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 "Evaluation of the Apoptotic and Scolicidal Effects of Crude and Flavonoid Extracts of *Allium noeanum* on Protoscolices and Hydatid Cyst Wall"

Author(s): Zahra Salemi, Mehrdad Goudarzi, Reza Hajihossein, Mitra Noori, Saeid Babaei, Zahra Eslamirad

Review Timeline:

Submit Date: 3 Aug 2019
Revised Date: 1 Sep 2020
Accepted Date: 21 Sep 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) 21 Sep 2019

Dear author,
Thank you for choosing JJNPP for publishing your manuscript. It is well written but it has some writing technical problems that should be addressed by the authors:

- The scientific name of plants should be written in italic form all over the text. (The genus name is written first, italicized and the first letter of genus is always capitalized. The species name is written second, italicized and the first letter of species is never capitalized.)
- “Herbal extracts preparation”: please mention the used part of the plant (for example root, leave, flower, aerial part,...)
- The herbarium number of plants should be written in text.
- Please mention to alcohol scientific name such as “ethanol”
- Please explain the details of preparing the method of flavonoid extract and chromatography methods.
- It was better to evaluate the total phenol and flavonoid content of both extracts.

- In the result part, there isn't any chromatography data.
- Please explain about "%": The "%V/V" or "%W/V" in which solvent?
- Please add the Scolicidal Effects of flavonoids or other groups of useful natural components, using some previous references, such as "Evaluation on Scolicidal Efficacy of Propolis"
- The figures are not clear.

Thanks.

REFEREE: Reviewer | **Revision (0)** 22 Sep 2019

Dear author,

Thank you for choosing JJNPP for publishing your study. This manuscript needs a major revision for publication in this journal. The suggestions are expressed in the attached file.

Good Luck!

REFEREE: Reviewer | **Revision (0)** 14 Nov 2019

Dear author,
Thank you for choosing JJNPP for publishing your manuscript. Here are some comments which need your attention:
1- Please delete "Echinococcus granulosus" and "Mortality" in the "keywords" section and add the "Total and Flavonoid Extract" and "Scolicidal Effects" to the words.
2- Please write "Echinococcus granulosus" in the italic form in in the whole article.
3- "softwires" is incorrect, please correct it in "Abstract" and other sections.
4- Please change the "The statistical analysis showed the kind of extract and its concentration and also exposure time have significant differences in the rate of protoscolices mortality ($p< 0.001$)." to "According to the statistical analysis, each form of extract has different dose and time-dependent rate of scolicidal activity", ($p< 0.001$)." in the "Abstract" section.
5- Please change "In the current research, the scolicidal ability of the Allium noeanum extract…" to "In the current research, the scolicidal ability of the Allium noeanum flavonoid extract…" in the "Conclusion" section.
6- Please explain the apoptotic cascade and the role of the caspase-3 in the progression of apoptosis briefly in the "Background" section.
7- Please allude to the novelty of this study in the "Abstract" and "Conclusion" sections.
8- Please allude to the exact Statistical test(s) in the "Statistical analysis" section.
9- Please allude to dose and time-dependent scolicidal activity of the extracts in the "Conclusion" section.

Good luck!

REFEREE: Associate Editor | **Revision (0)** 24 Dec 2019

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) 24 Dec 2019

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.

Dear Reviewers

I really appreciate your useful comments and the constructive criticisms of the reviewers. The manuscript has been modified accordingly and the modified parts are highlighted within the manuscript as follow.

Reviewers' Comments:

Reviewer 1: highlighted in Yellow in text of manuscript

- The manuscript is well written but it has some writing technical problems. The manuscript was edited again. The new edit certificate was also attached.
- *The scientific name of plants should be written in italic form all over the texts. (The genus name is written first, italicised and the first letter of genus is always capitalized. The species name is written second, italicised and the first letter of species is never capitalized.)* The revised was done.
- *"Herbal extracts preparation": please mention the used part of plant (for example: root, leave, flower, aerial part,...* The leaf of plant was used that added to text of manuscript.
- *The herbarium number of plant should be written in text.* (CMG1= Collection number, Mehrdad Goudarzi, determination by Mitra Noori)
- *Please mention to alcohol scientific name such as "ethanol".* Ethanol was used that added to text of manuscript.
- *Please explain the detail of preparing method of flavonoid extract and chromatography methods.* These methods added to "*Herbal extracts preparation "in* methods section.
- *It was better to evaluate total phenol and flavonoid content of both extracts.* Thanks to your valuable point of view, in the future studies, this point will be taken into consideration.
- *In result part there isn't any chromatography data.* The data was added to results section.
- *Please explain "%": %V/V or %W/V in which solvent?* Specified in the manuscript text.
- *Please add the Scolicidal Effects of flavonoids or other groups of useful natural components, using some previous references, such as "Evaluation on Scolicidal Efficacy of Propolis".* The desire information was added to discussion section. For this purpose, two references were added to manuscript (references 22 and 25).
- *The figures are not clear.* Figure resized. The mistake in the figure was also corrected. It should be noted that if we want to make the picture clearer, each diagram should be individually included in the article text, in which case the number of figures will be exceeded.

