Zahedan Journal of Research in Medical Sciences
Volume 23 · Issue 2 · e85049

OPEN PEER REVIEW

Pre-treatment Effect of Kombucha Tea on Analgesia and Inflammation in Male Rat

Zahra Rabiei, Zahra Lorigooini, Fatemeh Firuzi, Mohammad Rahimi-Madiseh

SUBMITTED	REVISED	ACCEPTED	DOI
20 Nov 2018	9 Mar 2020	25 Apr 2020	10.5812/zjrms.85049

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

0 comments

No public comments in this round.

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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.

Reviewer 1:- In material and methods, some of them have not reference: References were added.- Figures are not clear: - the comparison was done among groups or this comparison is between control and others? The comparison of all groups was made with the control.- where has been approved ethical? The study protocols were approved by the local Ethics Committee of Shahrekod University of Medical Sciences.- The references are old . The references were updated.

Reviewer 2:

1. In the Methods section, the method of preparing the solution prepared for intraperitoneal injection and how the concentrations were determined should be fully explained. Kombucha was in solution form and was injected directly, and morphine is dissolved in normal saline and then injected.

2. The title of the article is such that it indicates the application of the substance used in treatment, but in the method of performing the work the protective effects have been examined, because the substance in question was used before pain induction. The title was corrected3. Why was morphine not studied in figures number one and three. In accordance with the respected reviewer's opinion, the graphs underwent a minor change.4.In this study, the effect of the substance in question has been considered comparable with morphine as a powerful analgesic. In the Discussion section this subject should be analyzed in detail. Given that morphine was not used in all tests and stating this sentence with certainty is wrong, it was therefore removed.

2 Revision 1

0 comments

No public comments in this round.

3

Revision 2

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.

Reviewers' Comments:

Reviewer 1:
_Previouse comments didn't correct properly
_ You have 5 groups but comparison done among 4 groups. Your comment was done.
_ figures not proper. Your comment was done.
_ Discussion is weak Your comment was done.
_ Abstract is so long: Your comment was done.
_ Reference method is not matched with the journal: Your comment was done.
_Refferences are old: Your comment was done.

Reviewer 2:
Questions 1 and 3 have not been answered.

The questions have been answered and the figures have been changed.

[Translated from Persian by the Brieflands editorial office.]

3 Revision 2

4 comments · 20 Dec 2019 – 30 Dec 2019

Ali Reza Dashipour Reviewer

MAJOR REVISION 20 Dec 2019

In the method, specify the amounts of the ingredients in grams or ml instead of spoons or cups.
What does this sentence mean: "Kombuch was in solution and it was injected directly according to the weight of rats."?
How much acetic acid was used, and what were its characteristics? Please clarify the following sentence: " acetic acid 0.7% was injected intraperitoneally into rats."
How were the kombucha doses of 250, 500, and 1000 mg/kg calculated? Moreover, did you use kombucha or kombucha tea? Clarify this; the details must also be provided in the other section of the text.
- Which method was used to kill the rats?
- It seems that the timing and sequence of the tests (Acetic acid test, Pain tolerance test using tail flick test, Acute anti-inflammatory test) are ambiguous.
Add the time for the writhing count to figure 1.
In the discussion, the analgesic effect of kombucha tea was not discussed.
Why did the 1000 mg/kg group show a decrease in the results compared with the 250 and 500 mg/kg groups? Discuss this.
It is not in the proper format for acceptance.

Referee 1 Reviewer

ACCEPT 29 Dec 2019

This paper is acceptable.

Associate Editor

MAJOR REVISION 30 Dec 2019

Major Revision

Editor-in-Chief

MAJOR REVISION 30 Dec 2019

In the methods section, specify the ingredients in grams or mL instead of spoonfuls or cups.
What is the meaning of this sentence: "Kombuch was in solution and it was injected directly according to the weight of rats."
How much acetic acid was used, and what were its characteristics? Please address this sentence: " acetic acid 0.7% was injected intraperitoneally into rats."
How were the kombucha doses of 250, 500, and 1000 mg/kg calculated? Moreover, did you use kombucha or kombucha tea? Clarify this; these details must also be provided in the other section of the text.
- What method was used to kill the rats?
- It seems that the timing and sequence of the tests (Acetic acid test, Pain tolerance test using tail flick test, Acute anti-inflammatory test) are ambiguous.
In Figure 1, add the time for the writhing count.
In the discussion, the analgesic effect of kombucha tea was not discussed.

> Why does the 1000 mg/kg group show a decrease in the results compared with the 250 and 500 mg/kg groups? Discuss this.

