**Reviewer’s report**

**Title:** Effects of unaltered and bioconverted mulberry leaf extracts on cellular glucose uptake and antidiabetic action in animals

**Version:** 1  **Date:** 08 Oct 2018

**Reviewer:** Chong-Kuei Lii Lii

**Reviewer's report:**

In this study, the authors examine the anti-diabetic potency of bioconverted mulberry leaf extract (BMLE) in insulin-response C2C12 myotubes and adipocytes and insulin-secreting HIT-T15 pancreatic β-cells as well as in obese and streptozotocin/nicotinamide-induced type 2 diabetic mice. Results showed that, compared with unaltered mulberry leaf extract (MLE), BMLE exerts better anti-diabetic activity than that of MLE as evidence by improving the blood glucose, insulin, and glycated HBA1c levels as well as the HOMA-IR and QUICKI. Moreover, the greater anti-diabetic potency of BMLE is partly related to the greater amounts of trans-caffeic acid and syringaldehyde in BMLE, which are resulted by treating MLE with VIS. There are several concerns need to be clarified before accepting for publication.

**Major:**

1. Based on the dramatic reduction of body weight and increase in blood glucose concentrations following the STZ and NA administration as shown in Fig. 3A, these results indicate that the diabetes induced in this study is more likely to be a type I DM. The authors need to carefully interpret results obtained in this study.

2. Many mistakes and contradictions appear in the experimental methods. For instance, texts in the section of "Induction of obese type 2 diabetic mice" (lines 142-151) differ from that seen in the legend of Fig. 3 (lines 577-580). STA and NA are given at the 1st week (legend of Fig 3) or the 9th week (line 144). Lines 147-150 are hard to realize how animals are grouped. Rewritten of this section is needed. In addition, MLE and BMLE are given for a time period of 6 weeks, but not for 7 weeks (line 151). BMLE and MLE are given by oral route (line 151) or injection (line 580). According the standard protocol, it should be the "confluence" 3T3-L1 preadipocytes are used for initiation of the differentiation of adipocytes (line 204). 3T3-L1 cells are grown in DMEM with 10% FBS (line 208) or 1% FBS (line 216). "Mean ± standard error of the mean" appears twice in lines 229-230.

**Minor:**

1. Diabetes animal model is not simply induced by STZ and NA, HFD-induced obesity is also employed in this study. This needs to be addressed in the abstract.

2. Add 3T3-L1 adipocytes in line 80.
3. Move "unaltered mulberry extract" appeared in line 84 to line 81.

4. Fig 6A and B, significant symbols need to be added in case of 600 mg/kg BMLE is significantly higher than that noted in the MLE-treated mice.

5. Briefly describe the characteristics of VIS in the Materials and Methods.

6. The treating time for trans-caffeic acid and syringaldehyde as well as rosiglitazone and GLM needs to be given in the section of "glucose uptake measurement" and/or the legend of Figs. 1 and 2.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

Yes

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

Not relevant to this manuscript

**Quality of written English**
Please indicate the quality of language in the manuscript:

Acceptable

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