OPEN PEER REVIEW

Open Peer Review (OPR)

As a new feature for progressing towards transparency, we decided to open a new window for all of our editors as well as authors titled "**Open Peer Review**". We hope by this new facility, our reviewers will be more motivated and authors will be more satisfied with the review process. We believe that publishing our peer review reports could make a transparent and clear environment for all our efforts within a journal, but not all reviewers tend to publish their comments.

What is "Open Peer Review" process?

An "Open Peer Review" process is making the details of all review process (including reviewers, associate editors, and EICs comments) as "Public" as it is agreed by EIC, Authors, and reviewers.

Advantages of "Open Peer Review" process

- More transparency, constructiveness and tactful comments of the peer review process: leads to an increase in the quality of reviews
- More motivations for all involved roles in the review process
- Authors' satisfactions from the review process: Increases honesty between authors and reviewers
- Education of both authors and new students
- Prevents reviewers from following their individual agendas and leading to the detection of reviewers' conflicts of interests

You can find out more at:
https://sites.kowsarpub.com/kowsar/knowledgebase/category/tree.html#opr.html

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Peer Review Report for "Effect of Co-administration of *Agnus castus* Aqueous Leaf Extract and Cadmium Chloride on Testicular Function Indices"

Author(s): Tomilola Olaolu, Damilola Ajibola, Damilare Rotimi, Oghenerobor Akpor

Review Timeline:

Submit Date: 28 Oct 2019
Revised Date: 5 Jul 2020
Accepted Date: 28 Jul 2020

Revision (0)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | Revision (0)

15 Nov 2019

Dear Editor-in-cheif of Jundishapur J Nat Pharm Prod;

I would like to thank you for giving me this opportunity to review this interesting manuscript entitled “CO-ADMINISTRATION OF AGNUS CASTUS AQUEOUS LEAVES EXTRACT AND CADMIUM CHLORIDE ON TESTICULAR FUNCTION INDICES.”

Comments:
1- The effect of AGNUS CASTUS on sex hormones and antioxidant indices has been examined in the previous studies (doi: 10.1016/j.jcma.2016.05.006. Epub 2016 Aug 30). What is your rational of doing this study as well.
2- Please declare the novelty of your study? And what are (is) the implication for practicing this study?
3- What is the reason for the decrease in testicular protein at dose 100 mg/kg compared to other doses of Agnus Castus?

Good Luck!

REFEREE: Reviewer | **Revision** (0) 25 Nov 2019

Manuscript no. ID 99042
Dear editor-in-cheif;

The article entitled " CO-ADMINISTRATION OF AGNUS CASTUS AQUEOUS LEAVES EXTRACT AND CADMIUM CHLORIDE ON TESTICULAR FUNCTION INDICES", needs below considerations;

In the abstract section:
- The importance of cadmium toxicity and its mechanism must be clarifying.
- The P-value must be mentioned in abstract and result section.
- In the last sentence of the abstract define the groups comparison was applied between them.
- The race of rats and route of any administration must be mentioned in the abstract and in the text.
- Clarify that Agnus castus leaves was used or its aqueous extract.

In the introduction section:
- Does cadmium toxicity restrict to reproductive system? If it does, is there any reason for that?
- Discuss about the composition of Agnus castus leave extract.
- Pharmacokinetic of Agnus castus (the absorption, metabolism and exertion), also its lethal dose and side effects must be mentioned.

In the material and method section:
- The material should be separated from assays.
- The unites of each parameter must be identified.
- Also the method base of each kit and wave length that the OD was read in it, must be identified.
- The apparatuses used for measurement must be mentioned with theirs details.
- A brief discussion about the method which used in this study for measurement of each parameter must be mentioned.
- The extraction method and type of extract must be clearly discussed.
- The title and subtitle must be numbered.

In the result section:
- Identify that the comparison was done between which groups in the first paragraph of results. This section of manuscript could be misunderstood and needed to be revised completely.
- In the next paragraph, the testicular cholesterol levels must be clearly defined to its correspond treated group.
- The uniformity must be used for refer to figure overall the manuscript.
- The first comparison must be displayed between the treated groups and model group.

