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OPEN PEER REVIEW

Investigating the Factors Related to the Amount of Bleeding Due to Percutaneous Nephrolithotomy (PCNL)

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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 · 17 Jul 2025 – 6 Aug 2025

Referee 1 Reviewer

MINOR REVISION 17 Jul 2025

1- The title does not specify what type of study it is (cross-sectional? retrospective? analytical?), what population it was conducted in, or what variables were examined.
2- It is not clear why the present study is necessary. The final sentence hints at it, but it is not enough.
3- The number and location of the studies are specified, but the inclusion/exclusion criteria are not provided. This is a significant shortcoming.
4- Critical Note: Although dividing by the median is common, this method of analysis has lower statistical accuracy than continuous variable analysis. It is best to state why this method was used and whether the data were tested for normality.
5- Suggested rewrite:
"Among the 412 patients included in the study, 285 (69.2%) were male and 127 (30.8%) were female. The overall mean age was 47.6 ± [SD] years (range: 26–77 years)."
6- No physiological/pathophysiological explanation has been given as to why, for example, BMI or diabetes causes increased bleeding.
7- There is no mention of study limitations, biases, or generalizability of the data.
8- It does not make any practical or clinical recommendations.
- It would be better to add a more general statement at the end, for example:
"Future prospective studies with larger cohorts are needed to validate these findings."

Referee 2 Reviewer

MAJOR REVISION 3 Aug 2025

Dear Associate Editor
I thank the authors and express my appreciation to the researchers.
This is a clinically relevant and methodologically sound study addressing predictors of bleeding in patients undergoing PCNL. Given that hemorrhage is one of the most serious complications in PCNL, identifying risk factors is highly valuable. The study benefits from a relatively large sample size (n=412) and presents a clear statistical approach.

However, there are important issues that need to be addressed before this manuscript can be considered for publication:
1-Some sentences lack references (for example, the first sentence of the introduction). All sentences quoted from other articles must have references at the end.
2-The methods section in the abstract states that the study is prospective, whereas the main text describes it as retrospective (line 45). This inconsistency must be corrected.
3-There are minor grammatical issues (e.g., “renal hemorrhage post-surgery is a particularly frequent and concerning complication” could be reworded for clarity). The writing could benefit from professional English editing for clarity, flow, and precision.
4-The regression model itself is not described in detail: which variables were included, and what were the odds ratios and confidence intervals?
5-The study does not define the inclusion and exclusion criteria for patient selection. For instance:

*Were patients with coagulopathies excluded?

*Were patients on anticoagulants or antiplatelet agents included?

6-In Table 1, "Blood loos (median) ml 505.87±276 (476.2)" is poorly written and confusing. It's unclear whether 505.87 is the mean and 476.2 the median or vice versa.

7-The results mention a mean drop in hemoglobin of 1.57 ± 2.43 g/dL (abstract), but later in the discussion, the hemoglobin drop is reported as 2.43 ± 1.57 g/dL (line 97), suggesting either a typographical error or different values being confused.
8-All procedures were performed by a single surgeon—this enhances consistency but limits generalizability. This bias is not discussed.

Associate Editor

MAJOR REVISION 3 Aug 2025

Dear EIC,
I thank the authors and express my appreciation to the researchers. The manuscript is a valuable piece of research. But some revisions are needed. The authors should revise it based on the comments. Also, minor changes should be made to the text:
*Repetitive use of awkward or redundant phrases like “greater hemoglobin deficits” instead of “greater hemoglobin drop.”
*The authors do not discuss why some commonly cited variables like age, sex, or stone position (other than upper calyx) did not reach significance, nor do they compare their findings with the existing literature.

Editor-in-Chief

MAJOR REVISION 6 Aug 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.

Dear Editor,

We have carefully reviewed the reviewers' comments point by point and made the necessary revisions to the manuscript accordingly.

Thank you for your consideration.

