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OPEN PEER REVIEW

The Effect of Eight Weeks of Training on Positive and Negative Slopes with Royal Jelly Consumption on MGMT and ATPase Gene Expression Levels in the Hippocampus Tissue of Trimethyltin-Induced Alzheimer's Rats

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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

3 comments · 4 Jun 2021 – 7 Jun 2021

Referee 1 Reviewer

MAJOR REVISION 4 Jun 2021

Dear Authors:
Overall, this manuscript is interesting and is in line with the scope of the journal. I recommend it for publication, but major points should be clarified and corrected. They are:
1. Provide a structured abstract with the following headings: Background, Objectives, Methods, Results and Conclusions.
2. In the abstract, the authors mentioned 36 rats, while in the main text they talk about 42 male Sprague-Dawley rats. It is confusing. Please explain that.
3. Which software was used for statistical analysis?
4. Please add the statistical value (P. Value) for each comparison in the table.
5. Please provide the manufacturing company and country of origin for all materials used in the Methods section.
6. Please add the amounts of each substance in the Real time PCR reaction in the Methods section.
7. No limitations of the study are indicated. Please add “limitation and suggestion” at the end of the paper.
8. References did not follow the standard norms of the journal.

Associate Editor

MAJOR REVISION 7 Jun 2021

Based on the reviewers' comments and my reading of the manuscript, this manuscript needs major revisions, and the authors need to reply to the comments point by point.

Editor-in-Chief

MAJOR REVISION 7 Jun 2021

Based on the reviewers' comments and my reading, this manuscript needs major revisions, and the authors need to reply to the comments point by point.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear esteemed Editor-in-Chief of the *Journal of Gene, Cell and Tissue*,

Thank you so much for your continued attention to my scientific research manuscript entitled “The effect of eight weeks of training on positive and negative slopes with royal jelly consumption on MGMT and ATPase gene expression levels in the hippocampus tissue of trimethyltin-induced Alzheimer's rats.” All the comments proposed by the esteemed reviewers were followed in the text and the changes were made accordingly and marked in red. In addition, responses to the respected reviewers’ comments are presented below.

Responses to the Reviewers’ Comments:

Reviewer # 1:

1- Give background in abstract part. At first you start with objective.
Response: *In the abstract, the research background was presented and marked in red.*

2- Describe “MGMT” at first use.
Response: *At first use MGMG was fully described.*

3- In material and method part write this sentence “Rats were kept in Plexiglas cages and supplied with access to food and water ad libitum” and give this reference to this part (Abdolmaleki A, Zahri S, Bayrami A. Rosuvastatin enhanced functional recovery after sciatic nerve injury in the rat. European Journal of Pharmacology. 2020 Sep 5;882:173260.)
Response: *The above sentence together with the given reference was added to the materials and method part.*

4- Write the first part of material and methods in 3 or 4 paragraphs.
Response: *Based on the respected reviewer’s comment, the methods section was written in three to four separate paragraphs.*

Reviewer # 2:

1. Provide structured abstract with following headings: Background, Objectives, Methods, Results and Conclusions.
Response: *In the abstract section, the format of abstract writing was modified based on the esteemed reviewer’s comment.*

2. In the abstract; author mentioned 36 rates while in main text they talk about 42 male Sprague-Dawley rats. It is confusing. Please explain that.
Response: *Regarding the number of rats mentioned, it should be noted that due to the words limitation in the abstract, the author noted 36 rats with Alzheimer's disease and then the remaining number (6 rats) in the healthy control group were considered for investigation of the induction effect of Alzheimer's disease. However, in the methods section, the total number of rats (42 rats)*

purchased were noted altogether, while 36 of them were infected with Alzheimer's disease with trimethyltin and 6 rats were assigned in the healthy control group. In this vein, the number of rats was marked in red with a full explanation in the text.

3. Which software was used for statistical analysis?.
Response: *In the statistical analysis method section, the name of the software was presented along with the version and was marked in red.*

4. Please add the statistic value (P. Value) for each comparison in the table.
Response: *The figure captions were revised and the exact size of P value in each figure was mentioned and marked in red.*

5. Please write the manufacturing company and country of origin of all materials used in Methods section.
Response: *The materials and tools used in the research were presented with the name of the company and the country of origin and were marked in red in the text.*

6. Please added amounts of each substance in Real time PCR reaction in methods section.
Response: *Based on the esteemed reviewer's comment, the exact steps of Real Time PCR were provided; also, the amount and size of each substance used were presented in the text and were marked in red.*

