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OPEN PEER REVIEW

Evaluation of the Protective and Healing Effects of Heracleum lasiopetalum Boiss on a Modified Acetic Acid-Induced Ulcerative Colitis Model in Rats

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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.

More about open peer review: brieflands.com/knowledgebase/opr

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1 Original submission

1 comment · 16 Jan 2024

Referee 1 Reviewer

MAJOR REVISION 16 Jan 2024

Dear Editor
Have a nice day.
The author evaluated the protective and healing effects of Heracleum lasiopetalum Boiss on a modified acetic acid-induced ulcerative colitis model in rats.
I would suggest reconsidering the manuscript for publication only after the following major revision.
1. In some cases, the observed effects related to increasing the concentration of Heracleum lasiopetalum are not logical. Why?
2. Please mention the reason for the study on female rats.
3. Please revise the manuscript for language quality and typographical errors.
4. Please mention the appropriate reference for the "Preparation of Plant Extract" part.
5. Please mention the dose of the positive control drug (sulfasalazine).
6. All biological effects observed for Heracleum lasiopetalum Boiss should be classified.
7. Based on previous studies, the possible mechanism related to Heracleum lasiopetalum Boiss should be stated in the background and objectives.
8. Please mention the commercial source of all the materials and the model of the instrument used.
9. In the following sentence, despite the filter step, the calculation of 5% is wrong. "For the 5% extract, 5 grams of dried plant material were placed in a beaker, and 100 milliliters of water were added. Using a magnetic stirrer, the mixture was heated on a stirrer plate for 45 minutes. Subsequently, we employed a funnel and filter paper to carry out the filtration process".

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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.

16-February-2024

MS. ID.: 143801

MS title: **"Evaluation of the protective and healing effects of Heracleum lasiopetalum Boiss on a modified acetic acid-induced ulcerative colitis model in rats."**

Dear Editor,

Thank you very much for providing us with the opportunity to respond to the reviewers' comments and revise our manuscript. We are grateful for the encouraging commentary from the esteemed associate editor. Below are the verbatim comments from the reviewers, our responses, and how and where we have modified the manuscript to address these comments. All changes in the manuscript have been highlighted in yellow. In our response to the reviewers, the comments of the reviewers are in italics, and our responses are in bold.

Reviewers' Comments to Author:

Reviewer: 1
The manuscript is suitable in terms of topic and content, But you need to correct a few points.

1. The manuscript must have a conclusion and be added to the text.

Response: We thank the reviewer very much for their careful review and constructive suggestions regarding our manuscript. We have incorporated the conclusion section into the manuscript as suggested. It can now be found on page 13, lines 394-403.

2. It should be mentioned in the whole text that rats are female.

Response: We have ensured that throughout the entire text, it is explicitly mentioned that the rats used in the study are female.

3. In the abstract section; The complete study design should be mentioned, such as the number of rats; Animal grouping, etc.

Response: Thank you for your valuable feedback. We have revised the abstract section on page 1, lines 10-20, to include the complete study design, including details such as the number of rats, animal grouping, and other relevant study parameters.

4. Valid reference should be used for ketamine and xylazine dosage.

Response: A valid reference for ketamine and xylazine dosage has been incorporated into the manuscript on page 4, lines 123 and124.

5. In the abstract section, the first few lines are exaggerated, please summarize them.

Response: Thank you for bringing this to our attention. We have revised the abstract, addressing the content on page 1 lines 4-9, to eliminate any perceived exaggeration in the initial lines.

6. What is meant by acid in the method section? Mention the full name of the acid.

Response: "Acid" in the method section specifically refers to acetic acid. The full name "acetic acid" has been mentioned to ensure clarity and avoid ambiguity for the readers.

7. the text mentions that Maison's trichrome staining is used to check fibrosis.

Response: Thank you for pointing that out. We have revised the text accordingly. On page 6, lines 180-182, "Masson's trichrome staining" has been specified as the method used to assess fibrosis.

8. In part 2.1 of the method, the numbers were divided into 12 groups of 8. In part 2.5.1, the animals were divided into 6 groups of 8. Please correct it.

Response: We have revised the text accordingly. On page 3, lines 98-100, the grouping of animals in part 2.1 of the method now specifies that the rats were divided into 6 groups (with 8 rats per group) for each of two experiments.

9. The drugs in the drug pharmacopeia, such as corticosteroids and monoclonal antibodies, have a good effect on treating ulcerative colitis and are usually used in the form of multiple drug strategies. Considering that you used only one drug for positive control, please explain your reasons.

