Author’s response to reviews

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

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Response to Reviewer’s Comments on Manuscript “BCAM-D-18-01249R2”

General Comments – We thank the reviewers for their positive consideration of our manuscript (BCAM-D-18-01249R2). We have addressed three issues raised by both an Editor and reviewer 1 with adding some information, and changing some sentences to improve the presentation. All changes can be found in the revised version of manuscript that is a clean version and does not include track changes or highlighting. We hope that these efforts will make the points to clear to the reader and improve the overall presentation of the data.

Comments & Issues Answers & Modification

Editor
This revised manuscript has been improved a lot. However, according to the change of glucose and insulin data, the type 2 diabetic animal induced by STZ and nicotinamide was not succeeded. This animal model is not a type 2 diabetic model but trend to a type 1 diabetic model. Therefore, it is suggested that the author should use diabetic animals instead of type 2 diabetic animal when describing animal model in this manuscript.

Thank you for your comments. According to the Editor’s suggestion, we decided to use diabetic animals instead of type 2 diabetic animal when describing animal model in this manuscript. These changes can be found in Abstract, lines 33, 45 in page 2, Introduction section, line 86 in page 4, Methods section, lines 148, 151 in page 6, lines 162-167 in page 7, Results section, lines 314-315 in page 12, lines 327, 335, Discussion section, line 363 in page 14, lines 382, 390, 393 in page 15, Conclusions section, lines 409, 413 in page 16, and Figure legends, lines 668-669, 679-680, 686 in page 23, lines 689, 691, 698, 700 in page 24.

Reviewer 1

1) In the study of Tahara et al. (2011) (European Journal of Pharmacology 655 (2011) 108-116), they found that the levels of fasting blood glucose (mg/dl) in normal diet-fed non-diabetic mice, normal diet-fed diabetic (nicotinamide+streptozotocin) mice, high-fat diet-fed non-diabetic mice, and high-fat diet-fed diabetic mice are 139±7, 200±11, 181±11, and 264±9, respectively; the levels of plasma insulin (ng/ml) are 0.96±0.08, 1.08±0.10, 2.09±0.13, and 1.91±0.11, respectively. Tahara et al. found that both blood glucose and plasma insulin were properly increased in high-fat diet-fed diabetic (nicotinamide+streptozotocin) mice. It is a type 2 diabetic model. In the present study, the authors used the same animal model that used NA+STZ+HFD to induce obese type 2 diabetes. However, the results showed that was not a type 2 diabetic model, because the blood glucose level was higher to 400 mg/dL (Fig. 3B) and the plasma insulin level was lower than that in control mice (Fig. 5B). Therefore, the type 2 diabetic condition was exactly not to be induced successfully in this study.

Thank you for your comments. According to your comments and the Editor’s suggestion, we decided to use diabetic animals instead of type 2 diabetic animal when describing animal model in this manuscript. These changes can be found in Abstract, lines 33, 45 in page 2, Introduction section, line 86 in page 4, Methods section, lines 148, 151 in page 6, lines 162-167 in page 7, Results section, lines 314-315 in page 12, lines 327, 335, Discussion section, line 363 in page 14, lines 382, 390, 393 in page 15, Conclusions section, lines 409, 413 in page 16, and Figure legends, lines 668-669, 679-680, 686 in page 23, lines 689, 691, 698, 700 in page 24.
2) The in vitro experiments cannot support the conclusion. The results in in vitro experiments are still not convincing. The increased glucose uptake levels under insulin stimulation by tested compounds compared to insulin alone group in skeletal muscle cells or adipocytes are really limited (Figs. 1C, 2A, B). Similarly, the increased insulin secretion levels under glucose stimulation by tested compounds compared to glucose alone group in beta-cells are also limited (Fig. 2C).

Thank you for your valuable comments. We agree your comments and they are limited. However, our long-term experimental experiences tell us that in vitro experiments are unavoidable within limited condition, e.g., number of cells and limited biological activity in each well. To make the findings be scientific, we always repeatedly performed experiments until we acquired scientifically significant meaning.

Reviewer 2
No comments

Thank you for your positive consideration.

Reviewer 3
This paper described the effects of unaltered and bioconverted mulberry leaf extracts on cellular glucose uptake and antidiabetic action in animals. In general, the structure and originality of the paper is positive. The study methods appear to be well conducted, the results are technically sound, and the discussion is pertinent.

Thank you for your positive consideration.