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

Jentashapir Journal of Cellular and Molecular Biology
Article DOI: 10.5812/jjcmb.115014
Published in: Jentashapir Journal of Cellular and Molecular Biology: 12(2); e115014

Peer Review Report for "Effect of the Internal Septum Extract of the Walnut Kernel on the Mesenchymal Stem Cells Cycle and MSCs-derived Insulin-Producing B-cells Differentiation and Glucose Uptake"

Author(s): Fatemeh Aghapour SK, Sajjad Sisakhtnezhad

Review Timeline:

Submit Date: 4 Apr 2021
Revised Date: 26 May 2021
Accepted Date: 26 May 2021

Revision (0)

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

Aida Khakimova: Reviewer | **Revision** (0) 15 Apr 2021

Dear AE,
Unfortunately, the authors did not indicate which sort of walnut was used to isolate the septum, where the walnut grew, and how it was stored. It is not described how the partitions were crushed, how long they dried.
- Why did the authors choose such extraction conditions (boiling), what was the choice based on?
- The authors did not indicate which water-soluble biologically active components may be contained in the resulting solution, which is responsible for the studied effects.
- Why, when evaluating the effect of DISWF on the expression of target genes using quantitative real-time PCR (qRT-PCR), a DISWF concentration of 50 µg / ml and a treatment time of 24 hours was chosen for the treatment of cells?
- When analyzing the cell cycle of rBM-MSC treated with DISWF for 24 and 48 hours, what concentration was used, and what was the rationale for the choice of concentration?
- When evaluating the change in gene expression in IPCs derived from rBM-MSCs treated with DISWF, what concentration of DISWF was used and why?

- In view of the opposite effects of DISWF on the expression of various genes responsible for insulin production, it would be worth identifying priority areas for further research.
Thanks.

REFEREE: Reviewer | **Revision** (0) 19 Apr 2021

Dear AE,
- The article needs to be edited.
- Why is no insulin immunofluorescence analysis performed?
- Why is no Glut2 analysis performed? Because of GLUT2 uptakes glucose in insulin-releasing β-cells.
In both cases, the authors can use the following reference.
- Some references do not have a page number.
Thanks.

Layasadat Khorsandi: Reviewer | **Revision** (0) 20 Apr 2021

Dear AE,
Comments for the authors:
Introduction:
- More details about the septum of walnut fruit should be added to the introduction. For example: biological and pharmacological properties, and main bioactive compounds of the walnut septum should be explained.
Methods:
- mrBM-MSCs isolation and characterization part should be summarized.
- The method of differentiation of bone marrow stem cells into insulin-producing cells is incomplete, and with this way, inducing functional cells that can produce and secrete insulin are not possible.
- The authors have to measure insulin concentration (glucose challenge test).
- Why did the authors study the cell cycle? What does its relation to the differentiation of insulin-producing cells? It is better to remove it or to discuss the necessity of cell cycle assessment in this study.
Results:
- Fig. 4: the unit of TAC is not correct.
- Fig. 1-A: It seems to have a yeast contamination
Discussion
- Discussion part is very poor.
Thanks.

Seyyed Ali Mard: Associate Editor | **Revision** (0) 20 Apr 2021

Dear EIC,
Reviewers of this manuscript raised many questions and asked a major revision.
Thanks.

Seyyed Ali Mard: EIC | **Revision** (0) 20 Apr 2021

Dear Authors

Your manuscript needs a major revision because of having many methodological and topological errors. Make a complete revision on it and answer all questions/concerns were made by reviewers to avoid extra revision. Mentioning the Ethical approval, Author contributions, and Funding resources in the main text of the manuscript are mandatory. Figure legends needs to be completed.

Yours Sincerely

EIC, Dr. Mard

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

We would like to thank you for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have revised the manuscript and changes are written in bold and are highlighted in the text. Each question/comment is also responded as below (the reviewer's comments are in black and authors' responds are blue color).

Sincerely yours,

Reviewers' Comments:

Reviewer 1:

1- Unfortunately, the authors did not indicate which sort of walnut was used to isolate the septum, where the walnut grew, and how it was stored. It is not described how the partitions were crushed, how long they dried.

