Author's response to reviews

Title: Exploring new pharmacology and toxicological screening and safety evaluation of one widely used formulation of Nidrakar Bati from South Asia region

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Version: 3 Date: 21 February 2015

Author's response to reviews: see over
February 21, 2015

Dear Editor,

BMC-CAM.

Manuscript ID 5920041301434088

We are happy to get a review on our manuscript. Reviewer’s comments are appreciable and useful to revise the manuscript according to readers understanding. The pin point reviewer’s comments is followed and the manuscript is edited based on the comments. The author response to reviewer's comments is provided below.

Thank you very much for your consideration. Let know if still you need further revision.

Yours Sincerely,

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Author response to Reviewer comments

Reviewer-1: Jiefeng Cui

Reviewer-1:
The manuscript presented by Zaman A et al. completely evaluates the biological activities of mice administrated with herbal formulation of NKB in aspects of metabolic, analgesic and inflammatory, anxiolytic activities and psychopharmacological, neuropharmacological and toxicological effects. The study design is straightforward and data presented in the manuscript is convincing. It shows some interesting findings. However, final conclusion is obscure especially in effect concentration, safety concentration and toxic concentration. Some essential issues with the manuscript need to be improved before a decision for acceptance.

Author response:
First of all, thank you so much for the useful information and comments. The entire manuscript is fully revised and edited. Actually qualitative comments and suggestion were made at before. According to the reviewer comments, the comprehensive and quantitative conclusion has been written.

Reviewer-1:
Based on which evidence, high, medium and low doses of NKB were defined as 400,200 and 100mg/kg in the study. Additionally, about the dose of reference drug used in animal experiment such as diazepam (2mg/kg), Diclofenac (25, 50,100 mg/kg), Dexamethasone, etc the authors also should provide the related experiment evidences or references.

Author response:
Kilani-Jaziri Soumaya et al. BMC Complementary and Alternative Medicine 2013 used diclofenac, and dexamethasone in low, medium and high doses and according to this we used 25, 50, 100 mg/kg. Also, several references were mentioned in methods section. The dose of NKB was optimized during screening. And the NKB formulation widely used in Bangladesh, India and other south Asia is 200 to 300 mg/kg/day. So we designed our dose system based on these principles. Also, the widely used NKB found in Bangladesh and India is formulated with 200 mg/kg/day of herbal extract. So we used 400 mg/kg/day as higher dose.

Reviewer-1:

In the description of methods, anxiolytic activity assay and psychopharmacological effect assay are different methods, and there are some differences between anxiolytic activity assay and psychopharmacological effect assay, so there seem better if the figures in the manuscript are presented according to function analysis sequence. Except that, the legends for all figures in the manuscript are too brief, please add the detailed description, especially the content on significant differences between different groups for the reader to understand easily.

Author response:

Figure and legends are revised and edited based on the comments.

Reviewer-1:

Since it was mentioned in the text that “NKB is produced using many medicinal plants in many doses”, “The formulation of NKB is varied from region to region”, there is no evidence that the NKB you researched could be generalized to NKBs with other formulations. Is the NKB studied the most popular one in the market so that it can represent the efficacy of the whole NKB family? Is it better to revise your title and make it more specific like “Exploring
new Pharmacology and toxicological screening and safety evaluation of one widely used formulation of Nidrakar Bati from South East Asia Region”.

Author response:

Title is revised according to comments. We used the most common and widely used NKB in South Asia.

Reviewer-1:

Some error in spelling need to be checked. Also several mistakes like second personal pronouns “you” and “your” which attenuate the objectivity.

Author response:

Edited and corrected according to comments.
Author response to Reviewer comments

BMC Reviewer-2:sabrina sukardi

Reviewer-2:
- for all statistical analysis, did you do the Standard Error Means as I see error bars?

Author response:
Yes, in statistical analysis, standard deviation was determined. But in the graph, 5% error bar was shown.

Reviewer-2:
-please justify why you use the unpaired t test?

Author response:
The purpose of use for unpaired t test is to determine the effect of an intervention for NKB on the experimental group.

Reviewer-2:
-Please add numbers for all subheadings with a major heading on top for example test for analgesia (acetic acid writhing test), test for anti-inflammatory properties (formalin induced paw licking test etc) for easier understanding

Author response:
Methods with major heading, subheading and numbering are provided according to suggestion.
Reviewer-2:

-Please add percentage constituents of various plants in NKB

**Author response:**

Quantity of each plant used in NKB formulation has already mentioned in the method section. It is again mentioned in the table 1. Let know is this suitable? Or still percentage of use is more appropriate for readers understanding.

Reviewer-2:

-It is always difficult to ascertain what effects came from what plants in the NKB as most of the plants have the same effects and some reactions between effects of the plants may occur. Please add maybe in table form the effects of each plant constituent in NKB and the paper that published the effects

**Author response:**

A comprehensive review has been studied again on each herbs in the composition of NKB. The summary of review is provided in the Table 3. The mechanism of biological activity has already discussed. And now based on new review the conclusion is edited extensively. The precise mechanism of each herb is discussed elaborately also in the figure legend.

Reviewer-2:

-Soth East Asia is Malaysia Phillipines Indonesia Singapore Thailand Kampuchea Laos Vietnam and Brunei. India and others are in the South Asian Region

**Author response:**

Yes, South Asia is appropriate for SAARC countries. Title is revised.
-Please state why different gender of mice were used for different tests? Please stick to one gender to delete gender differences

**Author response:**

Both male and female are used in the NKB study. This is not scientific to omit female from the study because female animals are generally more sensitive to chemicals, so regulatory agencies OECD-423 prefer females for toxicological studies. Gender differences in xenobiotic metabolism may be an important factor in gender dependent differences in toxicity. Both gender was used in each method due to keep alert and assure the toxicology and abnormal pharmacological effects.