Reviewer 2: this manuscript need major edition for publication in this journal. The manuscript was fully edited and a new editing certificate was attached.

Reviewer 3: *highlight in Blue in text of manuscript*

1- Please delete "Echinococcus granulosus" and "Mortality" in the "keywords" section and add the "Total and Flavonoid Extract" and "Scolicidal Effects" to the words. The revise was done.

2- Please write "Echinococcus granulosus" in italic form in all of the article. The revise was done.

3- "softwires" in incorrect, please correct it in "Abstract" and other sections. The revise was done.

4- Please change the "The statistical analysis showed the kind of extract and its concentration and also exposure time have significant differences in rate of protoscolices mortality (p< 0.001)." to "According to the statistical analysis, each form of extract has difference dose and time-dependent rate of scolicidal activity (p< 0.001)." in the "Abstract" section. The revise was done.

5- Please change "In current research, the scolicidal ability of the Allium noeanum extract…" to "In current research, the scolicidal ability of the Allium noeanum flavonoid extract…" in "Conclusion" section. The revise was done.

6- Please explain the apoptotic cascade and the role of the caspase-3 in the progression of apoptosis briefly in "Background" section. The background section has been modified and the desired information was added to background and objective section.

7- Please allude to novelty of this study in "Abstract" and "Conclusion" sections. The novelty of the study was added to the desired sections of the manuscript.

8- Please allude to exact Statistical test(s) in "Statistical analysis" section. This information was added to the statistical analysis section.

9- Please allude to dose and time-dependency scolicidal activity of the extracts in the "Conclusion" section. This information was added to the conclusion section of the manuscript.

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.

Bahman Rahimi Esboei: Reviewer | **Revision** (1) — 1 Mar 2020

Dear author,
Thank you for corrections, but there are some other comments on your manuscript.
- This manuscript was full of grammatical errors.
- There were some scientific errors that I edited in the main file and put some comments on the text.
- The relationship between time and some actions were not logical. For example, you cannot count the live and dead cells in 30 seconds.
- I recommend that, please recheck the anti-protoscolesis effects (bu eosin) use 25, 50, 100, and 200 micro g/ ml of drugs after 5, 30, 60, 180 min and rewrite this section again.
- This low amount of concentration is not acceptable for scientists.

Thanks.

REFEREE: Reviewer | **Revision** (1) — 10 Mar 2020

Dear author,
Thank you for the corrections. The final revision of the manuscript is acceptable.
Thanks.

REFEREE: Associate Editor | **Revision** (1) — 27 Apr 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: Associate Editor | **Revision** (1) — 21 Jun 2020

Dear EIC,
After a thorough study of this manuscript, I came to the conclusion that due to the poor research structure and the lack of innovation it couldn't be published in this journal unless after major revisions by the authors.
- What is you purpose about total extract?

- You didn’t mention the used part of plant!
- How TLC can use for detecting the organic compounds?!
- You didn’t write the herbarium number of the used plant!
- Why you didn’t evaluate the total phenol and flavonoid content?

I hope you make it more perfect for publication by applying the comments provided by the referees.

Best wishes

REFEREE: EIC | **Revision (1)** 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 (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.

Dear Editor

I am pleased to resubmit the **new revised** version of our manuscript (Manuscript ID: 96180) entitled " **Evaluation of the Apoptotic and Scolicidal Effects of Crude and Flavonoid Extract of *Allium Noeanum* on Protoscolices and Hydatid Cyst Wall** " to the "**Jundishapur Journal of Natural Pharmaceutical Products"**. I really appreciate your useful comments and the constructive criticisms of the reviewers. The manuscript has been modified accordingly and the modified parts are highlighted within the manuscript by using the track changes mode in Microsoft Word. The detailed corrections are listed below point by point.