- **According to the comments of the reviewer, we have revised and completed the "Materials and methods" section of the manuscript and changes are written in bold and are highlighted in the revised manuscript.**

2- Why did the authors choose such extraction conditions (boiling), what was the choice based on?

- **Even though several studies investigated the composition and biological activities of different parts of the walnut tree, the internal septum of the walnut kernel is less evaluated. Interestingly, the aqueous decoction of the internal septum of walnut kernel (DISWK), which prepared by gently boiling of the walnut septum for 20-30 min in water, is used to decrease the human blood sugar in traditional and local medicine in some regions of Iran. Although different studies confirmed many biological activities of aqueous/alcoholic extracts of the walnut septum, there is no study regarding the biological effects of DISWK. Therefore, in the present**

study, this extraction condition was used to prepare an aqueous decoction of the walnut septum for instigation its effects on MSCs and MSCs-derived-IPCs.

3- The authors did not indicate which water-soluble biologically active components may be contained in the resulting solution, which are responsible for the studied effects.

- **To address the comment of the reviewer, we have introduced the possible biologically active components of DISWK, especially its water-soluble contents which are responsible for its biopharmaceutical effects in this study, in the "Introduction, Discussion and Conclusion" sections of the manuscript.**

4- Why, when evaluating the effect of DISWF on the expression of target genes using quantitative real-time PCR (qRT-PCR), a DISWF concentration of 50 µg / ml and a treatment time of 24 hours were chosen for the treatment of cells?

- **In the present study, the minimal cytotoxic effect of DISWK on rBM-MSCs was detected at concentrations of 50-100 µg/ml and a treatment time of 24 h, therefore a minimal concentration of 50 µg/ml was used for the treatment of MSCs-derived IPCs.**

5- When analyzing the cell cycle of rBM-MSC treated with DISWF for 24 and 48 hours, what concentration was used and what was the rationale for the choice of concentration?

- **In the present study, DISWK was used at a concentration of 50 µg/ml to investigate its effect on the cell cycle of rBM-MSCs at 24 and 48 h time points. The DISWK showed a minimal cytotoxic effect on rBM-MSCs at 50 µg/ml at different treatment time points, therefore this concentration was chosen to examine the DISWK effect on the cell cycle of DISWK-treated rBM-MSCs.**

6- When evaluating the change in gene expression in IPCs derived from rBM-MSCs treated with DISWF, what concentration of DISWF was used and why?

- **Due to the minimal cytotoxic effect of DISWK at 50 µg/ml, in the present study, we also used this concentration to treat the MSCs-derived IPCs for the gene expression assay.**

7- In view of the opposite effects of DISWF on the expression of various genes responsible for insulin production, it would be worth identifying priority areas for further research.

- **In the present study, the effect of DISWK was evaluated on the expression of genes involved in pancreatic insulin-producing β-cell commitment (pdx1) and blood glucose regulation and uptake (Insulin (Ins1/2), Insulin receptor (Insr), Glucose transporters 1 and 4 (Glut1 and 4)) in the rBM-MSCs-derived IPCs. We found that although DISWK significantly overexpressed Ins1/2, Insr, and Glut1 in the rBM-MSCs-derived IPCs, it significantly downregulated Pdx1 in the cells. Therefore, we suggest that further studies should be done to investigate these priority areas in depth, especially at protein level for Ins1/2, Insr, and Glut1 genes.**

  To address the comment of the reviewer and according to the above explanation, we have revised the "Discussion" sections of the manuscript and changes are written in bold and are highlighted in the text.

Reviewer 2:

1- The article needs to be edited.

- **The whole manuscript has been carefully revised and tried to avoid any grammar or spelling error.**

2- Why is no insulin immunofluorescence analysis performed?

- **As is clear from the question of the respected reviewer, the expression of insulin can be investigated at mRNA and protein levels. We have also interested to examine the expression of insulin at protein level by immunofluorescence assays in untreated-IPCs and DISWK-treated IPCs, but the immunofluorescence assays is costly and we don't have access to the insulin specific antibody to perform the**

immunofluorescence analysis. Therefore, in the present study which is the result of a master student thesis, we only examined the expression of insulin in the DISWK-treated IPCs at their mRNAs level using qRT-PCR. However, we also indicated that the exact mechanisms and the role of DISWK on the biology and characteristic of MSCs and IPCs are required to be elucidated in further study, especially at protein level. Now, with respect to the concerns raised by the reviewer, may I draw your attention to some papers which used only qRT-PCR to assess the effect of chemical and physical factors on the expression of genes in cells, such as MSCs and IPCs.

