underpower some results. Include a power calculation.
- Improve figure quality, use consistent fonts, and define all abbreviations clearly.
- A full grammar check or English editing is recommended for flow and readability. Some sentences are long, repetitive, or awkwardly phrased.
- While antioxidant and anti-inflammatory roles are shown, no specific signaling pathways (e.g., NF-κB, Nrf2) are investigated. Mention this as a limitation and a direction for future studies.
- Please explain why only chlorogenic acid was quantified. Yet, other key constituents are discussed in the literature.
- The hotplate test reflects thermal nociception but may not fully reflect chronic arthritic pain (which involves mechanical allodynia). Please add another experimental test, like the von Frey test.
- Please organize and rewrite the conclusion section.
- In the discussion section, include more critical comparisons with similar herbal extracts used in arthritis models.

Referee 2 Reviewer

MAJOR REVISION 20 May 2025

Title:
Typography correction: Change “CFA-induced arthritic rat model” to “CFA-induced arthritis rat model” for accuracy.
Abstract:
Abbreviations: Spell out CFA (Complete Freund’s Adjuvant) and all other abbreviations at first mention.
Statistical transparency: Include effect sizes, confidence intervals (or standard errors), and exact p-values where applicable.
Conclusion phrasing: Revise the conclusion for academic tone. Replace “These conclusions justify” with a more formal opening (e.g., “Our findings suggest that…” or “The results demonstrate…”).
Keywords:
Ensure keywords match Medical Subject Headings (MeSH) terms to optimize indexing and visibility.
Introduction:
Reference request: Provide a citation for the statement:
“At present, the commonly utilized medications against RA comprise analgesics, NSAIDs, glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs).”
Bioavailability evidence: Are there published data on the oral bioavailability of the hydroalcoholic extract of A. lappa root? If available, please cite supporting literature.
Methods:
Section 2.7 title: Change to “Hotplate test for thermal hyperalgesia” for clarity.
Hotplate test timing: Specify whether thermal hyperalgesia was assessed once or repeatedly. If performed

once, state the post-induction day of testing.
Results:
Equation X clarification: Define the components (A2, A3, C1, C2, 0.695) of the equation used for calculations.
Figure 1 (Standard details): Include the manufacturer, catalog number, purity, and concentration of the standard compound.
Optional: Consider adding H&E-stained images of the NC (normal control) group for comparative context.
Pathological scores: Report F-statistics and p-values for histopathological scoring to align with statistical reporting elsewhere.
Figure 7B visualization: The current color scheme hinders discrimination between cohorts. Use higher-contrast colors for clarity.
Figure 8 timeline: The figure's layout may imply RA was induced after treatment, whereas treatment began 6 days post-induction. Adjust labeling to avoid misinterpretation.
Discussion & Conclusion:
General feedback: The discussion and conclusion are well-structured and articulate. No major revisions needed.

Editor-in-Chief MAJOR REVISION 21 May 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.

Subject: Re-submission of a manuscript **(Manuscript ID: 162189)**

Title: Role of *Arctium lappa* L. root (burdock) extract in CFA-induced arthritis rat model: Impact on antioxidant activity and inflammation

Dear editor,

Thank you for the opportunity to revise our manuscript entitled "**Role of Arctium *lappa L*. root (burdock) extract in CFA-induced arthritis rat model: Impact on antioxidant activity and inflammation**". We truly appreciate all the constructive comments and suggestions from the reviewers. With this letter, we will be submitting a revised version of the manuscript **(Manuscript ID: 162189).** Please kindly notice that one-by-one responses to the reviewers' comments are provided in an MS Word file, and that all the new changes and inclusions are in the main body of the manuscript.

We sincerely hope that the revised manuscript has been efficiently improved and reached the level of acceptance in the **IJ Pharmaceutical Research**

Best Regards,

:Corresponding author *

Traditional Medicine and Hydrotherapy Research Center, Ardabil University of Medical Sciences, Ardabil, Iran

:Reviewer #1

1. **Explain how the doses of A. lappa were selected and justified**
   Response: Thanks for this comment. The doses of *Arctium lappa* L. root extract and duration of treatment were selected according to previous research.