Response: The selection of sulfasalazine as the sole positive control drug was based on its established status as a first-line treatment for ulcerative colitis and its frequent utilization as a reference drug in animal models of UC, as observed in studies conducted by Jedidi et al., Tekeli et al., and Helal et al. By selecting a single, standard therapeutic agent as a benchmark, we aimed to facilitate a clear comparison with the experimental Heracleum lasiopetalum extract. While we acknowledge that combination therapies are common in clinical practice, our focus in this initial investigation was to evaluate the effects of Heracleum lasiopetalum extract against a widely used solo therapy. This approach allowed us to assess its potential therapeutic efficacy before exploring synergistic effects with other agents. Future studies can build on these findings by incorporating additional experimental arms with combination drug therapies, such as corticosteroids + immunosuppressants, to more closely mimic real-world clinical management. Our goal in this study was to establish preliminary evidence of efficacy and dose-response, laying the groundwork for further research into the potential therapeutic benefits of Heracleum lasiopetalum extract in the

treatment of ulcerative colitis. These references have also been added to the article, on page 3, line 82.

10. Herbal compounds can have supportive effects along with FDA-approved drugs, so in the introduction and discussion, pay attention to this issue and change the text.

Thank you for your valuable comment. We have updated the text in the introduction (page 3, lines 80-86), discussion (page 11, lines 321-324), and (page 13, lines 389-393).

11. Please explain that the model you created for ulcerative colitis is similar to which stage of this disease.

Response: According to our previous study, the animal model inducing ulcerative colitis with acetic acid aims to replicate some key characteristics of an acute exacerbation or flare-up of inflammation in human ulcerative colitis. In patients, flare-ups of ulcerative colitis can range in severity but often involve the rapid onset of symptoms like diarrhea, rectal bleeding, abdominal pain, and inflammation/ulceration of the colonic mucosa. Our model using acetic acid similarly triggers mucosal erosion, ulceration, inflammation, and bleeding in the rat colon. Thus, we believe our rat model of acetic acid-induced colitis reflects aspects of an acute flare-up of inflammation resembling moderate ulcerative colitis, allowing us to study potential therapeutic interventions during this critical phase of the disease. This information has been incorporated into the discussion section on page 11, lines 318-322.

Reviewer: 2

The author studied evaluation of the protective and healing effects of Heracleum lasiopetalum Boiss on a modified acetic acid-induced ulcerative colitis model in rats. I would suggest reconsidering the manuscript for publication only after the following major revision.

1. In some cases, the observed effects related to increasing the concentration of Heracleum lasiopetalum are not logical. Why?

Response: We thank the reviewer very much for their careful review and constructive suggestions regarding our manuscript. Some of the observed effects related to increasing extract concentrations of Heracleum lasiopetalum were not entirely dose-dependent in our study. There are a few factors that may have contributed to these anomalies:
Firstly, since this was an initial exploratory study, we examined a limited range of only three concentrations. Using a narrow set of extract doses could have made distinguishing clear dose-response trends more difficult. Additionally, random biological variability and individual differences among the rats themselves could also have obscured clear dose-dependent patterns at times.
In future long-term studies, we plan to address this issue by investigating a wider range of Heracleum lasiopetalum concentrations in a larger number of experimental animals. This should provide greater clarity into the relationships between bioactive components in the

extract and contribute to more consistent dose-dependent responses. We appreciate the reviewer highlighting this opportunity to improve our methods moving forward.

2. Please mention the reason for the study on female rats.

Response: The decision to use female rats was based on several scientific considerations:
Relevance to Human Population: Ulcerative colitis (UC) affects both males and females, and it is important to consider the potential gender-specific differences in disease manifestation and treatment responses. By selecting female rats, our study aimed to contribute insights that are directly relevant to a significant portion of the human population.
Establishing a Baseline: Focusing on female rats allows us to establish a baseline understanding of the herb's effects in a specific gender, providing a foundation for potential future studies exploring gender-specific responses or comparisons between male and female cohorts.
Reducing Variability: Limiting the study to one gender, in this case, females, helps control for potential variations introduced by gender-related factors, thereby enhancing the internal validity of our findings. This clarification has been added to the discussion section, page, 10 lines 299-303.

3. Please revise the manuscript for lingual quality and typo mistakes.

Response: We appreciate the reviewer's attention to linguistic quality and typographical errors in our manuscript. We have revised the document to ensure clarity and correctness in language usage throughout.

4. Please mention the appropriate reference for the "Preparation of Plant Extract" part.

The relevant references have been added to the article, on page 4, line 120.

5. Please mention the dose of positive control drug (sulfasalazine).

Response: The dose of the positive control drug, sulfasalazine, used in our study was 100 mg/kg. This information has been mentioned in the abstract section (page 1, line 13) and in the experimental design section (page 5, lines 150 and 151).

6. All biological effects observed for Heracleum lasiopetalum Boiss should be classified.

Response: In the discussion section (page 13, lines 389-393), all biological effects observed for Heracleum lasiopetalum Boiss have been classified.