3- Why is no Glut2 analysis performed? Because of GLUT2 uptakes glucose in insulin-releasing β-cells.

- **GLUT1-4 are expressed in pancreatic beta cells, however GLUT1 and GLUT2 are the major glucose transporters in the human and rodent β-cells, respectively. GLUT1 facilitates the transport of glucose across the plasma membrane of mammalian cells in almost all tissues. Moreover, GLUT1 uptakes glucose in GLUT2-deficient insulin-releasing β-cells and play a role in the glucose-dependent insulin secretion and the glucose uptake by β-cells. In addition, GLUT4 is the major glucose transporter in muscle and adipocyte tissues, which are among the main tissues in glucose uptake in mammals. GLUT1 also cooperatively acts with other isoforms, especially GLUT4, in the insulin-sensitive tissues including fat and muscle. Therefore, this study aimed to evaluate the effect of DISWK on the expression of Glut1 and Glut4 at mRNA level in DISWK-treated rBM-MSCs, in a way that we will be able to generalize and compare the results to other tissues and the human model in our future studies. Nevertheless, it was good if the expression of Glut2 was also evaluated in this study, but it was not done. Unfortunately, at the moment, it is no longer possible for us to do this; because a lot of time has passed and we no longer have access to the samples.**

4- In both cases, the authors can use the following reference.

- **The reference did not attached by the reviewer.**

5- Some references do not have a page number.

- **We have checked and revised all references and the missed page numbers, DOI and PMID are added to them according to the journal`s format.**

Reviewer 3:

Introduction:

1- More details about the septum of walnut fruit should to be added to the introduction. For example: biological and pharmacological properties, and main bioactive compounds of the walnut septum should be explained.

- **It done according to the comment of the reviewer.**

Methods:

2- mrBM-MSCs isolation and characterization part should be summarized.

- **According to the comment of the reviewer and also the journals instruction for considering the maximum allowable of word counts in research article, the whole manuscript has been summarized.**

3- The method of differentiation of bone marrow stem cells into insulin-producing cells is incomplete, and with this way, inducing functional cells that can produce and secrete insulin are not possible.

- **In the present study, transdifferentiation of rat mesenchymal stem cells to functional insulin producing cells and thus the production of islet-like cell clusters was performed according to the established protocol by Neshati et al., 2010.**
    - **Neshati, Z., Matin, M. M., Bahrami, A. R. & Moghimi, A. 2010. Differentiation of mesenchymal stem cells to insulin-producing cells and their impact on type 1 diabetic rats. J. Physiol. Biochem., 66, 181-187.**

4- The authors have to measure insulin concentration (glucose challenge test).

- **Although it is good to measure insulin concentration for improving the quality of this study, unfortunately, at the moment, it is no longer possible for us to do this; because a lot of time has passed and we no longer have access to the samples.**

5- Why did the authors study the cell cycle? What does it's relation to the differentiation of insulin-producing cells? It is better to remove it or to discuss the necessity of cell cycle assessment in this study.

- **In this study, primarily, we aimed to evaluate the effect of DISWK on the transdifferentiation process of MSCs into IPCs during the differentiation period (4 weeks). However, our results showed that DISWK inhibited the MSCs proliferation and eventually led to cell death during the two weeks after differentiation process. Therefore, in continue, this study aimed to evaluate the effect of DISWK on survival, total antioxidant capacity, and proliferation of MSCs and on the expression of genes involved in beta cell differentiation and glucose uptake in MSCs-derived IPCs. In this regard, in the present study, PI-staining and flow-cytometry analysis was done to determine that the anti-proliferative effect of DISWK may influence on what stage of the MSCs cell cycle.**
  Therefore, according to the above explanation, the cell cycle assessment is not removed from this study, but the importance of the results obtained from the cell cycle analysis is discussed in the "Discussion" section of the manuscript.

Results:

6- Fig. 4: the unit of TAC is not correct.