In the discussion section:

- The discussion need essential revision according to proper style for medical writing.
- Avoid the repetition of results in the discussion.
- The references are not in unique style and must be corrected according to journal instruction guidelines.

Yours sincerely!

REFEREE: Reviewer | **Revision** (0) 28 Dec 2019

Dear author;
Thank you for choosing JJNPP for publishing your manuscript. Please consider the following comments;
1. The manuscript strongly needs English editing.
2. The abstract needs to be rewritten.
3. Delete these words in Keyword: testicular indices and antioxidant.
4. Complete the extraction steps of the leaves.
5. Why cadmium was not given to rats in drinking water because it is similar to human exposure to cadmium?
6. Why histopathological studies have not been performed?
7. In the method section, the materials and kits used should be listed as a separate item.
8. In the method section, the test method must be fully written.
9. To determine whether the extract itself may be toxic at the doses used, the maximum dose of extract alone should be used in a separate group. Why has not it tested?
10. There are three significant symbols at the top of the graph in Fig. 2, 3 and 4 but only one sign is indicated in the figure legend.
11. The discussion is weak.

Good Luck!

REFEREE: Associate Editor | **Revision** (0) 8 Jan 2020

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (0) 13 Jan 2020

Dear Author,
The reviewers' comments are mentioned. Please correct the details as mentioned above carefully according to reviewers' request.
Thanks.

OPEN PEER REVIEW

Revision (1)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewer's Comments	Response
Reviewer 1	
1- The effect of AGNUS CASTUS on sex hormones and antioxidant indices has been examined in the previous studies (doi: 10.1016/j.jcma.2016.05.006. Epub 2016 Aug 30). What is your rational of doing this study as well.	The study cited was carried out to evaluate the effect of *Agnus castus* **fruit extract** on loss of endocrine functions in **aging female mice** induced with D-galactose. Our current study however investigated the effect of *Agnus castus* aqueous **leaves** extract on function indices of the testes **of male rats**, administered with cadmium chloride. The rationale for this study: The leaf extract has been reported previously for its beneficial effects on female reproductive system with paucity of data on its effects on male reproductive system (Niroumand, 2018; Jelodar & Askar, 2017),
2- Please declare the novelty of your study? And what are (is) the implication for practice of this study?	To the best of our knowledge, presently there are no data associated with administration of *Agnus castus* on cadmium chloride-treated male Wistar rats. Exposure to heavy metals is a major environmental problem in developing countries including Nigeria. Cadmium especially has been implicated in causing damage to the male reproductive system. Agnus castus has been acclaimed to have beneficial effects on reproductive functions in females. Our study therefore aimed at investigating the effect of *Agnus castus* aqueous leaves extract on testicular function indices of cadmium chloride administered male Wistar rats.
3- What is the reason for the decrease in testicular protein at dose 100 mg/kg compared to other doses of Agnus castus?	This could have been as a result of their food intake, which was not measured in this current study, since it is not a nutritional research.
Reviewer 2	
In the abstract section: *- The important of cadmium toxicity and its mechanism must be clarifying.*	Done
- The P-value must be mentioned in abstract and result section.	Done
- In the last sentence of abstract define the groups comparison was applied between them.	Done
- The race of rats and route of any administration must be mentioned in abstract and in the text.	Done
- In abstract, clarify that Agnus castus leaves was used or its aqueous extract.	Done
In the introduction section:	
- Does cadmium toxicity restrict to reproductive system? If it does, is there any reason for that?	Clarified

- Discuss about the composition of Agnus castus leave extract.	Done
- Pharmacokinetic of Agnus castus (the absorption, metabolism and exertion), also its lethal dose and side effects must be mentioned.	Done
In the material and method section: *- The material should be separated from assays.*	Done
- The unites of each parameter must be identified. *- Also the method base of each kit and wave length that the OD was read in it must be identified.*	Done
- The apparatus used for measurement must be mentioned with their details. *- A brief discussion about the method which used in this study for measurement each parameter must be mentioned.* *- The extraction method and type of extract must be clearly discussed.*	Done
- The title and subtitle must be numbered. *In the result section:* *- Identify that the comparison between which group was done in the first paragraph of results. This section of manuscript could be misunderstood and needed to be revised completely.* *- In next paragraph, the testicular cholesterol levels must be clearly defined to its correspond treated group.* *- The uniformity must be used for refer to figure overall the manuscript.* *- In the result section the first comparison must be displayed between the treated groups and model group.* *In the discussion section:* *- The discussion need essential revision according to proper style for medical writing.* *- Avoid the replicate data in result and discussion.* *- The references are not in unique style and must be corrected according to journal instruction guideline.*	Done Done
In the introduction section:	
- Does cadmium toxicity restrict to reproductive system? If it does, is there any reason for that?	Clarified
Reviewer 3	
1. The manuscript strongly needs English	Done