Editor and Reviewer comments:
Reviewer #1: 1- There is a critical contradiction in the description of the experimental design. In the Methods section (2.1. Animals), the text states, "Twenty-four healthy rats were divided into four groups (n=6)." However, the subsequent description, all figures (1, 2, 3, 4, 5, 6), and figure captions clearly describe and present data for five distinct groups (Control, A.A, A.A + α-pi 50, A.A + α-pi 100, A.A + S.S). This discrepancy must be corrected. If five groups of n=6 were used, the total number of animals should be 30, and the text must be amended accordingly. This is a fundamental error that raises concerns about the accuracy of the methods section. We had mistakenly written the number 24, which we corrected.
2- Several figures contain statistical annotation symbols that are not defined in the corresponding captions. For example:
a. Figure 4C (CAT levels): A "^" symbol is used to compare the α-pi 100 group and the α-pi 50 group, but this symbol is not defined in the caption.
b. Figure 5A (NF-kB protein): "^^" symbols are used but not defined.
c. Figure 5D (Caspase 1 protein): A "^" symbol is used but not defined.
d. All statistical symbols used in graphs must be clearly and comprehensively defined in the figure captions for the results to be interpretable. Changes were made to the figures.
3- In Figure 2A, the Y-axis is labeled "Colon lenght/weight (cm/g)". This is unconventional and likely incorrect. The standard metric to assess edema and inflammation is the colon weight-to-length ratio, which should have units of g/cm. A higher value indicates greater inflammation. The data presented are consistent with a g/cm measurement (e.g., the A.A group value is ~0.5 g/cm), but the axis label is inverted. This must be corrected to "Colon weight/length ratio (g/cm)" or similar. The typo "lenght" should also be corrected to "length." The image label has been corrected.
4- In introduction: The statement, "As of now, there have been no reports on the effects of alpha-pinene on colitis," is a strong claim. While the authors' search may be correct, such definitive negative statements are risky. It is recommended to soften this to "To our knowledge, the effects of alpha-pinene on colitis have been minimally investigated..." or similar, after a thorough final literature search. To our knowledge, the effects of alpha-pinene on colitis have been minimally investigated
5- The description of the macroscopic disease score is vague in the methods section. The text states, "The severity of hyperemia, edema, and erosion was unambiguously scored from 0 to 4". For reproducibility, the authors should provide the specific criteria for each score (e.g., 0 = no damage; 1 = localized hyperemia, no ulcers; 2 = ... etc.). This level of detail is standard for such scoring systems. Please refer to and cite the following reference for more details:
Morus macroura Miq. Fruit extract protects against acetic acid-induced ulcerative colitis in rats: Novel mechanistic insights on its impact on miRNA-223 and on the TNFα/NFκB/NLRP3 inflammatory axis (https://doi.org/10.1016/j.fct.2022.113146) A complete description was written.
6- The discussion provides a solid mechanistic overview but could be strengthened by acknowledging the study's limitations. For instance, the acetic acid model primarily induces acute, localized chemical damage, which may not fully represent the chronic, immune-mediated nature of human ulcerative colitis. A brief discussion of this and the need for testing in other models (e.g., DSS or TNBS colitis) would add valuable context. Study limitations were added to the end of the discussion based on your suggestion.

Reviewer #2: The present study evaluated the effects of alpha-pinene on experimental colitis, focusing on the activity of the NLRP3-Caspase1 pathway as an underlying mechanism. The main findings suggest that alpha-pinene reduces oxidative stress and decreases NLRP3 pathway activity by inhibiting MAPK

