Reviewer's report

Title: Evaluating the antidiabetic effects of Chinese herbal medicine: Xiao-Ke-An in 3T3-L1 cells and KKAy mice using both conventional and holistic omics approaches

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Reviewer: Chung Yeng Looi

Reviewer's report:

This study by Yang et al. evaluated the effect of a traditional Chinese medicine XKA on both in vitro and in vivo anti-diabetic effects. The study was interesting but the data need further improvement. The XKA inhibit multiple signs of T2D including adipocyte differentiation, body weight, glucose tolerance etc. However, there is a fundamental weakness in this study because a mixture of many traditional herbs were being used for all tests.

Several points below should be taken into consideration to improve the current manuscript.

1. XKA are composed of eight herbal medicines of variety types, therefore a conclusive statement cannot be drawn. Hence, the author should clearly indicate what are the eight herbal medicine used in XKA? The percentage of each components, dosages and mixture methods of the eight compositions in XKA should be carefully described. It is also important to include the method of standardization for XKA mixture used in this study.

2. The authors should discuss what are the possible compounds in XKA that contribute to the anti-diabetic activity.

3. XKA leads to inhibition of adipocyte differentiation at high concentrations of 250 and 500 ug/ml. Please provide a clearer picture (bright field) to show the adipocyte differentiation. Please indicate what is the solvent used to dissolve XKA for the in vitro assay. The experiments should be repeated with this solvent as negative control.

4. Please show whether the XKA treatment affects insulin level in diabetic mice.

5. Microarray. It is unclear that for the microarray data, what is the concentration of the drug used in the treatment group and what is the tissue samples that were collected for RNA isolation?

6. Please show the values ±SD in the bar charts for Figure 5(A&B), Figure 6 (A&B) and Figure 7.

7. Figure 8 (network). Figure is not clearly seen. More comprehensive descriptions should be provided to explain the network.
8. Figure 9 (Top 10 upregulated genes) shows the top 10 upregulated genes in diabetic model and drug treatment groups. Please indicate what does drug treatment means (high or low dosage?). There is no descriptions in the text regarding Figure 9, so the dose, comparison made and other experimental details are unknown.

For most of the genes, we can detect that there are no differences among diabetic model and drug treatment. For some genes, decrease level are shown in drug treatment group. Error bar and statistical significance of the RS differences should be shown from (n=5), so that the effect of the XKA drug can be judged accordingly.

Authors should verify the microarray data by qPCR or Western blotting, especially those upregulated genes mentioned in Figure 9.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests.