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OPEN PEER REVIEW

Antidepressant Effect of Hydroalcoholic Extract of *Citrus medica* Fruit in Mice: Possible Role of Nitric Oxide

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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

4 comments · 5 Aug 2024 – 4 Oct 2024

Ashkan Barfar Reviewer — MINOR REVISION — 5 Aug 2024

Dear Authors,

Thank you for your efforts in preparing this manuscript. Here are a few comments and suggestions for your consideration:

1. The inclusion of DOIs for referenced articles is crucial for the completeness and credibility of your manuscript. Many referenced articles currently lack DOIs, and I strongly recommend their inclusion.
2. The text requires spelling and grammatical corrections.
3. In section 2.3, "Extraction Preparation," the fruits were purchased. Including an expert's opinion to confirm the correctness of the fruit species mentioned would be beneficial.
4. In section 2.3, "Extraction Preparation," you mention using filter paper. Please specify the brand and type of filter paper used.
5. Regarding the tests conducted on mice, how they were performed is generally described. Please add information on how many times each test was conducted on each mouse. Was it a single test per mouse?
6. When referring to subjects in scientific writing, the term "mice" should be used instead of "mouse."

Thank you for addressing these points.

Referee 1 Reviewer — MINOR REVISION — 16 Sep 2024

Dear Editor
The work has acceptable merit, but the following points should be included in the revised paper.
-The funding and acknowledgments section should be fully completed, since the funding body is possibly a university/research institute.
-The extraction solvent should be highlighted as “Ethanol XX%, (v/v)” in the abstract and the main text as well. Are the authors sure that the percentage of ethanol used was 97%?
-The anxiolytic activity of the CM extract (route of administration: i.p.) contradicts previous reports (for instance: ((10.1016/j.jnutbio.2011.03.017, Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin — are they prodrugs?)). This study supports the hypothesis that flavonoids act as prodrugs which are transformed into their active hydroxyphenylacetic acid metabolites by intestinal microflora.
-Regarding the above comment, the authors are required to discuss the anxiolytic/antidepressant compounds, including the intact compounds and their degradation products.
-Authors are required to provide suitable references for the concentration used (CM, Arg, AG, NAME, standard drug, …) in Fig. 9 and the other experiments.
-Discuss the antidepressant effects of flavonoids, using related papers, such as “Antidepressant-like effects of the hydroalcoholicextracts of Hemerocallis Citrina and its potentialactive components”.

Associate Editor — MINOR REVISION — 4 Oct 2024

Dear Authors,

I hope this message finds you well.

I am writing to inform you that your manuscript titled “Successful Treatment of Psoriasis Vulgaris with the Acyl-Flavonoid, InflAQ: Case Report with a Review of the Literature” has been reviewed and is currently under minor revision.
Please address the reviewers’ comments and submit your revised manuscript at your earliest convenience. We look forward to receiving your revisions and moving forward with the publication process.

Thank you for your valuable contribution to the Journal of Reports in Pharmaceutical Sciences.

Best regards,

Editor-in-Chief

MINOR REVISION 4 Oct 2024

Dear Authors,

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Please address the reviewers’ comments and submit your revised manuscript at your earliest convenience. We look forward to receiving your revisions and moving forward with the publication process.

Thank you for your valuable contribution to the Journal of Reports in Pharmaceutical Sciences.

Best regards,

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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.

Dear Editor of Journal of Reports in Pharmaceutical Sciences

We sincerely thank the reviewers for constructive criticisms and valuable comments, which were of great help in revising the manuscript. Accordingly, the revised manuscript has been systematically improved with new information and additional interpretations. Our responses to the referee's comments are given below and also, highlighted in yellow font in the text of manuscript.

Reviewer 1 comments:

Comment 1: Abstract: Line 15 should be corrected

Response: Line 15 has been corrected.

Comment 2: Abbreviations should not be used for the first time, please correct them: TST, FST

Response 2: The explanations were added.

Comment 3: The number of rats in the abstract is recorded in 9 groups of 7, but in the text (line 97) 9 groups of 5. Which one is correct?

Response 3: 9 group of 7 was corrected.

Comment 4: The grouping in the abstract is different from the text.

Response 4: The groups have been corrected.

