Reviewer’s report

Title: Zhenqing Recipe attenuates non-alcoholic fatty liver disease by regulating the SIK1/CRTC2 signaling in experimental diabetic rats

Version: 2 Date: 19 Jun 2019

Reviewer: Lindsay Brown

Reviewer's report:

Lines 57-59: "Therefore, attenuating the complication of T2DM is equally important to decreasing blood glucose levels in long-term therapies." This statement is not logical as the incidence of a pathological change does not define the importance of therapy, but rather the severity of the changes.

Line 98: ZOR or ZQR?

Lines 105-113: This information is insufficient and does not allow other scientists to repeat this study. The amount of each herb must be included and the compounds present in the extract should be identified. At least, a spectroscopic fingerprint of the extract used in this study must be included, rather than a reference to publication 26 from 2012.

Line 140: You cannot approximate a range; please give the range as numbers, or, preferably, give the value as the mean +/- SEM or SD.

Lines 149-151: The high fat diet (HFD) must be completely described so that the reader can assess the role of this diet.

Lines 150-151: STZ was injected after 4 weeks, but line 261 notes that "Injection of STZ (week 12)". Which time is correct? Was STZ given as a single dose, or multiple doses?

Results: Please present figures 1 and 2 as a Table so that readers can compare changes in a single interventional group across multiple parameters.

You have referred to the HFD+STZ treatment giving a model of type 2 diabetes (for example, line 383) yet body weight fell. Type 2 diabetics are usually overweight or obese. In contrast, type 1 diabetics, such as with STZ alone, show a decreased body weight as in your study. Please justify the description of your rat model as type 2 diabetes, rather than type 1 diabetes, using the physiological and biochemical data from your project. If the model really is one of type 1 diabetes, then your conclusions that ZQR may be a treatment for type 2 diabetes is an invalid extrapolation of the data.

Lines 254-255: "The HFD/STZ-induced diabetic rats showed classic diabetic symptoms of polyuria, polydipsia and weight loss." This statement cannot be validated as food intake, water intake and urine volumes have not been reported.

Line 256: "blood glucose level fluctuation from 20.09 to 30.61 mmol/L" - does this refer to individual rats, or to groups? Some groups, especially controls, had fasting blood glucose concentrations markedly lower than 20.09 mmol/L, so please clarify this comment.
Lines 257-260: What is the evidence that these rats died of hyperglycaemia?

Lines 300+: Please use Image J analysis to determine the percentage of area as lipid droplets and also islet and island size. These values can then be included in the new Table.

Were plasma concentrations of inflammatory markers measured in this study? This would seem to be highly relevant to this study.

Which unique understandings were added to the project by the inclusion of the metformin-treated group? This intervention could have been used to show the importance of AMP kinase up-regulation, but this was not determined.

An additional figure describing possible mechanisms of the ZQR would be appreciated.

**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.

No

**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.

I am able to assess the statistics

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Please indicate the quality of language in the manuscript:

Acceptable
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