- **The correction has been done according to the comment of the reviewer.**

7- Fig. 1-A: It seems to have yeast contamination

- **The Fig. 1A is a bone marrow-derived primary cell culture which contains floating single cells from the tissue. The small suspended spherical particles in Fig. 1A are erythrocytes and other bone marrow-derived floating cells, which have not yet been completely removed from the cell culture, and they are not yeast contamination.**

Discussion:

8- Discussion part is very poor.

- **To address the comment of the reviewer, we have revised the “Discussion” 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.

Seyyed Ali Mard: EIC | **Revision** (1) 12 May 2021

Dear Authors

I realized that title of your manuscript needs more edition.

Best

EIC, Dr. Mard

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 Reviewers

We would like to thank you for careful and thorough reading of this manuscript and for the thoughtful comments and constructive suggestions, which help to improve the quality of this manuscript. We have revised the manuscript and changes are written in bold and are highlighted in the text. Each question/comment is also responded as below (the reviewer's comments are in black and authors' responds are blue color).

Sincerely yours,

Reviewers' Comments:

Reviewer 1:

1- Unfortunately, the authors did not indicate which sort of walnut was used to isolate the septum, where the walnut grew, and how it was stored. It is not described how the partitions were crushed, how long they dried.

- **According to the comments of the reviewer, we have revised and completed the "Materials and methods" section of the manuscript and changes are written in bold and are highlighted in the revised manuscript.**

2- Why did the authors choose such extraction conditions (boiling), what was the choice based on?

- **Even though several studies investigated the composition and biological activities of different parts of the walnut tree, the internal septum of the walnut kernel is less evaluated. Interestingly, the aqueous decoction of the internal septum of walnut kernel (DISWK), which prepared by gently boiling of the walnut septum for 20-30 min in water, is used to decrease the human blood sugar in traditional and local medicine in some regions of Iran. Although different studies confirmed many biological activities of aqueous/alcoholic extracts of the walnut septum, there is no study regarding the biological effects of DISWK. Therefore, in the present**

study, this extraction condition was used to prepare an aqueous decoction of the walnut septum for instigation its effects on MSCs and MSCs-derived-IPCs.

3- The authors did not indicate which water-soluble biologically active components may be contained in the resulting solution, which are responsible for the studied effects.

- **To address the comment of the reviewer, we have introduced the possible biologically active components of DISWK, especially its water-soluble contents which are responsible for its biopharmaceutical effects in this study, in the "Introduction, Discussion and Conclusion" sections of the manuscript.**

4- Why, when evaluating the effect of DISWF on the expression of target genes using quantitative real-time PCR (qRT-PCR), a DISWF concentration of 50 µg / ml and a treatment time of 24 hours were chosen for the treatment of cells?

- **In the present study, the minimal cytotoxic effect of DISWK on rBM-MSCs was detected at concentrations of 50-100 µg/ml and a treatment time of 24 h, therefore a minimal concentration of 50 µg/ml was used for the treatment of MSCs-derived IPCs.**

5- When analyzing the cell cycle of rBM-MSC treated with DISWF for 24 and 48 hours, what concentration was used and what was the rationale for the choice of concentration?

- **In the present study, DISWK was used at a concentration of 50 µg/ml to investigate its effect on the cell cycle of rBM-MSCs at 24 and 48 h time points. The DISWK showed a minimal cytotoxic effect on rBM-MSCs at 50 µg/ml at different treatment time points, therefore this concentration was chosen to examine the DISWK effect on the cell cycle of DISWK-treated rBM-MSCs.**

6- When evaluating the change in gene expression in IPCs derived from rBM-MSCs treated with DISWF, what concentration of DISWF was used and why?

- **Due to the minimal cytotoxic effect of DISWK at 50 µg/ml, in the present study, we also used this concentration to treat the MSCs-derived IPCs for the gene expression assay.**

7- In view of the opposite effects of DISWF on the expression of various genes responsible for insulin production, it would be worth identifying priority areas for further research.