Comment 5: In line 101: extract at 2 doses (250 and 500 750 mg/kg) what does it mean? And also line 103

Response 5: The extract was prepared at 3 doses: 250 and 500 750 mg/kg

Comment 6: The figures are not of good quality: figure 5 is not visible - figure 3 is different

Response 6: They have been replaced with better qualified figures.

Reviewer 2 comments:

Comments 1: The inclusion of DOIs for referenced articles is crucial for the completeness and credibility of your manuscript. Many referenced articles currently lack DOIs, and I strongly recommend their inclusion.

Response 1: The DOIs were added.

Comments 2: The text requires spelling and grammatical corrections

Response 2: The grammatical editing has been done.

Comments 3: In section 2.3, "Extraction Preparation," the fruits were purchased. Including an expert's opinion to confirm the correctness of the fruit species mentioned would be beneficial.

Response 3: Thanks to your suggestion, after preparing the studied fruit, a pharmacognosy expert was used to confirm it.

Comments 4: In section 2.3, "Extraction Preparation," you mention using filter paper. Please specify the brand and type of filter paper used.

Response 4: The brand of paper was added: Whatman filter paper No. 1

Comments 5: Regarding the tests conducted on mice, how they were performed is generally described. Please add information on how many times each test was conducted on each mouse. Was it a single test per mouse?

Response 5: The tests were repeated 3 times with 5 min of separation.

Comments 6: When referring to subjects in scientific writing, the term "mice" should be used instead of "mouse."

Response 6: mouse was replaced.

Reviewer 3 comments:

Comments 1: Funding and acknowledgments section should be completely declared, since the funding body is possibly a University/Research institute.

Response 1: Funding and acknowledgments were completely declared.

Comments 2: The extraction solvent should be highlighted as “Ethanol XX%, (v/v)” in the abstract and the main text as well. Are the authors sure about % of used ethanol, as 97%?

Response 2: the authors sure about % of used ethanol, as 97%.

Comments 3: The anxiolytic of the CM extract (route of administration: i.p.) contradicts previous reports (for instance: ((10.1016/j.jnutbio.2011.03.017, Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin — are they prodrugs?)). This study supports the hypothesis that flavonoids act as prodrugs which are transformed into their active hydroxyphenylacetic acid metabolites by intestinal microflora -regarding the above (latter) comment, authors are required to discuss on the anxiolytic/antidepressant compounds, including the intact compounds and their degradation products.

Response 4: It was mentioned in discussion.

Comments 5: Authors are required to provide suitable references for the concentration used (CM, Arg, AG, NAME, standard drug, …) in Fig. 9 and the other experiments.

Response 5: the references of doses were added.

Comments 6: Discuss on the anti-depressant of flavonoids, using the related papers; like “Antidepressant-like effects of the hydroalcoholicextracts of Hemerocallis Citrina and its potentialactive components”

Response 6: the mentioned referenced was added in discussion.

2 Revision 1

3 comments · 14 Nov 2024 – 16 Nov 2024

Referee 1 Reviewer

MINOR REVISION 14 Nov 2024

Dear Editor
These two comments have not been included/highlighted in the revised manuscript (although the authors have declared that the comments have been discussed, they were not found by the referee/co-editor).

Comments 3: The anxiolytic effect of the CM extract (route of administration: i.p.) contradicts previous reports (for instance: (10.1016/j.jnutbio.2011.03.017, Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin — are they prodrugs?)). This study supports the hypothesis that flavonoids act as prodrugs which are transformed into their active hydroxyphenylacetic acid metabolites by intestinal microflora.
- Regarding the above (latter) comment, the authors are required to discuss the anxiolytic/antidepressant compounds, including the intact compounds and their degradation products.

Comment 6: Discuss the antidepressant effects of flavonoids.

Associate Editor

MINOR REVISION 16 Nov 2024

Dear Authors,
Please provide a point-by-point response addressing the comment. Highlight any specific data, methodologies, or conclusions that pertain to the comment.
Best regards,
E.I.C

Editor-in-Chief

MINOR REVISION 16 Nov 2024

Dear Authors,
Please provide a point-by-point response addressing the comment. Highlight any specific data, methodologies, or conclusions that pertain to the comment.
Best regards,
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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.

