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OPEN PEER REVIEW

Antiparasitic Effects and Cellular Mechanisms of Formononetin (a Natural Isoflavone) Against Hydatid Cyst Protoscoleces

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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

2 comments · 27 Sep 2022 – 16 Oct 2022

Referee 1 Reviewer

MINOR REVISION 27 Sep 2022

The manuscript has been written well and the English language is fine. The subject of the study is within the scope of the journal. I recommend the publication of the manuscript after minor revision.

Abstract:
• Line 4: Please provide a better background. It is so clichéd and inappropriate.
• Please add more details to the results section in the abstract for a better reflection of the data obtained in this study.
• The authors can make the conclusion section in the abstract more concise and instead add to the results section.
Introduction
• The introduction has appropriately explained the pathogenesis of the disease, but it has not properly included background on plant-based materials, such as essential oils, as well as the effects of plant-based compounds and essential oils on parasites and other pests. Please add some sentences about the application of essential oils and plant-based compounds against other pests and parasites. I suggest considering the recent paper mentioned below:
A review of effective essential oils and their biologically active compounds to protect the safety of food stored against insect pests. Journal of Essential Oil Research, (2022). 34(2), 111-122.
• Lines 63, 67, 139, and 140: Please correct "Formonontin" to "Formononetin". This must be done for the entire manuscript.
Materials and methods:
• Line 88: Please move figure 1 to the results section. Moreover, the quality of figure 1 must be improved, as it is not appropriate for publication in the journal.
• Line 99: "three hydatid cysts were …" Please revise the sentence for clarity. What is the injection?
• Line 117: "an" ELISA reader.
• Line 118: Please correct this line. It seems that the sentence is incomplete.
Results:
• Line 148: Correct the vertical caption for Fig 3.
• Line 164-166: Rewrite the sentence. It is too long and complex. For instance, what does "plasma membrane" refer to?
Discussion
• The authors should discuss the compounds in the formononetin and provide suggestions about how they can eliminate the parasite.
• Line 173: Please type "5 Discussion" instead of "1 discussion".
• Line 188: What is the relationship between the antimicrobial activity of formononetin and your study? Are you suggesting that antimicrobial and parasiticidal activities are related to each other? What is the mechanism of action of these antimicrobial and parasiticidal activities? How is it possible? Antimicrobial activity acts against prokaryote cells, but parasites belong to eukaryotes. How do you justify this?
• Line 196: "A noteworthy point …" The authors should provide justification for this outcome.
• Line 198-203: Again, the dilemma of eukaryote and prokaryote cells shows itself. In my opinion, your study is different from the studies on antibacterial or antiviral characteristics of formononetin, and I suggest only a brief mention of antimicrobial effects. The authors should focus on and compare their work with the effects of formononetin on other parasites and pests.

• Line 204: “In their study” should be corrected to “in another study,”.
• Line 208: “isofalone”? isoflavone?
• Line 212-220: The authors should explain the difference in the induction of apoptosis in microbial pathogens and hydatid cysts (protoscolices).
• Line 226: “isofalunoids”?
• Line 227: “isofalones”? Please correct these throughout the manuscript.
Conclusion:
• Line 234: The first sentence of the conclusion is an overgeneralization. The authors should focus on their outcomes.
• The conclusion must be improved. Please provide better suggestions for this section.

Editor-in-Chief MINOR REVISION 16 Oct 2022

Dear Authors,

Your manuscript has been scrutinized by our experts, and they believe a minor revision is required. Therefore, we will reconsider it after receiving the revised manuscript and the answer to the comments. Please highlight changes in the revised article.

Regards,
JJNPP EIC

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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.

Reviewer 1:

The manuscript is writing well but a minor revision is needed.
-For ex vivo test the concentration of 75, 150 and 300 µg/mL were used and for Effect on the caspase-3 like activity and Effect on plasma membrane permeability of protoscoleces, the concentration of 7.5, 15 and 30 µg/mL have been used. What is the reason of choosing these concentrations? Please explain about this.

Response: The authors should be thankful for your precise observation. Since, we performed the caspase-3 activity for maximum 3 hours, while the plasma membrane permeability was performed for 48 hours, so we must to use the lower concentration of extract foe evaluationg its effects on while the plasma membrane.

-Please correct some typographical errors like “isofalone formonontin”, “anti-hyperlipidemic, anti-hyperlipidemic”,and “in vitro and in vivo ex conditions”.

Response: Revisions were made in the text.

Reviewer 2:

The manuscript has been written well and the English language is fine. The subject of the study is within the scope of the journal. I recommend the publication of the manuscript, after minor revision.

Abstract:
• Line 4: Please provide a better background. It is so cliché and inappropriate.

Response: Revision was made.

• Please add more details to the results section in the abstract for a better reflection of the data obtained in this study.

Response: more details were added as the respected reviewer recommended.

• The authors can make the conclusion section in the abstract more concise and instead add to the results section.

Response: section was revised.

