Dear Editors and Reviewers,

Thank you for the kind assistance in processing our paper entitled "Huangqin decoction alleviates lipid metabolism disorders and insulin resistance in nonalcoholic fatty liver disease rats via triggering Sirt1/NF-κB pathway" for ***World Journal of Gastroenterology*** (Manuscript NO.: 85298, Basic Study). We greatly appreciate your consideration of our modified manuscript for publication. We have strictly revised our manuscript following the editors' and reviewers' comments and carefully explained the doubt of reviewers to meet the publication requirements. All revisions have been marked in the paper. Our responses to the editors' and reviewers' comments are listed below.

Sincerely,
Dr. Xian, Zheng
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Science editor:

1.-The manuscript has been peer-reviewed, and it' s ready for the first decision.

A1.-We would like to sincerely thank you for your time and extensive efforts to deal with our manuscript and will do our best to revise our manuscript following the points made by the editors and reviewers one by one.

Company editor-in-chief:

1.-Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add

the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022.

A1-Thanks for your careful review. As you suggested, decomposable Figures have been organized into a single PowerPoint file, which was denoted as "85298-Figures.pptx".

2.-Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: https://www.referencecitationanalysis.com/.

A2.-Thanks for your careful review. Article highlights have been generated and added with the help of Reference Citation Analysis (RCA).

Reviewer #1

1.-EX-527 was only applied to HepG2 cells and not to rats. The authors should explain why this animal group was not carried out (HFD + HQD + EX-527). It would strengthen the results and the mechanistic explanation of SIRT-1 action, if this animal group could be added to the experiments.

A1-Thanks for your professional review. In animal experiments, the therapeutic efficacy of HQD was assessed, and then the underlying mechanisms were preliminarily investigated. As there was no direct evidence that HQD had regulatory action on Sirt1, we first explored the correlation between HQD and Sirt1 *in vivo*, and at this stage, the supplement of EX-527 seemed logically unreasonable. Based on the *in vivo* results, EX-527 was introduced to HepG2 cells to validate the beneficial effects of HQD achieved through activating Sirt1, which provided convincing evidence that HQD could activate Sirt1, at least *in vitro*. We do very much recognize the opinion of the reviewer that adding the animal group (HFD+ HQD+EX-527) would further strengthen the results and the mechanistic explanation of

SIRT-1 action *in vivo*. However, it is considerably time-consuming for us to add this group (16 weeks). Indeed, we also consider applying EX-527 in our following study in which the main constituents of HQD will be used to intervene in HFD-induced NAFLD, and we sincerely appreciate your reminder and will keep it in mind in our further research.

2.-Especially the first part of the discussion is more introduction. Please shorten this part.

A2.-Thanks for your valuable comment. We have refined and shortened this part, following your suggestion (the first paragraph of the Discussion).

3.-Fenofibrate is as good as HQD in all parameters. Given the fact that Fen acts on a different pathway, this should be discussed by the authors..

A3.-Thanks for your professional review and constructive suggestions. Fenofibrate, as a peroxisome proliferator-activated receptor α (PPARα) agonist, offers potential therapeutic efficacy for NAFLD through inducing fatty acid oxidation and inhibiting inflammatory gene expression in the liver (*doi: 10.1016/j.metabol.2021.154798*; *doi: 10.1155/2022/5805398*). And clinical-based studies have shown that fenofibrate might have positive therapeutic outcomes for NAFLD/NASH (*doi: 10.1007/s12072-015-9633-1; doi: 10.1016/j.jacl.2018.08.003*). Herein, we found HQD could achieve comparable therapeutic effects with Fenofibrate via activating Sirt1. Ample studies have exhibited that Sirt1, as a key regulator of PPARα signaling, could trigger PPARα-modulated fatty acid oxidation in the liver, showing favorable effects for NAFLD (*doi: 10.1016/j.jff.2021.104686*; *doi: 10.1016/j.jhep.2016.11.020*; *doi: 10.1172/JCI97831*). As such, although different targets act by HQD and Fenofibrate, the upstream and downstream regulatory relationships between Sirt1 and PPARα make their similar therapeutic effects interpretable. In addition, corresponding information has been added in the "Discussion" section (the last paragraph of the Discussion).

4.- In the light of the Fenofibrate results: The sentence, that TCM is more suitable for treatment of NAFLD than monosubstances, is obviously wrong. The authors should omit that and discuss the fenofibrate results in comparision to the HQD results (see 3).

A3.-Thanks for your careful review and valuable comments. As suggested, the sentence has been reworded to "TCMs are promising complementary and auxiliary agents for metabolic diseases with multifactorial pathogeneses, such as NAFLD". In addition, careful discussion has been added, following your suggestion (the last paragraph of the Discussion).

Reviewer #2

1.- This is a very interesting piece of work in which power of traditional, natural medicine was evidenced and presented. This study may be a starting point for experimental and clinical studies concerning reintroduction of traditional, natural drugs to the belonging role in authentic, complex medicine. For this reason, I recommend this article for publication in the World Journal of Gastroenterology.

A1.-We sincerely appreciate the reviewer's careful assessment of our work and positive feedback and recognition of our study, which greatly encourages us to deepen our research.