Author’s response to reviews

Title: Protective effects of methanolic extract of Juglans regia L. leaf on streptozotocin-induced diabetic peripheral neuropathy in rats

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Response letter

Dear Editor

The corrections are highlighted in red

Reviewer 1:

1. Grammatical correction for 'increasion of polyol…' page no. 5 line 45.
Response: It was corrected (background section, page 5).

2. Grammatical correction for 'laboratory used and care' page no. 8 line 45.
Response: It was corrected (methods/animals section, page 8).

3. Omit the repetition of sentences on page no. 8 line 33-39 and line 48-54.
Response: It was corrected (methods/animals section, page 8).

4. Need to write number of animals used for the study and statistical test used, below the observation table and figure.

Response: It was corrected (figure legends section, page 37-39).

Reviewer 2:

- The title is concise. "Protective effects of methanolic extract of Juglans regia L. leaf on streptozotocin-induced diabetic peripheral neuropathy in rats" could be a complete form of the title.

Response: It was corrected.

- The authors have mentioned in "Abstract": "whereas other diabetic rats received only isotonic saline as the same volume of GRL leaf extract", but they have introduced the vehicle group as: "Vehicle group, which received only buffer citrate as the same volume of STZ"

Response: It was corrected (methods/ induction of diabetes and experimental design section, page 9).

- "Rats" and "Streptozocin" could be selected as keywords.

Response: It was corrected (keywords section, page 5).

- The time schedule of the experiment is written in some places weekly (line 13, page 10, etc.) and in other places daily (line 23, page 10, etc.). The authors must resolve this discrepancy.

Response: It was corrected (method/formalin test section and figures and tables, page 10).

- Why the researchers have administrated the extract from 5th week in "Curative group"? I mean how they can prove that peripheral neuropathy have started from 5th week?

Response: Treatment schedules were based on previous studies [22-24] and pilot experiments in our laboratory, in which peripheral neuropathy have been recognized in behavioral and
histopathological assessments at the end of 4th week (it is mentioned in the manuscript, methods section, page 9).

- The biochemistry tests were introduced very concisely. What do the authors mean this statement: "The absorbance of the supernatant was measured by spectrophotometry"? What supernatant?!!

Response: It was corrected (methods/biochemistry section, page 11 & 12).

- It is better to write the CAT NO. of antibodies were used in the experiment

Response: It was corrected (methods/immunohistochemistry section, page 12 & 13).

- The one-way ANOVA test is not appropriate for statistical analysis of the data, because all of the measurements repeated 4 times.

Response: It was corrected (methods/statistical analysis section, page 13).

- It is mentioned that "There was a significant difference (p<0.001) in the nociceptive score at the end of the study (8th week) between STZ and Preventive or Curative treatment group" (line 50, page 14), but the bars and antennas of figure 2 do not reveal any statistical difference at 8th week!

Response: The significant differences (**P<0.001) at the end of the study (8th week) is shown in figure 2 based on statistical analysis (refer to Figure 2 and its legend).

- All of the abbreviations should be written in complete form when they appear in the text for the first time, like FBG (line 50, page 6), GCMS (line 31, page 7), etc.

Response: It was corrected (page 6, 7 and throughout the text).

- The names of genus and species are written in italic form initiated by capital letter usually. Also, there are some typewriting errors like "anomal" (line 46, page 25)

Response: It was corrected (page 26 and throughout the text).
Reviewer 3:

1- How the neuropathy was confirmed in curative group before the initiation of Juglans regia leaf extract?

Response: Treatment schedules were based on previous studies [22-24] and pilot experiments in our laboratory, in which peripheral neuropathy have been recognized in behavioral and histopathological assessments at the end of 4th week (it is mentioned in the manuscript, methods section, page 9).

2- How the dose of Juglans regia leaf extract was determined?

Response: The dose was based on previous studies [15, 17] and pilot experiments in our laboratory, which was used in preventive (before of onset of neuropathy) and curative (after onset of neuropathy) groups. It is mentioned in the manuscript (methods section, page 9).

3- Why only one dose of the Juglans regia leaf extract was tested?

Response: The dose was based on previous studies [15, 17] and pilot experiments in our laboratory, in which significant attenuations of FBS levels and Neuropathic symptoms have been recognized at the end of 8th week (it is mentioned in the manuscript, methods section, page 9).

4- How the authors can determine if the protective and therapeutic effects of Juglans regia leaf extract on neuropathy was only contributed to the hypoglycemic effect or there is an additive neuroprotective effect rather than the glycemic control mechanism? Please discuss in the discussion.

Response: This point was discussed as much as possible in the text (discussion and conclusion sections, page 19, 21, 22).

Thanking you most sincerely for your time and consideration.

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