Yours Sincerely,

Zahra Eslamirad

Corresponding Author

Reviewers' Comments:

Reviewer 1:
Dear authors
This manuscript is was full of gramatically errors.

This article has been edited twice by professional editors and has been certified twice. The second edit has been done by the company that publishes your magazine, and an international certificate has been issued. Please advise me which center or centers to use to edit the article more accurately?

there was some scientific errors that i edited it in main file and put some comments on text.

Thanks to the honorable referee, but unfortunately no file has been uploaded for me so that I can use your valuable comments.

the time and concentration was not logic. For example you cannot count the live and dead cells in 30 seconds.

In the design of the experiment, the exposure time was initially considered from 5 to 30 minutes, but during the experiments, it was observed that different concentrations (except 25%) of both types of extract in 5 minutes lead to the 100% death of protoscolices (it can be observing in table 1 & 2), so the time of exposure to extracts were reduced and finally the design of the experiments was done as shown in the manuscript. In addition, as the referee is aware, the protoscolices is large and can be quickly counted under a microscope by a counter.

I recomended that, please recheck the anti-protoscolesis effects (bu eosin) use 25, 50, 100 and 200 micro g/ ml of drugs after 5, 30, 60, 180 min and rewrite this section again.
this concentration are not acceptable for scientists.

Thanks to the dear reviewer. Modifications were made to the main text and tables and subtitles of the images. These corrections were highlighted in blue.

Explanation: I need to mention that the preparation of the plant extract was done by our expert colleague at Arak University (Dr. Noori). The steps of preparing the extract and the amount of ingredients are all described in the section 3.2. Finally, she delivered two solutions containing crude and flavonoids extract to the parasitology department. We prepared the extracts in percentages (v/ v) and used them in the project. The extracts were not dry to provide a w / v concentration. Of course, the amount of active ingredient in each extract was known. The concentration of active ingredient was added to the manuscript.

Dear associate editor 2

Thanks to the dear reviewer, your valuable comments and suggestions were given to the author who provided plant and prepared the extract. Her answer to your questions will be presented to you.

Sincerely Yours

Zahra Eslamirad

Corresponding Author

1. *What is you purpose about total extract?*

Throughout the manuscript, the phrase "crude extract" replaced "total extract."

Explanation: Total extract is crude extract of the Allium noeanum leaves consisting of flavonoids and non-flavonoids (others) compounds. In order to remove the ambiguity in all section of the manuscript, the phrase "crude extract" replaced "total extract".

2. *You didn't mention the used part of plant!*

Leaves were used. Added to section of 3.2 and highlighted.

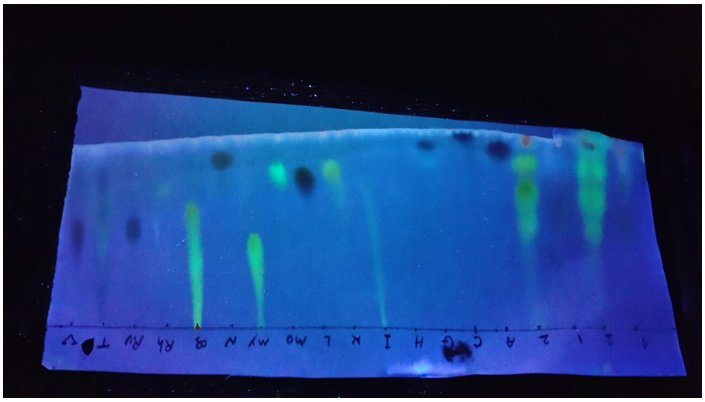
3. *How TLC can use for detecting the organic compounds?!*

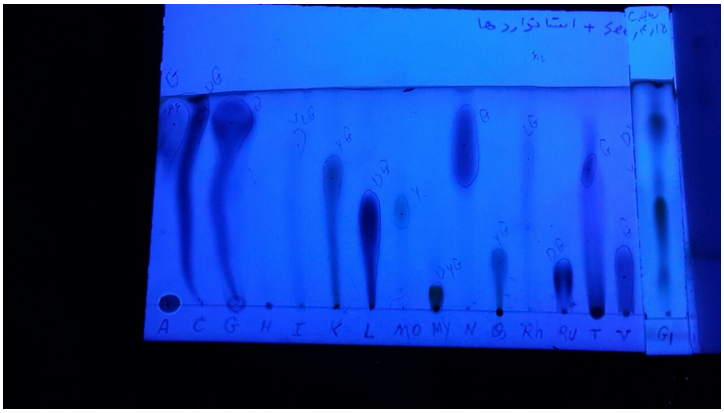
Second paragraph of 3.2 section was revised and highlighted.