7. Based on previous studies, the possible mechanism related to Heracleum lasiopetalum Boiss should be stated in the background and objectives.

Response: In the background and objectives section, the possible mechanisms related to Heracleum lasiopetalum Boiss have been incorporated (page 3, lines 75-79).

8. Please mention the commercial source of all the materials and the model of the instrument used.

Response: We have added the commercial sources for all materials and instrument model in the Methods section.

9. In the following sentence, despite the filter step, the calculation of 5% is wrong. "For the 5% extract, 5 grams of dried plant material were placed in a beaker, and 100 milliliters of water were added. Using a magnetic stirrer, the mixture was heated on a stirrer plate for 45 minutes. Subsequently, we employed a funnel and filter paper to carry out the filtration process".

We appreciate the reviewer's careful review of our extraction methodology. To clarify, the preparation of the 5% aqueous extract involved adding 5 grams of dried Heracleum lasiopetalum plant material to 100 milliliters of water, as outlined in the methods section. This initial dissolution of 5 grams of plant material in a total volume of 100 milliliters of water yields in a 5% extract concentration before filtration. The subsequent filtration process was conducted to eliminate any insoluble particulate matter, ensuring a purified dissolved extract for testing. It is important to note that the initial percentage is determined by the ratio of plant material to the starting volume before concentration. We apologize for any lack of clarity in the original description that may have caused confusion. The necessary revisions have been made on page 4, lines 108-120 for further clarification.

2 Revision 1

2 comments · 26 Feb 2024 – 16 Mar 2024

Referee 1 Reviewer

MINOR REVISION 26 Feb 2024

Dear Editor
Have a nice day.
The author evaluated the protective and healing effects of Heracleum lasiopetalum Boiss on a modified acetic acid-induced ulcerative colitis model in rats.
Acceptance for publication is recommended after the following minor changes.
1. Table 3-1 and Table 3-2 need to be modified.
2. Please report all obtained values to two decimal places.
3. Please check that all abbreviations are defined the first time they are used.

Associate Editor

MINOR REVISION 16 Mar 2024

Thank you for submitting your manuscript to Jundishapur Journal of Natural Pharmaceutical Products. Please address the questions of the reviewers in order to make your manuscript suitable for publication.

It would also be an honor to have the author team contribute as reviewers for this journal.
Your assistance as a reviewer for Jundishapur Journal of Natural Pharmaceutical Products aids the editorial board in reaching a decision, and also enables the author(s) to disseminate their work at the highest possible quality.
Thank you in advance for your contribution and time.

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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.

19-March-2024

MS. ID.: 143801

MS title: **"Evaluation of the protective and healing effects of Heracleum lasiopetalum Boiss on a modified acetic acid-induced ulcerative colitis model in rats."**

Dear Editor,

We are grateful for the opportunity to address the reviewers' feedback and revise our manuscript. We also appreciate the encouraging feedback from the associate editor. Below, we present the reviewers' comments, our responses, and the modifications made to the manuscript. Changes are highlighted in yellow in the manuscript. In our response to the reviewers, the comments of the reviewers are in italics, and our responses are in bold.

Reviewers' Comments to Author:

Reviewer: 1

The author studied evaluation of the protective and healing effects of Heracleum lasiopetalum Boiss on a modified acetic acid-induced ulcerative colitis model in rats.

It is recommended to be accepted for publication after the following minor changes.

1. Table 3-1 and Table 3-2 need to be modified.

Thank you for your valuable feedback. We have carefully revised Table 3-1 and Table 3-2. These tables have been modified accordingly to enhance clarity and accuracy. They can now be found on page 7, lines 214-217 of the manuscript.

2. Please all the obtained values are reported with two decimal places.

Response: We have ensured that all obtained values are reported with two decimal places throughout the manuscript.

3. Please check that all abbreviations are defined for first time.

Response: We have thoroughly reviewed the manuscript to ensure that all abbreviations are defined the first time they appear.

Reviewer: 2

The comments were reviewed. The author has answered the reviewer' questions very well. In my opinion, this article is suitable for accepting in the journal.

We thank the reviewer for their thoughtful evaluation and supportive recommendation regarding our manuscript. We are grateful for the insightful feedback provided during the peer review process, which has allowed us to clarify and strengthen various aspects of our work. We appreciate the reviewer's careful consideration and belief that our article is suitable for publication in this esteemed journal.

3 Revision 2

1 comment · 28 Mar 2024

Referee 1 Reviewer

ACCEPT 28 Mar 2024

Dear Editor
Have a nice day.
The addressed issues and concerns have been effectively resolved. Consequently, the reviewer agrees to proceed with the publication of this paper in its current state.