We thank the Editor and the reviewers for giving us an opportunity to improve the quality of the manuscript. The Manuscript has been revised carefully according to the reviewers’ suggestion as listed below.

**Reviewer** **1**

1. The authors identified that APPH contains lipolysis stimulating peptides in their early studies. They isolated the active peptides from APPH and demonstrated that the isolated peptides can stimulate the glycerol release in cell assay using 3T3-L1 adipocytes, suggesting that APPH contains lipolysis stimulating peptides. However, an increase of glycerol release may also result from an increase of glyceroneogenesis in 3T3-L1 cells induced by APPH. In this study, the authors emphasized that APPH acted on the liver cells and stimulated the lipolysis of liver in HFD fed rats. Thus, the fat deposited in the liver was decreased in HFD fed rats after treatment with APPH. However, the weight of HFD fed rats was not reduced after APPH treatment, suggesting the fat stored in adipocyte tissue was increased in APPH-treated rats. I concerned that the similar consequences of the animal experiments will be obtained, if APPH increases the glycerol biosynthesis in adipocytes. This action will increase the fixation of fatty acids in adipocytes and the deposition of triacylglycerol in the liver will be reduced. The authors should verify whether the glyceroneogenesis is occurred in adipocytes of the HFD fed rats mediated by APPH treatment.

Response:

Results from previous study by Lin et al. 2016 (reference no 16) clearly emphasis that, APPH treatment resulted in lipolysis in 3T3-L1 cells which was evident from phosphorylation and translocation of hormone-sensitive lipase (HSL) and over expression of adipose triglyceride lipase (ATGL). The results of the recent publication conclude that APPH treatment leads to lipolysis and not glyceroneogenesis. In this study, we documented that APPH with its lipolysis stimulating properties acted in the liver of HFD fed rats. Thus, the fat deposited in the liver was decreased in HFD fed rats after treatment with APPH. However, APPH treatment could not restore the weight induced by HFD in aged rats. We speculate that physical activity followed by prolonged APPH treatment could result in significant weight reduction in aged HFD-induced obesity model.

In this study we particularly emphasis on the anti-apoptotic and anti-fibrotic properties APPH treatment in HFD fed aged rats. Further molecular and biochemical studied are needed to determine the liver specific deposition of triacylglycerol and also to confirm that there is no glyceroneogenesis in liver tissue.

2. This manuscript needs to provide the evidence that no glyceroneogenesis is stimulated in 3T3-L1 induced by APPH treatment.

Response:

Previous report by Lin et al. 2016 from our lab reported that APPH treatment in 3T3-L1 cells resulted in phosphorylation and translocation of HSL and over expression of ATGL, which are responsible for 95% lipolysis in adipocytes. Therefore, it is evident that presence of triglyceride residues in 3T3-L1 cells is due to lipolysis and not because of glyceroneogenesis.

(Reference: Lin WT, Lee KI, Hong MC, Chiang WD. Production of Potato Protein Hydrolysates with Lipolysis-stimulating Activity and Study of Their Possible Regulation Mechanism. Taiwanese Journal of Agricultural Chemistry and Food Science, 2016)

3. APPH treatment can induce the glycerol release in 3T3-L1 cells. It remains unknown whether the lipolysis or lipogenesis is also occurred in hepatic cell lines after APPH treatment. The authors should demonstrate whether APPH can induce lipolysis or lipogenesis in the hepatic cell-lines.

Response:

APPH treatment in 3T3-L1 cells resulted in phosphorylation and translocation of HSL and over expression of ATGL which was primarily involve in lipolysis Lin et al. 2016. Hence, we believe the same mechanism (lipolysis) would involve in hepatic cells. The present study focuses on evaluating the effect of APPH to prevent apoptosis and fibrosis induced by HFD. Further studies are warranted in exploring the molecular mechanism of lipolysis induction by APPH in hepatic tissues. We will consider this aspect in our future studies.

(Lin WT, Lee KI, Hong MC, Chiang WD. Production of Potato Protein Hydrolysates with Lipolysis-stimulating Activity and Study of Their Possible Regulation Mechanism. Taiwanese Journal of Agricultural Chemistry and Food Science, 2016)

4. This manuscript should provide the evidence that lipolysis stimulating peptides were resistant to proteolytic digestion in gastrointestinal system of rats.

