Dear Reviewer:

Thank you for your thorough review and salient observations. We have carefully read and addressed the comments from reviewers in the revised manuscript. Please see the point-by-point responses. All the changes are highlighted and we hope the revised manuscript is suitable for publication.

Best regards,

Sincerely,

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Comments from the editors and reviewers:

Review opinions 1:

The article looks very interesting. I have a few queries

Suggestions:

1. Whether you have cited the following article Salvia miltiorrhiza Extract and Individual Synthesized Component Derivatives Induce Activating-Transcription-Factor-3-Mediated Anti-Obesity Effects and Attenuate Obesity-Induced Metabolic Disorder by Suppressing C/EBPα in High-Fat-Induced Obese Mice Please make a discussion about how it is different from the current article.

Response: Thank you for your review. Your suggestion is very valuable and this is a very comprehensive and meaningful article which gives us a lot of inspiration. Coincidentally, we cited this article in the Discussion section (line 511, page 18) before the review. We further compared the two articles and found that they discussed the therapeutic effects of *Salvia miltiorrhiza* extract (Sal) on obesity from different perspectives and mechanisms. Yueh-Lin Wu's research found that S.miltiorrhiza extract has an anti-obesity effects through ATF3-mediated C/EBP α downregulation and the CHOP pathway, while our research discuss the anti-obesity effects of Sal by regulating intestinal microbiota and lipid metabolism. Interestingly, it's showed that C/EBP α is closely related to lipid metabolism. C/EBP β activates the expression of PPAR to initiate the differentiation of adipocytes, which become the "necessary way" of cell differentiation and the loss of C/EBP β will directly hinder the differentiation of adipocytes. PPAR pathway plays an important role in adipogenesis, glucose and lipid metabolism by regulating the expression of related genes and is related to the occurrence and development of a variety of diseases such as diabetes, obesity,

hypertension, cancer, etc., which provides a revelation that the anti-obesity effect of Sal in regulating intestinal flora and lipid metabolism may be related to PPAR and C/EBP α pathways. In the next step, we can further inhibit the pathway of C/EBP α by gene knockout to identify the targets that regulate lipid metabolism and prove the relationship between gut microbiota, lipid metabolism and CEBP/ α which going to be a very promising experiment under the guidance of this article. In a word, thanks again for your suggestions and questions.

2. Table and Figure legends need more clarity.

Response: Thank you for your review. We have re-edited Figure Legends to make it clearer.

3. Moreover, check all the figures are 300dpi.
4. Improve the size of the writings of all figures; some figures are blurred.

Response: Thank you for your review. We have modified the font and sharpness of the pictures according to the requirements of the magazine and resubmitted the new figures to ensure that the resolution of the chart is above 300dpi.

5. Ms analysis need more valid interpretations.

Response: Thank you for your review. We re-edited the LC-MS/MS results, which can be seen on line 430-493, page 16-18. In the discussion, we analyzed the results of LC-MS/MS, including the roles of various metabolites in lipid metabolism and obesity (line 549-593, page 20-21); lipid metabolite pathway enrichment and the relationship with other indicators such as cAMP, PKA, HSL and FFA, etc. (line 594-616, page 21-22); the relationship between differential metabolites with gut microbiota and the regulation effect of Sal on gut microbiota and lipid metabolism (line 617-662, page 22-24).

6. The abstract should be more valid with all the results included in a very crisp manner

Response: Thank you for your review. We had re-edited the abstract and you can see that in line 53-96 , page 3-4.

7. The purpose of doing the experimental setting needs to be clearer in the introduction part.

Response: Thank you for your review. We further clarify the purpose of this experiment in the introduction part in line 157-159, page 6.

8. It would be better to have a graphical abstract.

Response: Thank you for your review. Your suggestion is very valuable. We have drawn a graphical abstract to illustrate the mechanism more visually in line 1132,