   21. Jaani S, Mirazi N. Anti-nociceptive effect of Arctium lappa l. leafh hydroethanolic extract in male mice. Med J Tabriz Uni Med Sciences. 2017;39(5):28-35.
   22. Cao J, Li C, Zhang P, Cao X, Huang T, Bai Y, et al. Antidiabetic effect of burdock (Arctium lappa L.) root ethanolic extract on streptozotocin-induced diabetic rats. Afr J Biotechnol. 2012;11(37):9079.

2. **Prednisolone Dose Seems Extremely High. 250 mg/kg/day orally for 30 days is unrealistically high and likely toxic. Check and correct this dose. If it's a typo, clarify. If accurate, explain the rationale and cite relevant toxicological tolerance data**
   Response: Thank you so much for your comment. Yes, there was a typo mistake in the text, which is now rewritten in the revised manuscript. We provided the following citations to support this statement.

   Asar S, Gravandi MM, Khazaei H, Fakhri S, Iranpanah A, Mohammadi-Noori E, Rashidi K, Aneva IY, Naseri M, Farzaei MH. Fraxinus excelsior L. Hydromethanolic Extract Modulates Rheumatoid Arthritis Induced by Complete Freund's Adjuvant in Rats Emphasizing Inflammatory and Antioxidant Pathways. Jundishapur Journal of Natural Pharmaceutical Products. 2025;20(2).

3. **Only n=5 per group was used. This small sample size may underpower some results. Include a power calculation**
   Response: We sincerely thank the reviewer for their insightful comment regarding the sample size. We agree that using n=5 per group may limit the statistical power for detecting smaller effect sizes, and we acknowledge this as a limitation of the current study. However, our choice of group size was based on several prior peer-reviewed studies employing the CFA-induced arthritis model with similar endpoints and comparable sample sizes. Notably, the study titled "Fraxinus excelsior L. Hydromethanolic Extract Modulates Rheumatoid Arthritis Induced by Complete Freund's Adjuvant in Rats Emphasizing Inflammatory and Antioxidant Pathways" also utilized n=5 per group and demonstrated statistically significant outcomes in inflammation and oxidative stress parameters, validating the methodological approach. Moreover, in our study, multiple parameters (e.g., TNF-α levels, paw edema, SOD activity) demonstrated strong statistical significance ($p < 0.001$), suggesting sufficient power to detect biologically relevant effects. We have also added a statement regarding this limitation in the revised manuscript and clarified the rationale in the "Methods" section. While a priori power calculation was not performed due to ethical and practical limitations inherent in animal studies, we believe the consistency of our findings with previous literature supports the validity of our conclusions.

4. **Improve figure quality, use consistent fonts, and define all abbreviations clearly.**
   Response: The reviewer's valuable comment has been made.

5. **A full grammar check or English editing is recommended for flow and readability. Some sentences are long, repetitive, or awkwardly phrased.**
   Response: We agree with the reviewer's assessment. Accordingly, throughout the manuscript, we have revised
6. **Antioxidant and anti-inflammatory roles are shown, but no specific signaling pathways (e.g., NF-κB, Nrf2) are investigated. Mention this as a limitation and a direction for future studies**
   Response: Thanks for this comment. We added the limitations of this study in the last paragraph of the "Discussion" in the revised manuscript (Limitations of the study).

7. **Please explain why only chlorogenic acid was quantified. Yet, other key constituents are discussed in the literature**
   Response: According to the literature, chlorogenic acid is one of the main components of *Arctium lappa* L. root. Since we had access to this compound and limited availability and budget for other substances, we chose to use chlorogenic acid as the standard in this study.

8. **The hotplate test reflects thermal nociception but may not fully reflect chronic arthritic pain (which involves mechanical allodynia). Please add another experimental test, like the von Frey test**
   Response: We appreciate the reviewer's comments. Since the current study has concluded, and we cannot review this test, we mention it in the limitations section of the study. Hopefully, you will find it logical

9. **Please organize and rewrite the conclusion section**
   Response: We appreciate the reviewer's comments. The corrections were highlighted in the conclusions section.