Response:

Previous study by Lin et al. 2016 from the same lab reported that APPH were resistant to gastrointestinal digestion by proteases at lower pH and revealed that APPH have lipolysis property.

(Reference: Lin WT, Lee KI, Hong MC, Chiang WD. Production of Potato Protein Hydrolysates with Lipolysis-stimulating Activity and Study of Their Possible Regulation Mechanism. Taiwanese Journal of Agricultural Chemistry and Food Science, 2016)

5. The scale bar must be included in Figure 3, 4 and 7. Figure 4 has the wrong labeling. The first and second rows represent DAPI and TUNEL, respectively.

Response:

As per reviewer suggestion, in Figure 3, 4 and 7 magnification has been mentioned in figure legends of respective figures. In Figure 4, the labelling of DAPI and TUNEL has been corrected.

6. No band representing phospho-PI3K in probucol (PB) treatment of Figure 5 was observed. The authors must repeat this data. In addition, the authors also need to put western blotting of PI3K and AKT in Figure 5. The quantitative analysis for p-PI3K/beta-actin and pAKT/beta-actin in Figure 5 is not accurate. The authors must re-calculate and re-plot the figures.

Response:

As per reviewer suggestion, blots with appropriate exposure are now been provided in the revised manuscript. Quantitative analysis of the blots were also been revised accordingly.

7. The quantitative analysis for fas/beta-actin, FADD/beta-actin, Bax/beta-actin and caspase 3/beta-actin is not accurate. The author must re-calculate and re-plot the figures.

Response:

Qualitative analysis for the protein blots in figure 6 were re-calculated and re-plotted.

8. The quality of Figure 7 is no good.

Response:

As per reviewer suggestion Figure 7 with better quality has been provided with the revised manuscript.

**Reviewer 2**

Major points

1. The English writing for the whole manuscript is not good.

Response:

As per reviewer suggestion the whole manuscript has been revised and the language of the presentation has been improved

2. The figure 4 is not clear, the label of TUNEL and DAPI staining are not correct. In addition, the statistical data for TNUEL assay should be provided.

Response:

As per reviewer suggestion in figure 4 clarity has been improved and labelling of TUNEL and DAPI has been corrected.

3. The abbreviations in referring animal groups are not coherent as indicated in Figures 2, 5, 6 and Figures 3, 4, 7.

Response:

As per reviewer suggestion labelling of animal groups in Figures 2, 5, 6 and Figures 3, 4, 7 were changed and similar to figure legend.

Minor points

1. The full name for abbreviations, IACUC (line 97), TC (line 210), should be cited.

Response:

As per reviewer suggestion IACUC and TC were abbreviated in the main text.

2. The concentration for probucol should be given.

Response:

As per reviewer suggestion, the concentration for probucol (500 mg/kg body weight) has been mentioned in the Animal Experiment subheading.

3. Manufacturers’ information for chemicals or instruments only upon its first appearance (Zeiss Axiophot…).

Response:

As per reviewer suggestion, the manuscript has been checked and corrections were carried out in manufacturers’ information for chemicals and instruments only upon its first appearance.

4. It is necessary to properly cite reference papers for many sentences in introduction and discussion quoting published information.

Response:

As per reviewer suggestion, references of published articles were cited in the introduction and discussion section of the manuscript.

5. Not correct description in final paragraph in Discussion (p10, line 251), there is no significant changes in body weight (p7, line 158).

Response:

As per reviewer suggestion, particular sentences in results and discussion part has been changed.

6. It is not necessary to repeatedly writing the animal groups in each of figure 2-7 legends.

Response:

Necessary changes have been made according to the reviewer’s suggestion.

7. APPH, sometimes use “APPH”, but sometimes it is referred as “lipolysis stimulating APPH”. Are they different forms of APPH?

Response:

Both “APPH” and “lipolysis stimulating APPH” refers to the same. To avoid confusion we have now replaced lipolysis stimulating APPH with “APPH”.

8. There is no unit in Figure 2.

Response:

As per the reviewer suggestion, unit for Figure 2 has been included in figure and figure legend

9. In Figure 5, the label for p-PI3K is not good and not consistent with writing in main text.

Response:

As per the reviewer suggestion, labelling for the Figure 5 in figure legend has been changed and now consistent with the main text.

Thank You

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