p38 activity, leading to a reduction in the expression of NF-κB, NLRP3, and Caspase 1, as well as lower levels of IL-1β and IL-18. The article reports the results of a well-planned research study. However, some points have to be addressed:
Major comments
Introduction:
- The introduction provides a comprehensive background on Alpha-pinene. However, the level of detail in the first paragraph may be excessive for an introduction. The second sentence could be removed. The explanation of alpha pinene in the introduction was made more concise and the second sentence was deleted.
-Please revise the English of the last paragraph of the introduction. The last paragraph of the introduction was revised.
Methods:
- Section 2.1: Details on the environmental conditions, such as humidity and temperature control, should be provided. The requested information has been added.
- Number of used animals. The authors mentioned that 24 rats were used in this study. There is no information in the results or legends. I'm unsure how the authors assigned all animals to each experiment.
- Please revise the number of groups described in the phrase: "Twenty-four healthy rats were divided into four groups (n=6)." Four or five groups? In the procedure text, we had mistakenly written 24 instead of 30, which we corrected.
- What was the rationale for choosing the doses of 50 and 100 mg of alpha-pinene? Some reference? (Rahimi, Rezaie, Allahverdi, Shahriari, & Taheri Mirghaed, 2025a; Rahimi, Rezaie, Allahverdi, Shahriari, & Taheri Mirghaed, 2025b; Rahimi, Shirvani, Sanaie, Javadi, & Khademi, 2023)
-Section 2.2: Describe the conditions under which the induction of colitis was performed, including the anesthetic conditions. The description was written in full.
- How long after colitis induction were the animals euthanized? Please provide this information in Section 2.3, Sample Preparation. The description was written in full.
Results:
- For a better understanding of the results, add a brief description of the importance of the measured proteins/ mechanism. The description was written in full.
- Concerning the DSH levels measurement, describe the result of the sulfasalazine group. Explanation added.
- 3.4: Please, rephrase the sentence. ...." The groups treated with a-pi 50 mg/kg and a-pi 100 also showed significant differences from the control group ($p< 0.001$ and $p< 0.05$, respectively)." It does not mean anything. Changes were applied.
- 3.5: Please revise the following sentence: "The level of 1L-1β in the sulfasalazine and a-pi 50 mg/kg groups was lower than the A.A group ($p<0.01$, and $p< 0.05$, respectively)". Instead of a-pi 50 mg/Kg, the figure shows that a-pi 100 mg/Kg was lower than A.A. Changes were applied.
Discussion:
- The discussion would benefit from a stronger linkage between the general background (IBD/oxidative stress/downstream signaling molecules activated by ROS) and the specific focus of the study. Adjust the structure of this text in parallel with the results of the present study for better clarity and flow. The discussion of the alpha-pirene effects occurs only at the end of the text. Changes were applied.

- Based on evidence from the literature, the authors discuss the anti-inflammatory effects of alpha-pirene, which involve the inhibition of MAPKs and the NF-κB pathway in mouse peritoneal macrophages. In sequence, the authors discuss its beneficial effects in reducing the production of interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and nitric oxide (NO) induced by LPS. It also inhibits the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in LPS-stimulated macrophages. However, no reference is provided in the text. Please insert the corresponding references. References were identified.

- Please revise the manuscript carefully for typographical errors and English. The grammar of the article text was checked.

Rahimi, K., Rezaie, A., Allahverdi, Y., Shahriari, P., & Taheri Mirghaed, M. 2025a. The effects of alpha-pinene against paracetamol-induced liver damage in male rats. ***Physiol Rep***, 13(3): e70227.

Rahimi, K., Rezaie, A., Allahverdi, Y., Shahriari, P., & Taheri Mirghaed, M. 2025b. The effects of alpha-pinene against paracetamol-induced liver damage in male rats. ***Physiological Reports***, 13(3): e70227.

Rahimi, K., Shirvani, N., Sanaie, P., Javadi, A., & Khademi, M. 2023. The effects of alpha-pinene on the Nrf2-HO1 signaling pathway in gastric damage in rats. ***Mol Biol Rep***, 50(10): 8615-8622.

2 Revision 1

4 comments · 21 Aug 2025 – 30 Aug 2025

Referee 1 Reviewer — ACCEPT 21 Aug 2025

Approved with the amendments made.

Referee 2 Reviewer — ACCEPT 21 Aug 2025

Dear Authors,
Thank you for correcting pitfalls and answering my questions.

Associate Editor — ACCEPT 22 Aug 2025

Dear EIC,
I read the manuscript, and the authors corrected the requested items. The article could be accepted at this stage.
Sincerely;

Editor-in-Chief — ACCEPT 30 Aug 2025

Accept