Dear Editor of Journal of Reports in Pharmaceutical Sciences

We sincerely thank the reviewers for constructive criticisms and valuable comments, which were of great help in revising the manuscript. Accordingly, the revised manuscript has been systematically improved with new information and additional interpretations. Our responses to the referee's comments are given below and also, highlighted in yellow font in the text of manuscript.

Reviewer 1:

These two comments have not been included/highlighted in the revised manuscript (although the authors have declared that the comments have been discussed, but not found by the referee/co-editor)

Comments 3: The anxiolytic of the CM extract (route of administration: i.p.) contradicts previous reports (for instance: ((10.1016/j.jnutbio.2011.03.017, Route of administration determines the anxiolytic activity of the flavonols kaempferol, quercetin and myricetin — are they prodrugs?)). This study supports the hypothesis that flavonoids act as prodrugs which are transformed into their active hydroxyphenylacetic acid metabolites by intestinal microflora -regarding the above (latter) comment, authors are required to discuss on the anxiolytic/antidepressant compounds, including the intact compounds and their degradation products.

Response: we have used the total extract of *Citrus medica* fruit not pure flavonols which is mentioned in the above article and also based on the following reference (no. 1) *Citrus medica* has many Flavanones, Flavanols and Flavones such as Eriocitrin, Hesperidin, Eriodyctiol, Sakuranetin, Rutin, Luteolin which are not mentioned and tested in the above article. Also, several studies have been used flavonoids via i.p. injections and they showed high efficacy in both peripheral and central systems (no. 2 -5):

1. Mateus ARS, Teixeira JD, Barros SC, Almeida C, Silva S, Sanches-Silva A. Unlocking the Potential of *Citrus medica* L.: Antioxidant Capacity and Phenolic Profile across Peel, Pulp, and Seeds. *Molecules*. 2024; 29(15):3533. https://doi.org/10.3390/molecules29153533

2. Takahashi K, Morikawa A, Kato Y, Sugiyama T, Koide N, Mu MM, Yoshida T, Yokochi T. Flavonoids protect mice from two types of lethal shock induced by endotoxin. FEMS

Immunol Med Microbiol. 2001 Jul;31(1):29-33. doi: 10.1111/j.1574-695X.2001.tb01582.x. PMID: 11476978.

3. Coskun O, Kanter M, Korkmaz A, Oter S. Quercetin, a flavonoid antioxidant, prevents and protects streptozotocin-induced oxidative stress and beta-cell damage in rat pancreas. Pharmacol Res. 2005 Feb;51(2):117-23. doi: 10.1016/j.phrs.2004.06.002. PMID: 15629256.

4. Fernández SP, Wasowski C, Loscalzo LM, Granger RE, Johnston GA, Paladini AC, Marder M. Central nervous system depressant action of flavonoid glycosides. Eur J Pharmacol. 2006 Jun 13;539(3):168-76. doi: 10.1016/j.ejphar.2006.04.004. Epub 2006 Apr 6. PMID: 16698011.

5. Sabogal-Guáqueta AM, Muñoz-Manco JI, Ramírez-Pineda JR, Lamprea-Rodriguez M, Osorio E, Cardona-Gómez GP. The flavonoid quercetin ameliorates Alzheimer's disease pathology and protects cognitive and emotional function in aged triple transgenic Alzheimer's disease model mice. Neuropharmacology. 2015 Jun;93:134-45. doi: 10.1016/j.neuropharm.2015.01.027. Epub 2015 Feb 7. PMID: 25666032; PMCID: PMC4387064.

Therefore, it is not possible to make a definite conclusion based only on one article that studied a limited number of flavonoids (3 numbers).

Comment 6: Discuss on the anti-depressant of flavonoids.

Response: Added.

3 Revision 2

2 comments · 5 Jan 2025 – 5 Jan 2025

Associate Editor

ACCEPT 5 Jan 2025

Dear Authors,

I hope this message finds you well. I am writing to extend my heartfelt congratulations on the acceptance of your article titled “Antidepressant Effect of Hydroalcoholic Extract of Citrus medica Fruit in Mice: Possible Role of Nitric Oxide” in the Journal of Reports in Pharmaceutical Sciences.
Thank you for your significant contribution to pharmaceutical sciences. I look forward to reading more of your work in the future.

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E.I.C

Editor-in-Chief

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