Response to Reviewers

Reviewer 1:

1) N/A, because this is an editorial article. 2) See below. 3) N/A, because this is an editorial article. Gao et al. reported that a novel intervention for alcohol-related liver diseases. Bezafibrate, a PPAR-alpha activator, has been shown to improve lipid and glucose metabolism. Please discuss below. Bezafibrate is shown to be effective for primary biliary cholangitis (PMID: 12825134). Authors should compare the elafibranor with bezafibrate and pemafibrate (Zhu YW, Li D, Ye TJ, Qiu FJ, Wang XL, Yan XF, Lu YL, Xu W, Li H, Hu XD. The Study of Yin-Chen-Hao-Tang Preventing and Treating Alcoholic Fatty Liver Disease through PPAR Signaling Pathway Based on Network Pharmacology and RNA-Seq Transcriptomics. Evid Based Complement Alternat Med. 2021 Dec 31;2021:8917993. doi: 10.1155/2021/8917993. PMID: 35003311; Iwasa M, Sugimoto R, Eguchi A, Tamai Y, Shigefuku R, Fujiwara N, Tanaka H, Kobayashi Y, Ikoma J, Kaito M, Nakagawa H. Effectiveness of 1-year pemafibrate treatment on steatotic liver disease: the influence of alcohol consumption. Eur J Gastroenterol Hepatol. 2024 Jun 1;36(6):793-801. doi: 10.1097/MEG.0000000000002766. PMID: 38526942). Where the reference of Koizumi A in the reference lists? This is important, and ask editorial office. As prevention of intracellular 4-HNE accumulation by bezafibrate, protected hepatocytes from TNF killing via NF-κB activation in male C57BL/6 mice (PMID: 18703563), PPAR alpha agonists may be effective for patients with alcohol related liver disease. Authors should discuss more. It was reported that PPAR delta is also involved in various liver diseases (PMID: 34719638; PMID: 32810487). Combination of both PPAR alpha agonist and PPAR delta agonist seems to have stronger effects on alcohol-related liver diseases. Authors may discuss about abstinence from alcohol. How about

the drugs for abstinence from alcohol? Authors should discuss more. Li TH et al. (PMID: 30602573) reported that elafibranor interrupts adipose dysfunction-mediated gut and liver injury in mice with alcoholic steatohepatitis. See: Liu L, et al. (PMID: 33326461).

Response: Thank you very much for your insightful comments on our work. We have carefully revised the manuscript according to your suggestions. Our detailed response is provided below, and all revised sections are highlighted in the manuscript.

1. Please discuss below. Bezafibrate is shown to be effective for primary biliary cholangitis (PMID: 12825134). Authors should compare the elafibranor with bezafibrate and pemafibrate (Zhu YW, Li D, Ye TJ, Qiu FJ, Wang XL, Yan XF, Lu YL, Xu W, Li H, Hu XD. The Study of Yin-Chen-Hao-Tang Preventing and Treating Alcoholic Fatty Liver Disease through PPAR Signaling Pathway Based on Network Pharmacology and RNA-Seq Transcriptomics. Evid Based Complement Alternat Med. 2021 Dec 31;2021:8917993. doi: 10.1155/2021/8917993. PMID: 35003311; Iwasa M, Sugimoto R, Eguchi A, Tamai Y, Shigefuku R, Fujiwara N, Tanaka H, Kobayashi Y, Ikoma J, Kaito M, Nakagawa H. Effectiveness of 1-year pemafibrate treatment on steatotic liver disease: the influence of alcohol consumption. Eur J Gastroenterol Hepatol. 2024 Jun 1;36(6):793-801. doi: 10.1097/MEG.0000000000002766. PMID: 38526942).

Response:

We appreciate the reviewer's valuable suggestions and comments. We have expanded the discussion to include comparisons between elafibranor, bezafibrate, and pemafibrate.

2. Where the reference of Koizumi A in the reference lists? This is important, and ask editorial office.

Response:

Thanks for your reminder. We have inserted this article in our manuscript.

3. As prevention of intracellular 4-HNE accumulation by bezafibrate, protected hepatocytes from TNF killing via NF-κB activation in male C57BL/6 mice (PMID: 18703563), PPAR alpha agonists may be effective for patients with alcohol related liver disease. Authors should discuss more.

Response:

Thank you for the suggestions. We have added a discussion on the role of PPARα and 4-HNE in the pathogenesis of alcohol-related liver disease.

4. It was reported that PPAR delta is also involved in various liver diseases (PMID: 34719638; PMID: 32810487). Combination of both PPAR alpha agonist and PPAR delta agonist seems to have stronger effects on alcohol-related liver diseases. Authors may discuss about abstinence from alcohol. How about the drugs for abstinence from alcohol? Authors should discuss more. Li TH et al. (PMID: 30602573) reported that elafibranor interrupts adipose dysfunction-mediated gut and liver injury in mice with alcoholic steatohepatitis. See: Liu L, et al. (PMID: 33326461).

Response:

Thanks very much for your useful suggestions. Following your advice, we have included a discussion focusing on alcohol cessation therapies.