10. **In the discussion section, include more critical comparisons with similar herbal extracts used in arthritis models**
    Response: The reviewer's valuable comment has been made (discussion section).

Reviewer #2

Title:

a. **Typography correction: Change "CFA-induced arthritic rat model" to "CFA-induced arthritis rat model" for accuracy**
Response: The reviewer's valuable comment has been made

:Abstract

a. **Abbreviations: Spell out CFA (Complete Freund's Adjuvant) and all other abbreviations at first mention**
Response: We appreciate the reviewer's comments. The corrections were highlighted in the main text.

b. **Statistical transparency: Include effect sizes, confidence intervals (or standard errors), and exact p-values where applicable.**
Response: Thank you for your comments. The information suggested was added in the Abstract section.

c. **Conclusion phrasing: Revise the conclusion for academic tone. Replace "These conclusions justify" with a more formal opening (e.g., "Our findings suggest that…" or "The results demonstrate…").**
Response: We thank the reviewer for pointing this out. We have revised the statement as suggested.

Keywords:

a. **Ensure keywords match Medical Subject Headings (MeSH) terms to optimize indexing and visibility**
Response: The reviewer's valuable comment has been made.

Introduction:

a. **Reference request: Provide a citation for the statement: "At present, the commonly utilized medications against RA comprise analgesics, NSAIDs, glucocorticoids, and disease-modifying antirheumatic drugs (DMARDs)."**
Response: As suggested by the respected reviewer, the reference has been inserted and highlighted.

b. **Bioavailability evidence: Is there published data on the oral bioavailability of the hydroalcoholic extract of A. lappa root? If available, please cite supporting literature.**
Response: Thank you for your comments. There are very limited studies on the effect of the hydroalcoholic extract of A. lappa root and assessment of oral bioavailability, antioxidant, and inflammatory factors in several models.

Methods:

a. **Section 2.7 title: Change to "Hotplate test for thermal hyperalgesia" for clarity**

Response: The reviewer's valuable comment has been made.

b. **Hotplate test timing: Specify whether thermal hyperalgesia was assessed once or repeatedly. If performed once, state the post-induction day of testing**
Response: Thank you for your comments. Thermal hyperalgesia was assessed using the hotplate assessment. Each rat underwent the test three times with 5-minute intervals between trials, and the average response time was determined.

Results:

a. **Equation X clarification: Define the components (A2, A3, C1, C2, 0.695) of the calculation equation.**
Response: Thank you for your comments. The information suggested was added to the result section.

b. **Figure 1 (Standard details): Include the manufacturer, catalog number, purity, and concentration of the standard compound**
Response: Thank you for your comments. The information suggested was added to the method section (Standardization of Plant Extract).

c. **Optional: Consider adding H&E-stained images of the NC (normal control) group for comparative context**
Response: Thank you for your comments.

d. **Pathological scores: Report F-statistics and p-values for histopathological scoring to align with statistical reporting elsewhere.**
Response: Thank you for your comments. The information suggested was added to the result section.

e. **Figure 7B visualization: The current color scheme hinders cohort discrimination. Use higher-contrast colors for clarity.**
Response: Thanks for your comment. Figure 7B was corrected according to the editor's suggestion.

f. **Figure 8 timeline: The figure's layout may imply RA was induced after treatment, whereas treatment began 6 days post-induction. Adjust labeling to avoid misinterpretation.**
Response: The reviewer's valuable comment has been made.

Discussion & Conclusion:

b. **General feedback: The discussion and conclusion are well-structured and articulate. No major revisions needed.**

Response: Thanks for your comment.

2 Revision 1

2 comments · 9 Jun 2025 – 10 Jun 2025

Referee 2 Reviewer

ACCEPT 9 Jun 2025

All the corrections were made.

Editor-in-Chief

ACCEPT 10 Jun 2025

Accept