4

Revision 3

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.

In the method determine the ingredients as gram or ml instead spoon or cup .Edited

What is the mean of this sentence : "Kombuch was in solution and it was injected directly according to the weight of rats." That is, kombucha was in liquid form and was injected directly intraperitoneally according to the weight of the animals.

How much of acetic acid and with kind of characteristics was used attention in this sentence:" acetic acid 0.7% was injected intraperitoneally into rats." Acetic acid was diluted with normal saline and reached a concentration of 7 percent.

How was calculated the kombucha at 250, 500, and 1000 mg/kg, more over you used kombucha or kombucha tea? clear that, in another section of text detail must be write too.

These doses were calculated based on the weight of the rats with a simple calculation, and kombucha tea was injected into the rats. - which kind method was used to killing of rats? Spinal cord injury- It seems the time of study (Acetic acid test, Pain tolerance test using tail flick test, Acute anti-inflammatory test) and sequence is ambiguous.

For each experiment, 40 male rats were used, which were divided into 4 groups of 10, and the tests were performed separately. Add in the figure 1, the time of writhing number. The number of writhings was counted for 30 minutes In discussion, the analgesic effect of Kambucha tea hadn’t discussed. editedWhy the 1000 mg/kg. group has decrease in the results against 250 and 500, discus it. edited

4 Revision 3

3 comments · 7 Jan 2020 – 13 Jan 2020

Ali Reza Dashipour Reviewer

MAJOR REVISION 7 Jan 2020

1- What is meant by i.p, which appears before the groups in the manuscript? Please write it in accordance with writing conventions.
“control group i.p received normal saline in the same amount of the drug. Groups that i.p received""”
2- Why is this phrase italicized?
“2.1. Preparation of Kombucha Tea:”
3- Is the amount of added sugar correct? It seems very low.
“was boiled and a 200 mg of sugar added”
4- Why is the unit for dried tea ml? Also, what is meant by dried tea, where was it obtained, and what were its specifications?
“Then, 30 ml of high quality ordinary dried tea were added”
5- What is meant by fungi in the following phrase? Please state this clearly, including the name and specifications.
“The fungi were washed and added to the container”
6- Specify the storage conditions, such as light and temperature, during the approximately ten-day period. Also, using words such as “about” or “approximately” and similar terms is not appropriate in scientific articles. The methods must be precise enough for another person, even someone without much expertise in the article's field, to carry out the procedure by following the authors' methods. (Now judge your own article.)
7- The phrase you added, “Kombucha in liquid form and directly injected intraperitoneally to animals.”, makes the reader think that you converted Kombucha into a liquid, whereas you used the solution in which Kombucha had grown. The amount used, whether this solution was sterilized before injection, and other details are unclear. The English phrase itself is also incorrect.
8- In my opinion, 7/0 % differs from the dilution to 7% in the following sentence:
“acetic acid 0.7% (Acetic acid was diluted with normal saline to a concentration of 7%)”
9- Why has this word been pluralized (“writhings”)?
10- What does this abbreviation mean: “i.pl injection”?
11- This phrase is misleading: “ascorbic acid [B vitamins (including folic acid B9)]”. As written, it means that the vitamins within the brackets and parentheses are vitamin C.
12- The timing of the interventions remains unclear. Were all three interventions performed on all mice? In other words, did each mouse undergo abdominal pain induction, tail pain assessment, and ear inflammation induction? If so, please check the timing, because after injection, you measured abdominal pain, the tail test response, and inflammation during the same period (at least, this is what the wording suggests). If each mouse received only one of these interventions, this must be stated in the methods. Also, if all mice received all interventions, what is the effect of these simultaneous interventions?
13- The most important finding is usually stated at the beginning of the discussion and then analyzed, explained in terms of different mechanisms, and compared with the findings of others.
14- The lack of an effect of the 1000 dose on reducing inflammation must be discussed in terms of possible or established mechanisms. The material added to the discussion is not appropriate.
15- The article has many writing errors.
16 – Add recent references.

