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OPEN PEER REVIEW

Involvement of the Dopaminergic and Serotonergic Systems in the Antidepressant-like Effect Caused by Ethanolic Extract of *Pistacia lentiscus* in Tail Suspension Test

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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 · 6 Oct 2023 – 16 Oct 2023

Seyed-Amirabbas Ahadiat Reviewer

MINOR REVISION 6 Oct 2023

Dear author

Thank you for your valuable work.

Please mention the limitations of your work and the ethical code at the end of the article, if your manuscript has any.

Referee 1 Reviewer

MAJOR REVISION 16 Oct 2023

This manuscript titled "Involvement of the Dopaminergic and Serotonergic Systems in the Antidepressant-Like Effect Caused by Ethanolic Extract of Pistacia lentiscus in Tail Suspension Test" has some notable flaws:

Abstract:

The abstract lacks a concise summary of the specific findings. It should briefly mention the key results to give readers an overview of the research's significance.
The abstract does not include the exact magnitude of the observed effects (e.g., the percentage increase in antidepressant-like effect).
Introduction:

The introduction provides a general overview of depression and the need for new treatments but lacks a clear statement of the study's objectives or hypotheses. The research questions should be explicitly stated.
The introduction should provide a more focused review of relevant literature to highlight the gap that this study aims to fill.
Methods:
The methods section should detail the selection criteria for the animal model and justify the choice of the tail suspension test as the specific model.
The descriptions of the drugs used, their doses, and their routes of administration could be more comprehensive.
The preparation of the EEPL is not described in adequate detail. The extraction process should be thoroughly documented.
Statistical methods are mentioned briefly but require more detailed explanation and justification.
Results:
It is unclear whether there were any control groups or negative controls in the experiments.
The interpretation of results is somewhat limited. The significance of the findings should be discussed in the context of existing literature.
Discussion:

The discussion does not adequately address the limitations of the study. For example, it mentions that this is a preliminary study, but further discussion of the study's limitations and potential sources of bias is needed.
The mechanisms of action of EEPL are proposed, but they are not supported by experimental evidence or references to previous studies.
The study's relevance to clinical applications should be discussed more thoroughly. The jump from animal models to potential human treatments should be made clear.

The conclusion could be more concise and should emphasize the practical implications and future directions for research.
Overall, the manuscript would benefit from improved organization, with clearly defined sections and subsections for each aspect of the study.
Grammar and syntax issues should be addressed throughout the manuscript to improve readability.

Associate Editor

MAJOR REVISION 16 Oct 2023

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.
ABSTRACT:
The study design should be mentioned in the first line of the method section of the ABSTRACT.

Editor-in-Chief

MAJOR REVISION 16 Oct 2023

Dear Author,
Thank you for submitting the article. It needs some revision. Please revise it based on the reviewers' and AE's comments.

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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.

Journal: ***Archives of Neuroscience***

Manuscript #: **140852**

Title of Paper: **Involvement of the dopaminergic and serotonergic systems in the antidepressant-like effect caused by ethanolic extract of *Pistacia lentiscus* in tail suspension test**

Date Sent: **November 12, 2023**

Editor-in-chief of Archives of Neuroscience

Dear Professor Madjid Samii,

We highly appreciate the detailed, valuable comments of the dear reviewers on our manuscript of **140852**. The suggestions are quite helpful for us and we incorporate them in the revised paper. During the last weeks, we have referred to different literature and papers and reconstructed the manuscript to improve the quality of our paper. Please find attached a point-by-point response to dear editor and dear reviewers concerns. We hope that you find our response satisfactory and that the manuscript is now acceptable for publication.

*** Changes to the manuscript are shown in yellow, green,blue and gray highlights for dear reviewers 1- 3 and dear editor, respectively.**

Response to comments from Dear Reviewer # 1

Thank you for your valuable work. Please mention the limitations of your work and ethical code at the end of the article, if your manuscript has any.

-Thank you very much for agreeing with us on the intention of this manuscript. As suggested by the dear reviewer, the limitations of our work were mentioned. Moreover, the study's ethical number was mentioned in the footnote section. So, that it may not be visible to the journal's referees. Meanwhile, all experimental procedures used in the present study that involved laboratory animals were confirmed by the Ethics Committee of IAUUB to care for and use laboratory animals (IR.IAU.URMIA.REC.1401.094).

Response to comments from Dear Reviewer # 2

This manuscript titled "Involvement of the Dopaminergic and Serotonergic Systems in the Antidepressant-Like Effect Caused by Ethanolic Extract of Pistacia lentiscus in Tail Suspension Test" has some notable flaws:

-We highly appreciate the positive feedback from the dear reviewer to submit a revised draft of the manuscript. We have read your comments carefully and tried our best to address them one by one.

Abstract:

The abstract lacks a concise summary of the specific findings. It should briefly mention the key results to give readers an overview of the research's significance. The abstract does not include the exact magnitude of the observed effects (e.g., the percentage increase in antidepressant-like effect).

- We appreciate the reviewer's insightful comment. As suggested by dear reviewer, the specific findings of the study and exact magnitude of the observed effects (the percentage) were mentioned.

Introduction:

The introduction provides a general overview of depression and the need for new treatments but lacks a clear statement of the study's objectives or hypotheses. The research questions should be explicitly stated.

- Thank you for pointing this out. The reviewer is correct, and we have mentioned the study novelty.

- The introduction should provide a more focused review of relevant literature to highlight the gap that this study aims to fill.

- Thank you for the comment, the correction has been made.

Methods:

The methods section should detail the selection criteria for the animal model and justify the choice of the tail suspension test as the specific model.