editing.	
2. The abstract needs to be rewritten.	Done
3. Delete these words in Keyword: testicular indices and antioxidant.	Done
4. Complete the extraction steps of the leaves.	Done
5. Why cadmium was not given to rats in drinking water because it is similar to human exposure to cadmium?	We will not be able to quantify (in mg) the exact amount ingested by each rat if it's in drinking water.
6. Why histopathological studies have not been performed?	This study, just as most other studies by researchers in developing countries was funded by personal funds, only using the private university laboratory space. We therefore had to restrict our research to biochemical assays and methods that could be done within the confines of our research environment due to cost.
7. In the method section, the materials and kits used should be listed as a separate item	Done
8. In the method section, the test method must be fully written.	
9. To determine whether the extract itself may be toxic at the doses used, the maximum dose of extract alone should be used in a separate group. Why not tested?	The LD_{50} has already been carried out in a previous study which is much higher than the doses used in this current study, 17.21 g/kg body weight (Sahib *et al.*, 2014)
10. There are three significant symbols at the top of the graph in Fig. 2, 3 and 4 but only one sign is indicated in the figure legend	Revised
11. The discussion is weak.'	

OPEN PEER REVIEW

Revision (1)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (1) 2 May 2020

Dear author;
1- The structure of the discussion section needs a major revision. Authors had separated this section in many subdivisions that it is not according to academic essay writing and instruction of JJNPP. These subdivisions should be removed.

2- Although paragraph unity is important, it is not the only factor that needs to consider in writing a successful paragraph of discussion. In order to write well structured paragraphs, they must be coherent. For coherence in writing, the sentences must hold together; that is, the movement from one paragraph to the next must be logical and smooth. There must be no sudden jumps. Each paragraph should flow smoothly into the next one.
Also, be sure that each paragraph includes concluding sentences to complete the paragraph.

Good Luck!

REFEREE: Associate Editor | **Revision** (1) 5 May 2020

Dear EIC,
The manuscript is studied, and there are some comments which should be addressed by the author. According to the comments, the document needs major revision.
Kind regards,

REFEREE: EIC | **Revision** (1) 6 May 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this document needs minor revision. Please follow their comments as requested.
Thanks.

OPEN PEER REVIEW

Revision (2)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewer's Comments	Response
Reviewer 1: *the structure of the discussion section needs a major revision. Authors had separated this section in many subdivisions that it is not according to academic essay writing and instruction of JJNPP. These subdivisions should be removed.* *Although paragraph unity is important, it is not the only factor that needs to consider in writing a successful paragraph of discussion. In order for paragraphs to be well structured, they must be coherent. For coherence in writing, the sentences must hold together; that is, the movement from one paragraph to the next must be logical and smooth. There must be no sudden jumps. Each paragraph should flow smoothly into the next one.* *Also, be sure that each paragraph includes concluding sentences to complete the paragraph.*	The authors have corrected this.

Dear editor, please find the response to the reviewers below:

OPEN PEER REVIEW

Revision (2)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (2) 11 Jun 2020

Dear author;
Please do consider the following comments;

1. The Manuscript must be edited in English.
2. In graphs, in compression between groups; first, the cadmium group only should be compared with the control group and the star symbol should be used; then, the groups receiving cadmium + extracts should be compared with the cadmium group only and another symbol should be used.
3. The mechanism of cadmium toxicity, its transmission, human contact with it, etc. should be explained in the introduction section.
4. The method section: For each test, the protocol must be explained, the names of the devices used, and the names of the kits used must be provided with the full address and specifications of the kits and devices.
5. The discussion section: A comprehensive explanation of the result should be given at the beginning of the discussion, followed by a discussion of each of the results.
6. The conclusion section: Re-explaine results if needed to be rewritten.
7. On which basis are cadmium doses selected? Based on human exposure? Convert dose to mice? Please explaine by mentioning the references. In addition, in the grouping of mice section, at least two references should be given with cadmium dose.

