Author's response to reviews

Title: Acute and repeated dose 28 day oral toxicity studies of a Siddha medicine Nuna Kadugu in Sprague Dawely rats

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Author’s response to reviews: see over
Dear Sir/Madam,

Subject: Manuscript entitled “Acute and repeated dose 28-day oral toxicity studies of a Siddha medicine “Nuna Kadugu” in Sprague Dawely rats” - Submission of revised manuscript – Regarding

Herewith we are submitting the revised (second revision) form of the manuscript entitled “Acute toxicity and the 28-day repeated dose study of a Siddha medicine “Nuna Kadugu” with a new title “Acute and repeated dose 28-day oral toxicity studies of a Siddha medicine “Nuna Kadugu” in Sprague Dawely rats” to be considered for publication in BMC Complementary and Alternative Medicine. Appropriate changes were made as suggested by the reviewers. The response to reviewers comment is appended with the covering letter.

With the submission of this revised manuscript I, as corresponding author oblige to state that the above mentioned manuscript has not been published elsewhere or accepted for publication elsewhere or under editorial review for publication elsewhere and also declare no conflicts of interest amid the authors. Animal experimental protocol was approved by Institutional Animal Ethical Committee (IAEC), Sri Ramachandra University, Chennai, India and the guidelines of “Guide for the Care and Use of Laboratory Animals” (Institute of Laboratory Animal Resources, National Academic Press 1996; NIH publication number #85-23, revised 1996) were strictly followed in animal handling and care.

Looking forward for your favorable consideration

Thanking you,
Yours Sincerely,

Ramaswamy
(Corresponding author)
Response to Editorial request

1. Reviewer: Nicola Stagg

Reviewer's report

Comment:
1. Title page

Major compulsory revisions -
I do not like the title change that was recommended by one of the other reviewers. These are two toxicology studies, acute and 28-day. It is not an acute toxicity and the 28-day repeated dose study. That doesn't make sense. I would recommend reverting to the original title.

Authors Response:

Title of the manuscript was now reverted to the original title as suggested by the reviewer

2. None of my comments were addressed only the scanned revisions I suggestions.

Authors Response:

In earlier revision, we addressed the scanned revisions only because we received only the scanned pdf and we didn’t receive any separate report.
2. Reviewer: Akihiro Hagiwara

Reviewer's report:

The introduction and discussion sections are well described, but the materials and methods section and results section should be precisely noted.

1. P8L11-12&L26-29 (section 2.7. Repeated dose 28-day toxicity study). This study was performed according to the OECD guideline, TG 407. However, functional observations should be conducted in the fourth exposure week was not described in the present study.

Author response:

As per reviewer suggestions, the necessary description for the clinical observations in the method section was included in the revised manuscript.

2. P10L19-20 (section 3.2. Acute oral toxicity study) and Fig.2. The term of “…body weight gain …” should be corrected to “…body weight change…”, since body weight curves were presented in Fig.2.

Author response:

As per reviewer suggestions, we made the changes in the revised manuscript.

3. P10L28-29 (section 3.3. Repeated oral toxicity study:) and Table 2 The term of “…body weight gain …” should be corrected to “…body weight change…”, since only average body weights ± SEM, but not body weight gain, were presented in Table2. Body weight data at commencement (Week 0) should be noted in Table 2. Bodyweight retardations were apparent in 600 mg/kg/day from week 1 to 4 and in 900mg/kg /day from week 1 and 2. No statistical significance? Is there any reason? Please delete all data concerning MF (n=10) in Table 2, because of no meaning of combination. In footnote, a sentence of “Significance with…..and **P<0.01 vs control group” should be deleted, since no significant change was appeared in Table 2.

Author response:

• As per reviewer suggestions, we included the 0th week body weight in Table 2.

• Body weight changes were found to be insignificant between control and NK treated groups, this reveals that it did not adversely affect the basic metabolic processes of the experimental animals.

• As per the reviewer suggestions, we made all the changes in the present manuscript.

4. P10L29-P11L1 (section 3.3. Repeated oral toxicity study:) and Tables 3 & 4 Statistical analysis could not be performed for food and water consumption data, because sample size of each group was one (animals were housed in groups of 3-5/cage)(refer P7L12-15). How did you calculate average and SEM? Please note in footnote accurately, such as n=1 cage of 5 animals per group.

Author response:

During acclimatization period, animals were housed (3-5/cage). But for the study, animals were housed individually in a separate cage.
5. P11L1-4 (section 3.3. Repeated oral toxicity study :) and Table 5 The description cited a reference “…were found to be well within the clinical range of rats [18] in …” should be moved to Discussion section. In this section, results of statistical significant parameters should be noted clearly.

Author response:
As per the reviewer suggestions, we made all the corrections in the manuscript.

6. P11L4-11 (section 3.3. Repeated oral toxicity study:) and Tables 6 and 7
Same as comment #5.

Author response:
As per the reviewer suggestions, we made necessary changes in the manuscript.

7. P11L14-16 (section 3.3. Repeated oral toxicity study:) and Table 9 Table 9 should be deleted, since no histopathological alteration was found in any animal/sex/group.

Author response:
As per the reviewer suggestions, we deleted Table 9 in the manuscript.

8. P11L16-19 (section 3.3. Repeated oral toxicity study:) A sentence of “Representative histopathological…(Fig not shown).” should be deleted, because of no meaning. However, histopathological findings of control and treated animals killed at recovery phase should be noted.

Author response:
As per the reviewer suggestions, we included necessary changes in the manuscript.

9. Tables 2-8
Data should be tabulated for males, and then for females, separately, because comparison between groups must be done for each gender. Gender is the important factor to evaluate the data. Please delete all data concerning MF (n=10), because of no meaning. In footnote, a sentence of “Significance with…..and **P<0.01 vs control group” should be deleted, since no significant change was appeared in the table.

Author response:
As per the reviewer suggestions, we deleted the combined data in the manuscript.