- As suggested by the reviewer, we have detailed the selection criteria for the animal model.

The descriptions of the drugs used, their doses, and their routes of administration could be more comprehensive.

The preparation of the EEPL is not described in adequate detail. The extraction process should be thoroughly documented.

- Thank you for the comment, the correction has been made.

Statistical methods are mentioned briefly but require more detailed explanation and justification.

-Thank you for the comment, the correction has been made.

Results:

It is unclear whether there were any control groups or negative controls in the experiments.

The interpretation of results is somewhat limited. The significance of the findings should be discussed in the context of existing literature.

- Thank you for pointing this out, the correction has been made.

Discussion:

The discussion does not adequately address the limitations of the study. For example, it mentions that this is a preliminary study, but further discussion of the study's limitations and potential sources of bias is needed. The mechanisms of action of EEPL are proposed, but they are not supported by experimental evidence or references to previous studies.

- We think this is an excellent suggestion. But I should mention that this is the first study to show findings that indicate an anti-depressant-like effect of EEPL and its underlying mechanisms.Morover, most of the P. *lentiscus* biological or pharmacological activities are related to the phenolic composition of this plant (Ref No in manuscrpit:19,23-29).

The study's relevance to clinical applications should be discussed more thoroughly. The jump from animal models to potential human treatments should be made clear.

-We completely agree with the reviewers' suggestion. According to the valuable opinion of dear referee, we have removed the focus of the study on clinical studies (due to the lack of coverage with current results and the need for further studies). Hence, we only limit to our results.

The conclusion could be more concise and should emphasize the practical implications and future directions for research.

- Thank you for the comment, the correction has been made.

Overall, The manuscript would benefit from improved organization, with clearly defined sections and subsections for each aspect of the study. Grammar and syntax issues should be addressed throughout the manuscript to improve readability.

- Thank you for pointing this out. The grammar and syntax issues have been corrected on revised manuscript**.**

Response to comments from Dear Reviewer # 3

I should say thank you for select this object: Involvement of the dopaminergic and serotonergic systems in the antidepressant-like effect caused by ethanolic extract of Pistacia lentiscus in tail suspension test. I think the idea of this study is good. The authors evaluate the depression as a very important object I human society. The study was designed very well. There are small points for notification.

It seems that this study should be designed in 2 part acute and chronic phase because identification of the drug effects is very difficult and by just behavioral test could not achieve results that indictor of the effectiveness of the extract.

- Thank you very much for dear reviewer positive feedback and kind letter. Thank you for pointing this out. But, our experimental design is exactly based on previous studies:

-Ishola IO, Agbaje EO, Akinleye MO, Ibeh CO, Adeyemi O. Antidepressant-like effect of the hydroethanolic leaf extract of Alchorneacordifolia (Schumach. &Thonn.) Mull. Arg.(Euphorbiaceae) in mice: Involvement of monoaminergic system. J Ethnopharmacol. 2014; 158:364-372.

- Hassanzadeh SA, Abbasi-Maleki S, Mousavi Z. Anti-depressive-like effect of monoterpene trans-anethole via monoaminergic pathways. Saudi J Biol Sci. 2022;29(5):3255-61. doi:10.1016/j.sjbs.2022.01.060.

-Ostadhadi, S., Norouzi-Javidan, A., Nikoui, V., Zolfaghari, S., Moradi, A., & Dehpour, A. R. (2018). Nitric oxide involvement in additive antidepressant-like effect of agmatine and lithium in mice forced swim test. Psychiatry research, 266, 262–268.

-etc.

In addition, the monoaminergic system consists of different receptors that are involved in different drug mechanisms of action. Hence, in this (acute)part of the study we use a large number of animals. On the other hand, if we examine the chronic effect of EEPL, we should use new animal groups because of our behavioral models.

Also, for confirmation of the behavioral results it is better to evaluate molecular test such as receptor distribution of each neurotransmitters.

- Thank you for pointing this out. Unfortunately, we euthanize the animals and at this time we don't have any samples for assessing brain neurotransmitters. We certainly use dear reviewer's recommendation in our future studies.

But overly all of the section were done very well. I suggest graphs column design with different themes to differentiate with each other more.

- - Thank you for pointing this out. As suggested by dear reviewer, we design colored figures for better understanding the groups. On the other hand, for better understanding the figures,we use the same color for each receptor antagonist pathway.

Associate Editor's Comments:

Associate Editor 1:

Dear EIC,

Thanks to the authors and appreciation to the researchers. The manuscript is a valuable research. But some revisions are needed.

ABSTRACT:

Study design should be mentioned in first line of method section of ABSTRACT

- - Thank you for pointing this out. The correction has been made.

Dear reviewers: It should be mentioned that the main limitation in this journal (Archives of Neuroscience) is the word limitation (3500 words, 5 figures, and 34 cited references for original research). So, in most parts of the manuscript, we have deleted extra explanations. In present form and after revision, our manuscript word counts increased to . Dear referees, thank you very much for understanding our conditions.

- ✓ We look forward to hearing from you in due time regarding our submission and to responding to any further questions and comments you may have.

Sincerely yours,

Corresponding author

2 Revision 1

4 comments · 9 Dec 2023 – 9 Dec 2023

Seyed-Amirabbas Ahadiat Reviewer — ACCEPT 9 Dec 2023

Thank you for revising.

Referee 1 Reviewer — ACCEPT 9 Dec 2023

Dear AE.
Previous errors have been corrected, and there are no further recommendations.

Associate Editor — ACCEPT 9 Dec 2023

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 9 Dec 2023

Dear Authors.
Thanks for your valuable efforts in carefully revising the manuscript.