- **In the present study, the effect of DISWK was evaluated on the expression of genes involved in pancreatic insulin-producing β-cell commitment (pdx1) and blood glucose regulation and uptake (Insulin (Ins1/2), Insulin receptor (Insr), Glucose transporters 1 and 4 (Glut1 and 4)) in the rBM-MSCs-derived IPCs. We found that although DISWK significantly overexpressed Ins1/2, Insr, and Glut1 in the rBM-MSCs-derived IPCs, it significantly downregulated Pdx1 in the cells. Therefore, we suggest that further studies should be done to investigate these priority areas in depth, especially at protein level for Ins1/2, Insr, and Glut1 genes.**

  To address the comment of the reviewer and according to the above explanation, we have revised the "Discussion" sections of the manuscript and changes are written in bold and are highlighted in the text.

Reviewer 2:

1- The article needs to be edited.

- **The whole manuscript has been carefully revised and tried to avoid any grammar or spelling error.**

2- Why is no insulin immunofluorescence analysis performed?

- **As is clear from the question of the respected reviewer, the expression of insulin can be investigated at mRNA and protein levels. We have also interested to examine the expression of insulin at protein level by immunofluorescence assays in untreated-IPCs and DISWK-treated IPCs, but the immunofluorescence assays is costly and we don't have access to the insulin specific antibody to perform the**

immunofluorescence analysis. Therefore, in the present study which is the result of a master student thesis, we only examined the expression of insulin in the DISWK-treated IPCs at their mRNAs level using qRT-PCR. However, we also indicated that the exact mechanisms and the role of DISWK on the biology and characteristic of MSCs and IPCs are required to be elucidated in further study, especially at protein level. Now, with respect to the concerns raised by the reviewer, may I draw your attention to some papers which used only qRT-PCR to assess the effect of chemical and physical factors on the expression of genes in cells, such as MSCs and IPCs.

3- Why is no Glut2 analysis performed? Because of GLUT2 uptakes glucose in insulin-releasing β-cells.

- **GLUT1-4 are expressed in pancreatic beta cells, however GLUT1 and GLUT2 are the major glucose transporters in the human and rodent β-cells, respectively. GLUT1 facilitates the transport of glucose across the plasma membrane of mammalian cells in almost all tissues. Moreover, GLUT1 uptakes glucose in GLUT2-deficient insulin-releasing β-cells and play a role in the glucose-dependent insulin secretion and the glucose uptake by β-cells. In addition, GLUT4 is the major glucose transporter in muscle and adipocyte tissues, which are among the main tissues in glucose uptake in mammals. GLUT1 also cooperatively acts with other isoforms, especially GLUT4, in the insulin-sensitive tissues including fat and muscle. Therefore, this study aimed to evaluate the effect of DISWK on the expression of Glut1 and Glut4 at mRNA level in DISWK-treated rBM-MSCs, in a way that we will be able to generalize and compare the results to other tissues and the human model in our future studies. Nevertheless, it was good if the expression of Glut2 was also evaluated in this study, but it was not done. Unfortunately, at the moment, it is no longer possible for us to do this; because a lot of time has passed and we no longer have access to the samples.**

4- In both cases, the authors can use the following reference.

- **The reference did not attached by the reviewer.**

5- Some references do not have a page number.

- **We have checked and revised all references and the missed page numbers, DOI and PMID are added to them according to the journal`s format.**

Reviewer 3:

Introduction:

1- More details about the septum of walnut fruit should to be added to the introduction. For example: biological and pharmacological properties, and main bioactive compounds of the walnut septum should be explained.

- **It done according to the comment of the reviewer.**

Methods:

2- mrBM-MSCs isolation and characterization part should be summarized.

- **According to the comment of the reviewer and also the journals instruction for considering the maximum allowable of word counts in research article, the whole manuscript has been summarized.**

3- The method of differentiation of bone marrow stem cells into insulin-producing cells is incomplete, and with this way, inducing functional cells that can produce and secrete insulin are not possible.

- **In the present study, transdifferentiation of rat mesenchymal stem cells to functional insulin producing cells and thus the production of islet-like cell clusters was performed according to the established protocol by Neshati et al., 2010.**
    - **Neshati, Z., Matin, M. M., Bahrami, A. R. & Moghimi, A. 2010. Differentiation of mesenchymal stem cells to insulin-producing cells and their impact on type 1 diabetic rats. J. Physiol. Biochem., 66, 181-187.**

4- The authors have to measure insulin concentration (glucose challenge test).