7. No limitations of the study are indicated. Please add "limitation and suggestion in end of paper.
Response: *The limitations were presented at the end of the discussion. Also, in line with the limitations, some research suggestions were presented and marked in red.*

8. References did not follow the standard norms of the journal.
Response: *References were modified according to the format of the journal.*

Reviewer # 3:

There are grammatical errors in some parts. Corrections need to be made in these areas. In some places the references are incomplete. Noura et al. n.d., Deh Bozorgi et al. n.d. and (Hosseini et al. n.d. and other places.
Response: *The manuscript was proofread; also, the final references were reviewed and completed.*

This reference needs to be modified: Haeri, Azarbayjani, and Peeri 2020.
Response: *The reference was double checked and modified.*

This sentence " During the research protocol, standard conditions for keeping animals including temperature (22 ± 2° C), humidity (55 to 65%), dark-light cycle (12 hours of darkness and 12 hours of light) were observed. " needs to be corrected.
Response: *In the methodology section, this sentence was reviewed and marked in red.*

What is the meaning of this phrase" trimethyltin-induced Alzheimer's (TMT)" and its use needs to be corrected in several cases.
Response: *Regarding the esteemed reviewer's comment, this part was reviewed and rephrased. It is noteworthy that due to the Alzheimer's-like effects of trimethyltin, the author has tried to explain the method of induction of the disease using this method. Accordingly, the text was revisited the word was modified.*

What are "ET" methods? What is that abbreviation?
Response: *ET means endurance training, i.e., both positive and negative slope training with the duration of the present study are endurance training, so the researcher used ET which stands for endurance training. It was also fully described the first time used in the text and marked in red.*

What do you mean? "control+injectable sodium chloride"
Response: *In the methodology, the injection of sodium chloride into royal jelly solvent was modified and was mentioned as the sham group, which is written and marked in red.*

This "Hassanlouei et al. 2020" is not included in the reference.
Response: *The reference was reviewed and included in the final references.*

The full name of the materials and kits used should be mentioned along with the name of the company and the country.
Response: *The names of all instruments, materials and kits used in this article were pointed in the methodology and marked in red.*

How was the Alzheimer's induction evaluated and approved?
Response: *The issue was explained in the text and marked in red as follows:*
To evaluate the Alzheimer's induction, the results of Y maze and shuttle box test in the TMT injection group were compared with the healthy control group. In addition to observing clinical signs such as aggression, bruising and bleeding around the eyes, rats tail tremors were other symptoms that the researcher used to identify rats with Alzheimer's disease.

Apparently, this gene has been used as a reference gene. Unfortunately, because exercise is associated with inflammatory and immune responses, this gene does not appear to be suitable for this test. The Implication and Significance of Beta 2 Microglobulin: A Conservative Multifunctional Regulator. Chin Med J (Engl). 2016 Feb 20; 129(4): 448–455. doi: 10.4103/0366-6999.176084.
Response: *As a matter of fact, the point mentioned by the respected reviewer was really a valuable and scientific one which was noteworthy to the authors from now on, so that this point will definitely be taken into consideration in the conducting the research. However, given the literature review, the researcher used this internal control gene. In this regard, Mikami et al. also used the Beta 2 Microglobulin gene in 2018 along with high intensity interval training. Thus, due to the recent inclusion of sports science into the field of molecular cells and measurement by gene expression, the need to study this gene is also felt during exercise. In this vein, the authors hope that their argument for using this internal control gene with the available reference is acceptable by the honorable reviewer.*

Miyamoto-Mikami, E., Tsuji, K., Horii, N., Hasegawa, N., Fujie, S., Homma, T., ... & Iemitsu, M. (2018). Gene expression profile of muscle adaptation to high-intensity intermittent exercise training in young men. Scientific reports, 8(1), 1-14.

Statistical analysis is not complete. This needs to be edited.
Response: *Statistical analysis was reviewed according to the esteemed reviewer's comment.*

Associate Editor's Comments:
Associate Editor 1:

Based on the reviewers' comments and as I read, this manuscript needs major revisions and reply to the comment point by point.

2 Revision 1

3 comments · 13 Jul 2021 – 31 Jul 2021

Referee 1 Reviewer

ACCEPT 13 Jul 2021

The revised manuscript has been improved and is coherent, and I wish the authors the best.

Associate Editor

ACCEPT 31 Jul 2021

Based on the reviewer's comments and my reading of the manuscript, the revisions were done well. Thus, this manuscript can be accepted for publication in GCT.

Editor-in-Chief

ACCEPT 31 Jul 2021

Based on the reviewer's and AE's comments, the revisions were done well. Thus, this manuscript can be accepted for publication in GCT.