**Author's response to reviews**

**Title:** Hypoglycemic effect of Carica papaya leaves in streptozotocin-induced diabetic rats

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**Author's response to reviews:** see over
Dear Dr. Rowles:

Attached please find the revised version of the manuscript MS: 2759287117668435 Hypoglycemic effect of Carica papaya leaves in streptozotocin-induced diabetic rats Isela E Juarez-Rojop et al., we are re-submitting for possible publication in BMC Complementary and Alternative Medicine.

Changes are highlighted in yellow in the revised version. In addition, we have made corrections according the reviewer’s suggestions as follows:

Reviewer Sreenivasan Sasidharan:

1. Abstract

   Please indicate the P value in the result section of the abstract in “The aqueous extract of Carica papaya (0.75 g and 1.5 g/100 mL) significantly (P<?????) decreased blood glucose. The P value (p<0.05) for blood glucose after treatment with 0.75 g or 1.5 g/100 mL of C. papaya extract is indicated.

2. Methods
   2.1 Animals

Please provide animal ethical clearance number. Without this manuscript cannot be accepted for publications. We agree. We have checked and modified this part in the study design (Page 6, lines 4). The animal clearance number has been included in the methods section (001-10/CICUAL/DACS)

   2.2 Chemical and plant products.

Please provide the herbarum voucher number. The herbarium voucher number has been included (32307)

   2.3 Carica papaya leaf processing

Please give detail of extraction process. The extraction process is now described in detail in the Carica papaya leaf processing section (page 5; line 12-15).

   2.4 Study design
Please explain briefly why use 0.75, 1.5 y 3.0 g/100 mL *C. papaya* aqueous extracts. How the author determined the concentration. The aqueous extract was obtained by weighing 0.75, 1.5 or 3 g of *C. papaya* leaves; they were homogenized with distilled water and adjusted to a final volume of 100 mL after being filtered (page 5; line 15-17)

Reviewer Ignacio Parraga:

1. **To include a clarification or explanation for using the number of fasting blood glucose levels # 250 mg/dL as a criterion for inclusion in the study.** As it is mentioned in the study design section, the inclusion criterion for rats in this study of 250 mg/dL or higher blood glucose level was used after the Gupta et al. communication (2004).

2. **Regarding the methodology of the study, it is advisable to clarify if there has made a sample calculation and parameters used to calculate it.** No formula was used to calculate the adequate n number. The number of animals is in accord to international guideline in research in compliance with the principles of replacement, reduction and refinement, any experiment should use the minimum number of animals necessary to test the hypotheses (Guidelines for the treatment of animals in behavioural research and teaching, *Animal Behaviour*. 2012; 83: 301–309) and internal guideline. In this line many pharmacological articles have been reported with this number of animals (references 15)

3 **In the discussion it seems appropriate to include comments on the limitations of the study.** It is recommended t express that provided results should be interpreted taking into account aspects such as:

   a. Preliminary data are presented.
   
   b. The number of subjects in each group.
   
   c. Animals have DM type 1 induced by a drug.
   
   d. Time of administration of extract of *Carica papaya* was only 4 weeks.

We have included in the discussion section a paragraph that points out the limitations of our study such as preliminary data, small number of animals in each group, drug induction of type 1 diabetes, and length of *C. papaya* treatment was given only during four weeks.
4. Regarding the conclusion section, I consider that the statement: “These results suggest that the aqueous extract of *C. papaya* may provide an alternative therapy to prevent diabetic complications” should be amended, because it is not clear from the results presented. The statement “the results suggest that the aqueous extract of *C. papaya* may provide an alternative therapy to prevent diabetic complications” was modified. It now says: “These results suggest that the aqueous extract of *C. papaya* may improve the metabolic disruption produced by diabetes”.

5. It is advisable to review statements in the introduction using bibliographical references with the number 1 and 2. Reference n° 1 corresponds to a magazine published in Hungarian (Impact factor?), which causes a difficulty to know its content. The reference n° 2 refers to the case-control study and does not mention experimental models. References 1 and 2 were substituted by two other that analyze the improvement of strategies in the management of diabetes and its research perspectives (Fonseca et al., Diabetes. 2012, 6:1338-1345 and Tricco et al., Lancet. 2012, 9833:2252-2261).

Minor essential revisions

**First of all, it is advisable to justify why streptozotocin (STZ) has been used and why the dose of 60 mg/Kg.** As it is mentioned in the second paragraph of the Discussion section, STZ-induced diabetes is an adequate model to evaluate plant products with hypoglycemic effect in rodents. The SZT dose of 60 mg/Kg was chosen in accordance with previous reports from our laboratory (Juárez–Rojop et al, 2006; Junod et al. 1969).

**In this sense, it would be appropriate to indicate the reasons why they have used doses of 0.75, 1.5 and 3 g/100 ml extract of *Carica papaya*.** The reason why we used doses of 0.75, 1.5 and 3 g/100 mL of *C. papaya* extract is mentioned in the *Carica papaya* processing section: we chose these doses from a previous pilot study using up to 15 g of leaves per 500 ml, so we decided to limit the upper dose to 3 g/100 ml.

1. **En el apartado de resultados sería aconsejable incluir algún intervalo de confianza que permita clarificar la información mostrada.** We included only the p value as most of the authors do. We think it is more reader friendly when the authors only include p. (Otsuki et al., Ethnopharmacol. 2010, 127:760-767)
2. We do not know the number of animals that were administered STZ and those who were excluded from the study. In the study design section we included the total number of animals that received the STZ injection, as well as those that were excluded from the study.

3. In the results section it would be advisable to include a confidence interval that allow to clarify the information displayed. The answer has already been given in point 3 (immediately above) of this reply to Dr. Ignacio Parraga.

Editorial comments:

1. Please remove your tables from the main text of your manuscript, and instead include them at the end of your manuscript file, in accordance with our formatting guidelines. Corrected.

2. We recommend that you ask a native English speaking colleague to help you copyedit the paper. Corrected.