- **Although it is good to measure insulin concentration for improving the quality of this study, unfortunately, at the moment, it is no longer possible for us to do this; because a lot of time has passed and we no longer have access to the samples.**

5- Why did the authors study the cell cycle? What does it's relation to the differentiation of insulin-producing cells? It is better to remove it or to discuss the necessity of cell cycle assessment in this study.

- **In this study, primarily, we aimed to evaluate the effect of DISWK on the transdifferentiation process of MSCs into IPCs during the differentiation period (4 weeks). However, our results showed that DISWK inhibited the MSCs proliferation and eventually led to cell death during the two weeks after differentiation process. Therefore, in continue, this study aimed to evaluate the effect of DISWK on survival, total antioxidant capacity, and proliferation of MSCs and on the expression of genes involved in beta cell differentiation and glucose uptake in MSCs-derived IPCs. In this regard, in the present study, PI-staining and flow-cytometry analysis was done to determine that the anti-proliferative effect of DISWK may influence on what stage of the MSCs cell cycle.**
  Therefore, according to the above explanation, the cell cycle assessment is not removed from this study, but the importance of the results obtained from the cell cycle analysis is discussed in the "Discussion" section of the manuscript.

Results:

6- Fig. 4: the unit of TAC is not correct.

- **The correction has been done according to the comment of the reviewer.**

7- Fig. 1-A: It seems to have yeast contamination

- **The Fig. 1A is a bone marrow-derived primary cell culture which contains floating single cells from the tissue. The small suspended spherical particles in Fig. 1A are erythrocytes and other bone marrow-derived floating cells, which have not yet been completely removed from the cell culture, and they are not yeast contamination.**

Discussion:

8- Discussion part is very poor.

- **To address the comment of the reviewer, we have revised the “Discussion” of the manuscript.**

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) 24 May 2021

Dear AE,
The authors took into account all the comments. However, I wanted to see more accurate names and formulas of polyphenols, which are responsible for the observed effects.
Thanks.

Seyyed Ali Mard: Associate Editor | **Revision** (2) 24 May 2021

Dear EIC,
In accordance with the respected final reviewer comments, a minor revision is needed. In my perspective, this manuscript can be published in JJCMB after doing a minor revision.
Thanks.

Seyyed Ali Mard: EIC | **Revision** (2) 24 May 2021

Dear Authors,
Thank you for considering JJCMB for publishing your research manuscript. Your manuscript is now provisionally accepted for publishing in this journal. However, there is a minor revision has to revised before getting scientific acceptance. Mentioning Ethical approval, and Funding resources are mandatory in this journal. To write the author contribution, please follow journals style by visiting JJCMB home page. I do appreciate a quick submission of revision.
Yours Sincerely
EIC, Dr. Mard

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.

Dear Reviewer

With many thanks to you, we have revised the manuscript for the second time and changes are written in bold and are highlighted in the text. Your comment is also responded as below.

Sincerely yours,

Reviewers' Comments:

Reviewer 1:

1- The authors took into account all the comments. However, I wanted to see more accurate names and formulas of polyphenols, which are responsible for the observed effects.

- **According to the comment of the respected reviewer, we have introduced accurate names of polyphenols, which are responsible for the observed effects, in the manuscript and changes are written in bold and are highlighted in the text.**

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.

Seyyed Ali Mard: EIC | **Revision** (3) 25 May 2021

Dear Authors,
Your edition needs more revision.
Yours Sincerely
EIC, Dr.Mard

OPEN PEER REVIEW

Revision (4)

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 Reviewer

With many thanks to you, we have revised the manuscript for the second time and changes are written in bold and are highlighted in the text. Your comment is also responded as below.

Sincerely yours,

Reviewers' Comments:

Reviewer 1:

1- The authors took into account all the comments. However, I wanted to see more accurate names and formulas of polyphenols, which are responsible for the observed effects.

- **According to the comment of the respected reviewer, we have introduced accurate names of polyphenols, which are responsible for the observed effects, in the manuscript and changes are written in bold and are highlighted in the text.**

OPEN PEER REVIEW

Revision (4)

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

Seyyed Ali Mard: EIC | **Revision** (4) 26 May 2021

Dear Authors,
I realized that you revised your manuscript in accordance with the final reviewer comments.
Therefore, I am agreed to accept.
Best Regards
EIC, Dr. Mard