Good Luck!

REFEREE: Associate Editor | **Revision** (2) 22 Jun 2020

Dear EIC
The reviewer(s) have recommended publication, but also suggest some minor revisions to the manuscript. Therefore, I invite the author to respond to the reviewer(s)' comments and revise his manuscript.
Kind regards,

REFEREE: EIC | **Revision** (2) 28 Jun 2020

Dear Author,
Your article is reviewed by the reviewers carefully. According to their comments, this

document needs minor revision. Please follow their comments as requested.

Thanks.

OPEN PEER REVIEW

Revision (3)

Reply to Reviewers

Ideally, the reviewing process can significantly improve the submitted manuscripts by allowing the authors to take into account the advice of reviewers. Author(s) must reply to all reviewers' comments in a separate Word file, point by point. A "**Reply to Reviewers**" document is submitted along with revised manuscript during submission of revised files, summarizing the changes that the authors made in response to the reviewers' comments. The responses to reviewers' comments specifies how the authors addressed each comment the reviewers made.

You can read the authors' responses to the reviewers' comments in the next page.

Reviewers' Comments:	**Authors' response**
1. The Manuscript must be edited in English.	*Done, using "grammarly".*
2. In graphs, in compression between groups; first, the cadmium group only should be compared with the control group and the star symbol should be used; then, the groups receiving cadmium + extracts should be compared with the cadmium group only and another symbol should be used.	*Done*
3. The mechanism of cadmium toxicity, its transmission, human contact with it, etc. should be explained in the introduction section.	*Done*
4. The method section: For each test, their protocol must be explained, the names of the devices used, and the names of the kits used must be provided with the full address and specifications of the kits and devices.	*Done*
5. The discussion section: A comprehensive explanation of the result should be given at the beginning of the discussion, followed by a discussion of each of the results.	*Done*
6. The conclusion section: Re-explained results if needed to be rewritten.	*Done*
7. On what basis are cadmium doses selected? Based on human exposure? Convert dose to mice? ... Be explained by mentioning the references. In addition, in the grouping of mice section, at least two	Othman *et al.,* 2014 (Othman, M. S., Nada, A., Zaki, H. S., & Moneim, A. E. A. (2014). Effect of Physalis peruviana L. on cadmium-induced testicular toxicity in rats. *Biological trace element research*, *159*(1-3), 278-287.)

references should be given with cadmium dose	Dkhil *et al.,* 2014 (Dkhil, M. A., Al-Quraishy, S., Diab, M. M., Othman, M. S., Aref, A. M., & Moneim, A. E. A. (2014). The potential protective role of Physalis peruviana L. fruit in cadmium-induced hepatotoxicity and nephrotoxicity. *Food and Chemical Toxicology*, *74*, 98-106.) Höfer *et al.,* 2009 (Höfer, N., Diel, P., Wittsiepe, J., Wilhelm, M., & Degen, G. H. (2009). Dose-and route-dependent hormonal activity of the metalloestrogen cadmium in the rat uterus. *Toxicology letters*, *191*(2-3), 123-131.)

OPEN PEER REVIEW

Revision (3)

Here, you can see the **Reviewers**, **Associate Editors** and **EICs'** comments from the beginning to the end of the revision process.

REFEREE: Reviewer | **Revision** (3) 18 Jul 2020

Dear author;
Corrections made and the manuscript can be accepted.

With best wishes!

REFEREE: Associate Editor | **Revision** (3) 22 Jul 2020

Dear EIC
Based on the authors' answers to the reviewers' comments, the reviewer(s) have recommended publication.
Kind regards.

REFEREE: EIC | **Revision** (3) 28 Jul 2020

Dear Author,
The document is reviewed carefully by the reviewers. According to their comments and your revisions as requested, this manuscript is accepted.
Thanks