Associate Editor

MAJOR REVISION 13 Jan 2020

1- What is meant by i.p, which appears before the groups in the manuscript? Please write this in accordance with proper writing conventions.
“control group i.p received normal saline in the same amount of the drug. Groups that i.p received""”
2- Why is this phrase italicized?
“2.1. Preparation of Kombucha Tea:”
3- Is the amount of added sugar correct? It seems very small.
“was boiled and a 200 mg of sugar added”
4- Why is ml used as the unit for dried tea? Also, what is meant by dried tea, where was it obtained, and what were its specifications?
“Then, 30 ml of high quality ordinary dried tea were added”
5- What is meant by fungi in the following phrase? Please state this clearly, including the name and characteristics.
“The fungi were washed and added to the container”
6- Please specify the storage conditions, such as light and temperature, during the period of approximately ten days. Also, words such as “about,” “approximately,” and similar terms are not appropriate in scientific articles. The methods must be precise enough for another person, even someone who is not particularly specialized in the article's field, to carry out the procedure by following the authors' methods. (Now judge your own article in this respect.)
7- The phrase you added, “Kombucha in liquid form and directly injected intraperitoneally to animals.”, makes the reader think that you converted Kombucha into a liquid, whereas you used the solution in which Kombucha had grown. The amount used, whether this solution was sterilized before injection, and other details are not clear. The English phrase itself is also incorrect.
8- In my view, 7/0 % differs from the dilution to 7% in the following sentence.
“acetic acid 0.7% (Acetic acid was diluted with normal saline to a concentration of 7%)”
9- Why is this word plural (“writhings”)?
10- What does the abbreviation in “i.pl injection” mean?
11- This phrase is misleading: “ascorbic acid [B vitamins (including folic acid B9)]”. As written, it means that the vitamins within the brackets and parentheses are vitamin C.
12- The timing of the interventions remains unclear. Were all three interventions performed on all mice? In other words, did each mouse undergo abdominal pain testing, tail pain assessment, and ear inflammation assessment? If so, please check the timing, because you measured abdominal pain, the tail test response, and inflammation simultaneously during the same period after injection (at least, this is what the wording suggests). If each mouse received only one of these interventions, this must be stated in the Methods. Also, if all mice received all the interventions, what is the effect of these simultaneous interventions?
13- The Discussion usually begins with the most important finding, which is then analyzed, explained in terms of different mechanisms, and compared with the findings of others.
14- The lack of an effect of the 1000 dose on reducing inflammation should be discussed in terms of possible or established mechanisms. The material added to the Discussion is not appropriate.
15- The manuscript has many writing errors.
16 – Please add a new reference.

Editor-in-Chief

MAJOR REVISION 13 Jan 2020

1- What does i.p mean where it appears before the groups in the manuscript? Rewrite this in accordance with writing conventions.
“control group i.p received normal saline in the same amount of the drug. Groups that i.p received""”
2- Why is this phrase italicized?
“2.1. Preparation of Kombucha Tea:”
3- Is the amount of added sugar correct? It seems very low.
“was boiled and a 200 mg of sugar added”
4- Why is ml used as the unit for dried tea? Also, what is meant by dried tea, where was it obtained, and what were its specifications?
“Then, 30 ml of high quality ordinary dried tea were added”
5- What does fungi mean in the following phrase? State this clearly, including the name and specifications.
“The fungi were washed and added to the container”
6- Specify the storage conditions, such as light and temperature, during the approximately ten-day period. Also, using words such as “about,” “approximately,” and similar terms is not appropriate in scientific articles. The methods must be precise enough for another person, even someone without much expertise in the article's field, to carry out the work by following the authors' methods. (Now judge your own article.)
7- The phrase you added, “Kombucha in liquid form and directly injected intraperitoneally to animals.”, makes the reader think that you converted kombucha into liquid form, whereas you used the solution in which kombucha had grown. The amount used, whether this solution was sterilized before injection, and other details are unclear. The English phrase itself is also incorrect.
8- In my opinion, 7/0 % differs from the 7% dilution described in the following sentence:
“acetic acid 0.7% (Acetic acid was diluted with normal saline to a concentration of 7%)”
9- Why has this word been made plural (“writhings”)?
10- What does the abbreviation in “i.pl injection” mean?
11- The phrase “ascorbic acid [B vitamins (including folic acid B9)]” is misleading. As written, it means that the vitamins within the brackets and parentheses are vitamin C.
12- The timing of the interventions remains unclear. Were all three interventions performed on all mice? In other words, did each mouse undergo abdominal pain induction, tail pain assessment, and ear inflammation induction? If so, please check the timing, because after injection you measured abdominal pain, the tail test response, and inflammation within the same period (at least, this is what the wording suggests). If each mouse received only one of these interventions, this must be stated in the methods. Also, if all mice received all the interventions, what is the effect of these simultaneous interventions?
13- At the beginning of the discussion, the most important finding is usually stated first, followed by analysis, explanations based on different mechanisms, and comparisons with the findings of others.
14- The fact that the dose of 1000 had no effect on reducing inflammation must be discussed in terms of possible or established mechanisms. The material added to the discussion is not appropriate.
15- The manuscript has many language errors.
16 – Add new references.