Introduction
• The introduction has appropriately explained the pathogenesis of the disease, but it has not properly included the backdrop about plant-based materials, such as essential oils, as well as

the effects of plant-based compounds and essential oils on parasites and other pests. Please add some sentences about the application of essential oils and plant-based compounds against other pests and parasites. I suggest the consideration of recent paper mentioned below:
A review of effective essential oils and their biologically active compounds to protect the safety of food stored against insect pests. Journal of Essential Oil Research, (2022). 34(2), 111-122.

Response: Required sentences were added to the text.

• Line 63, 67, 139, and 140: please correct “Formonontin” to “Formononetin”. This must be done for the entire manuscript.

Response: In throughout of the manuscript, Formonontin” was replaced by “Formononetin

Materials and methods:
• Line 88: please move figure 1 to the results section. Moreover, the quality of figure 1 must be improved and it is not appropriate for publication in the journal.

Response: Revisions were made in the text.

• Line 99: “three hydatid cysts were …” please revise the sentence for more clarification. What is the injection?

Response: Revision was made.

• Line 117: “an” ELISA reader.

Response: Revision was made.

• Line 118: Please correct this line. It seems that the sentence is not completed.

Response: Revision was made.

Results:
• Line 148: correct the vertical caption for Fig 3.

Response: Revision was made.

• Line 164-166: rewrite the sentence. It is too long and complex. For instance, “plasma membrane” refers to what?

Response: Revision was made.

Discussion
• The authors should discuss the compounds in the formononetin and provide suggestions about how they can eliminate the parasite.

Response: Revision was made in discussion section.

• Line 173: Please type “5 Discussion” instead of “1 discussion”.

Response: Revision was made.

• Line 188: What is the relationship between the antimicrobial activity of formononetin and your study? Are you suggesting that antimicrobial and parasiticidal activities are related to each other? What is the mechanism of action of these antimicrobial and parasiticidal activities? How is it possible? Antimicrobial activity performs against prokaryote cells, but parasites are belonging to eukaryotes. How do you justify this?

Response: The author should be thankful for your valuable comment. That is true, however, parasites as the main microbial pathogens that generally antimicrobial agents have similar mechanisms in them.

• Line 196: “A noteworthy point …” authors should provide justification for this outcome.

Response: was added to the text.

• Line 198-203: Again, the dilemma of eukaryote and prokaryote cells shows itself. In my opinion, your study is different from the studies on antibacterial or antiviral characteristics of formononetin and I suggest only a hint about antimicrobial effects. The authors should focus on and compare their work with the effects of formononetin on other parasites and pests.

Response: According to our knowledge, there is no documented study on antimicrobial mechanisms of formononetin, therefore, we discussed flavonoids in general.

• Line 204: “In their study” should be corrected to “in another study,”.

Response: Revision was made.

• Line 208: “isofalone”? isoflavone?

Response: Revision was made.

• Line 212-220: Authors should explain the difference in the induction of apoptosis in microbial pathogens and hydatid cysts (protoscolices).

Response: was discussed in the section.

• Line 226: “isofalunoids”?

Response: Revision was made.

• Line 227: “isofalones”? Please correct these in the entire manuscript.

Response: Revision was made.

Conclusion:
• Line 234: the first sentence of the conclusion is over generalization. Authors should focus on their outcomes.

Response: Revision was made.

• Conclusion must be improved and please provide better suggestions for this section.

Response: **The section was improved.**

2 Revision 1

1 comment · 6 Dec 2022

Editor-in-Chief

MAJOR REVISION 6 Dec 2022

Dear Authors,

Reviewers believe major changes are still required. Please revise your manuscript according to the provided comments and upload it with your response or any rebuttal.

Kind regards,
JJNPP EIC

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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.

Reviewer 1:

Dear Authors,
Overall, your manuscript is well-written, clear, and informative. The introduction is relevant and theory-based. Enough information about the previous studies is presented.
The methods are comprehensive and well-characterized. The results are clear and logical. To the point of discussion, the main findings of the study are according to the relevant and up-to-date literature.
However, there are some minor typing and grammatical mistakes that should be corrected.

Response: The authors should be thankful for your positive comments. Throughout the manuscript was significantly improved

Reviewer 2:

- The text needs to be edited for grammar and scientific writing

Response: Throughout the manuscript was significantly improved

- Please replace the word: “Caspase-3 like” with the Caspase-3 phrase

Response: Revision was made as the respected reviewer recommended.

- The abstract section lacks the exact elucidation of the used methods. The comparison of the treated group with the control group is not included. In addition, the names of the methods that were used to determine caspase-3 activity and membrane permeability are not included.

Response: Revisions were made

- The main concise results of the study must be mentioned in the first paragraph of the discussion section.

Response: Revision was made as the respected reviewer recommended.

- Please compare the results of the present study with the results of the other parasiticidal effects of formononetin or other isoflavonoids

Response: Revisions were made as the respected reviewer recommended.

3 Revision 2

1 comment · 29 Jan 2023

Editor-in-Chief

ACCEPT 29 Jan 2023

Dear Authors,

I am pleased to inform you that your manuscript has been accepted for publication in JJNPP in its current form. We congratulate you and look forward to receiving your future valuable research results.

We will send it to the publisher for further processing.

Yours sincerely,
JJNPP EIC