Explanation: We did not use just TLC for detecting flavonoids. First I used 2-dimesional paper chromatography for understanding presence flavonoids compounds and their groups (aglycons, flavone *C-& C-/O* glucosides and flavonoid sulphates) in crude extract. Then flavonoids extract

was separated using acid hydrolysis method adding hydrochloric acid and placing in water bath at 100°C for 30 minutes. After cooling, ethyl acetate was added for separation flavonoids from the non-flavonoids extract. Obtained flavonoids extract was dried using Heidolph Rotary evaporator Laborota 4000/G1 (Noori 2002), dissolved in MeOH 80%. Co-chromatography with standards was also performed. Flavonoid standards available for comparison during the study were apigenin, chrysin, genistein, hesperidin, isorhamnetin, kaempferol, luteolin, morin, myricetin, naringenin, quercetin, rhamnetin, rutin, tricine and vitexin (all obtained commercially, Rutin from Merck, apigenin and luteolin from Sigma and the rest from Fluka). Cellulose sheet TLC plate were used and after running in three solvents (BAW, CAW and Ferostal) seperately, then were viewed in UV245 nm each spot R_f -values and color comparing to standards helped flavonoids identification (Markham 1982, Mabry et al 1970). R_f values were calculated and in comparison with used flavonoid standards identification and concentration of each spot were determined using Camag UV 254 and 366 nm, chrogramatographic map and UV spectroscopy.

The following two photos show these steps. Usually these photos were not provided in the manuscript, so they are not seen in the current article.





4. *You didn't write the herbarium number of the used plant!*

The following description was added to section of 3.2 and highlighted.

Allium noeanum (CMG1)= Mehrdad Godarzi Collection Number in Arak University Herbarium, not listed in herbarium index). *A. noeanum* was authenticated by taxonomist Dr. Mitra Noori and the voucher specimen (CMG1, 07 June 2016) was deposited at the Department of Biology, Faculty of Science, Arak University, Iran.

5. *Why you didn't evaluate the total phenol and flavonoid content?*

Thanks to your valuable point of view. Yes, it would have been better if the effect of phenolic extract had been studied and compared with the results of flavonoid extract. However, this paper is extracted from a research project in which only the study of crude and flavonoid extracts was predicted, so the separation of phenolic extract was not performed. We hope to use this valuable point of view in future projects.

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) 1 Aug 2020

Dear author,

Thanks for your attention. Some cases have remained uncorrected. The authors should correct the cases:

1- Please add a related reference(s) after “method.” in line 141.
2- Please allude to the versions of “Excel” and “SPSS” in line 187.
3- “behavior” in line 227 is not an appropriate word, please change it.
4- Please add a related reference(s) after “diseases.” in line 244.
5- Please add a related reference(s) after “composition.” in line 245.
6- Please add a related reference(s) after “literature.” in line 247.
7- You should allude to the “critical times” regarding this sentence “In contrast, all concentrations of the flavonoid extract of A. noeanum could kill all protoscolices.” in lines 255-256.
8- Please write “in vivo” in the Italic form in line 293.
9- You should explain the “limitations” of the study in the “Discussion” section.
10- You should allocate separate sections to “Availability of data” and “Author contributions” after the “Funding/support” section and explain related issues in the sections.
11- Reference number 10 is not up-to-date, please substitute the reference with an up-to-date reference.
12- Sizes of figures; 2 and 3 are not appropriate, please correct the issue.
13- You should add the original results of “chromatography methods” to the article.

Thanks.

REFEREE: Associate Editor | **Revision** (2) 10 Aug 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) 17 Aug 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.

August 2020 26

Dear Associate Editor's

I am pleased to resubmit the **new revised** version of our manuscript (Manuscript ID: 96180) entitled " **Evaluation of the Apoptotic and Scolicidal Effects of Crude and Flavonoid Extract of Allium Noeanum on Protoscolices and Hydatid Cyst Wall** " to the "**Jundishapur Journal of Natural Pharmaceutical Products"**.

I really appreciate your useful and constructive comments of the reviewer. The manuscript has been modified accordingly and the modified parts are highlighted within the manuscript by using the track changes mode in Microsoft Word. The detailed corrections are listed below one by one.