5

Revision 4

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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1- What is meant by i.p, which is written before the groups in the article? Write it in a way that follows the writing rules. i.p means intraperitoneal injection. We had written Intraperitoneal injection in the article, and the previous respected reviewer had asked us to write its abbreviation. control group i.p received normal saline in the same amount of the drug. Groups that i.p received""2- Why is this phrase italic? The format has been corrected based on the journal style, according to which it must be italic. 2.1. Preparation of Kombucha Tea:3- Is the amount of added sugar correct? It seems very low: mg had been written in the text by mistake instead of grams, which was corrected. was boiled and a 200 mg of sugar added4- Why is the unit of dry tea ml? In addition, what is meant by dry tea, and from where and with what specifications was it obtained? Corrected Then, 30 ml of high quality ordinary dried tea were added5- What is meant by fungi in the phrase below? It should be written clearly, with name and specifications? Corrected The fungi were washed and added to the container6- The storage conditions, such as light and temperature, during the approximately ten days should be stated; in addition, in scientific articles using words such as about or approximately and the like is not correct; the method should be so precise that another person who is not very specialized in the field of the article can carry it out based on the author's method. (Now judge your own article yourself) ? Corrected 7- This phrase you have added, Kombucha in liquid form and directly injected intraperitoneally to animals., is such that the reader thinks you have made kombucha into a liquid, whereas you have used the grown kombucha solution; how much was used, whether or not you sterilized this solution before injection, and other details are also not clear. In addition, the English phrase above itself has problems. This answer was added at the request of the previous respected reviewer. The solution was sterile. Corrected 8- In my opinion, 0.7 % differs from the 7% dilution method in the sentence below Corrected acetic acid 0.7% (Acetic acid was diluted with normal saline to a concentration of 7%)9- Why has this word been pluralized (writhings) Corrected 10- What is meant by this abbreviation ? i.pl injection Intraperitoneal injection; it was written this way at the request of the previous reviewer 11- This phrase is misleading ascorbic acid [B vitamins (including folic acid B9)], the way you have written it means that the vitamins inside the brackets and parentheses are vitamin C Corrected 12- What is still ambiguous is the time order of the interventions: were all three interventions performed on all the rats, that is, were abdominal pain, tail pain measurement and ear inflammation all performed on each rat? If yes, please check the time sequence, because after the injection you measured abdominal pain, the tail test and inflammation in the same time period simultaneously (at least that is how it appears from the way it is written); and if each rat received only one of these interventions, you should write it in the Methods; and also, if they received all the interventions, what is the effect of these simultaneous interventions? Studied groups: For each experiment, 40 male rats were divided into 4 groups of 10 rats each. Rats were divided into 4 groups as follows: The control group i.p received normal saline. Groups that i.p received kombucha tea at 250, 500, and 1000 mg/kg.

In this section we have written that for each experiment we used 40 rats, which are divided into different groups, and there is no ambiguity.

13- At the beginning of the discussion, the most important finding is usually stated, and then the analysis, justification and comparison are made using different mechanisms and the findings of others Corrected 14- The fact that in inflammation the 1000 dose had no effect on reducing inflammation should be discussed with possible or proven mechanisms; the material added to the discussion is not appropriate, Corrected 15- The article has many writing errors Corrected 16 – New references should be added. Corrected

5 Revision 4

2 comments · 28 Feb 2020 – 29 Feb 2020

Ali Reza Dashipour Reviewer

MAJOR REVISION 28 Feb 2020

With greetings and respect,
The revised portions of the edited article have not been marked or bolded, so it cannot be reviewed.

Associate Editor

MINOR REVISION 29 Feb 2020

Minor Revision

6

Revision 5

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

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In this section we have written that for each experiment we used 40 rats, which are divided into different groups, and there is no ambiguity.

13- At the beginning of the discussion, the most important finding is usually stated, and then the analysis, justification and comparison are made using different mechanisms and the findings of others Corrected 14- The fact that in inflammation the 1000 dose had no effect on reducing inflammation should be discussed with possible or proven mechanisms; the material added to the discussion is not appropriate, Corrected 15- The article has many writing errors Corrected 16 – New references should be added. Corrected

6 Revision 5

3 comments · 22 Apr 2020 – 25 Apr 2020

Ali Reza Dashipour Reviewer

ACCEPT 22 Apr 2020

The referencing and formatting should be checked.

Associate Editor

ACCEPT 25 Apr 2020

Accept

Editor-in-Chief

ACCEPT 25 Apr 2020

Accept