Yours Sincerely,

Zahra Eslamirad

Corresponding Author

Reviewers' Comments:

Reviewer 1:
Thanks for your valuable comments. The revise was done as the following.

1- Please add related reference(s) after "method." in line 141.

It was added and highlighted.

2- Please allude to the versions of "Excel" and "SPSS" in line 187.

It was alluded and highlighted.

3- "behavior" in line 227 is not appropriate word, please change it.

It was changed.

4- Please add related reference(s) after "diseases." in line 244.

The related reference was added and highlighted. This issue is mentioned in the last two paragraphs of this reference.

5- Please add related reference(s) after "composition." in line 245.

The related reference was added and highlighted.

6- Please add related reference(s) after "literature." in line 247.

The related reference was added and highlighted.

7- You should allude to the "critical times" regarding the "In contrast, all concentrations of the flavonoid extract of A. noeanum could kill all protoscolices." in lines 255-256.

The critical time was alluded in manuscript and it was highlighted.

8- Please write "in vivo" in Italic form in line 293.

The change was done.

9- You should explain the "limitations" of the study at "Discussion" section.

It was added in line 248-249.

10- You should allocate separate sections to "Availability of data" and "Author contributions" after "Funding/support" section and explain related issues at the sections.

The sections of author contribution and "availability of data" were added and highlighted.

I did not find any available of data section in your issued papers, so the discrepancy was explained by support team and accordingly was proceeded.

11- Reference number 10 is not up-to-date, please substitute the reference with up-to-date reference.

It was substituted with new reference and highlighted.

12- Sizes of the figures; 2 and 3 is not appropriate, please correct the issue.

The size of figures was corrected (900 dpi).

13- You should add original results of "chromatography methods" to the article.

A figure of chromatography results was added to manuscript (figure 1). Due to the addition of a figure to the manuscript, the number of previous figures in the text and the caption of the figures were changed.

Associate Editor's Comments:

Dear Associate Editor 1:

Thanks again for your kindly attention. The revised was proceeded as listed as below.

1- Please add related reference(s) after "method." in line 141.

It was added and highlighted.
2- Please allude to the versions of "Excel" and "SPSS" in line 187.

It was alluded and highlighted.
3- "behavior" in line 227 is not appropriate word, please change it.

It was changed.
4- Please add related reference(s) after "diseases." in line 244.

The related reference was added and highlighted. This issue is mentioned in the last two paragraphs of this reference.

5- Please add related reference(s) after "composition." in line 245.

The related reference was added and highlighted.

6- Please add related reference(s) after "literature." in line 247.

The related reference was added and highlighted.

7- You should allude to the "critical times" regarding the "In contrast, all concentrations of the flavonoid extract of A. noeanum could kill all protoscolices." in lines 255-256.

The critical time was alluded in manuscript and it was highlighted.

8- Please write "in vivo" in Italic form in line 293.

The change was done.

9- You should explain the "limitations" of the study at "Discussion" section.

It was added in line 248-249.

10- You should allocate separate sections to "Availability of data" and "Author contributions" after "Funding/support" section and explain related issues at the sections.

The sections of author contribution and "availability of data" were added and highlighted.I did not find any available of data section in your issued papers, so the discrepancy was explained by support team and accordingly was proceeded.

11- Reference number 10 is not up-to-date, please substitute the reference with up-to-date reference.

It was substituted with new reference and highlighted.

12- Sizes of the figures; 2 and 3 is not appropriate, please correct the issue.

The size of figures was corrected (900 dpi).

13- You should add original results of "chromatography methods" to the article.

A figure of chromatography results was added to manuscript (figure 1). Due to the addition of a figure to the manuscript, the number of previous figures in the text and the caption of the figures were changed.

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) 15 Sep 2020

Dear author,
Thanks for your attention and appropriate point-by-point corrections.
- Please write “In vitro” in the Italic form in line 343.
- You should clear that “All authors read and approved the final manuscript.” at the end of the “Authors Contribution” section.
- There are some additional figures at the end of the article, please correct the issue.

Note: Please correct the mentioned issues in the final version of the article.

Thanks.

REFEREE: Associate Editor | **Revision** (3) 20 Sep 2020

Dear EIC,
After considering this manuscript and also based on reviewers, I find it suitable for publishing in JJNPP.
Best Regards,

REFEREE: EIC | **Revision** (3) 21 Sep 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.