
Name of Journal: *World Journal of Gastroenterology*

Manuscript Number: 45961

Manuscript Title: Freeze-dried Si-Ni-San powder can ameliorate high-fat-diet-induced NAFLD

Dear Editor,

Thank you for your letter and for the reviewers' comments concerning our manuscript. Those comments are all valuable and very helpful for revising and improving our paper, as well as the important guiding significance to our researches. Based on these comments and suggestions, we have made careful modifications on the original manuscript. Main revised portion are marked in red in the paper. Below you will find our responses to the reviewers' comments.

We hope that these revisions are satisfactory and that the revised version will be acceptable for publication.

Thank you very much for your work concerning our paper.

Sincerely yours,

Yong-Min Li

Answer to Reviewers :

Authors are thankful to the reviewers. Their comments will definitely help to improve the quality of the manuscript.

Below are the answers to each reviewer.

List of Revisions Made to Manuscript No. 45961

Reviewer's code: 02702057

Comment: I read this manuscript entitled “Freeze dried Si-Ni-San powder can ameliorates high-fat diet induced NAFLD” that deals with an important issue of medical liver biology. The primary purpose of this study was to investigated the effects of Si-Ni-San freeze-dried powder on high-fat diet induced NAFLD in mice. The authors concluded that the beneficial effects of Si-Ni-San freeze-dried powder on high-fat diet induced NAFLD in mice may be associated with its anti-inflammatory and changing intestinal microbiota effects. Manuscript's content is interesting and well written, scope is sufficient and concisely expressed, format is appropriate. The paper is original and innovative. However, there are some minor and concerns that should be resolved before recommend publication. Please reformulate the introduction section, it is poor and misses in important and fundamental details. It must be improved and updated. The authors should go deeper into different and relevant aspects of Fatty liver disease. I recommend checking the following interesting and fundamental papers and comment them in relation to the study topic: Early effects of high-fat diet, extra-virgin olive oil and vitamin D in a sedentary rat model of non-alcoholic fatty liver disease. *Histol Histopathol.* 2018 Nov;33(11):1201-1213. doi: 10.14670/HH-18-008. Epub 2018 Jun 1. PubMed PMID: 29855033. Echocardiography and NAFLD (non-alcoholic fatty liver disease). *Int J Cardiol.* 2016 Oct 15;221:275-9. doi: 10.1016/j.ijcard.2016.06.180. Epub 2016 Jun 29. PubMed PMID: 27404689. Fatty liver disease and lifestyle in youngsters: diet, food intake frequency, exercise, sleep shortage and fashion. *Liver Int.* 2016 Mar;36(3):427-33. doi: 10.1111/liv.12957. Epub 2015 Sep 28. PubMed PMID: 26346413. 4Ps medicine of the

fatty liver: the research model of predictive, preventive, personalized and participatory medicine-recommendations for facing obesity, fatty liver and fibrosis epidemics. EPMA J. 2014 Dec 7;5(1):21. doi: 10.1186/1878-5085-5-21. eCollection 2014. Review. PubMed PMID: 25937854; PubMed Central PMCID: PMC4417534. Please strengthen and improve the conclusion, adding the clinical relevance of your work and some important suggestions for the scientific community. Please add also consideration/limits of your study Please refresh and update the reference list section.

Response: Thank you very much for your suggestions. Based on your valuable suggestions, we have revised our manuscript as follows.

(1) To improve introduction section, we have added following sentences to go deeper into different and relevant aspects of fatty liver disease.

“Nonalcoholic fatty liver disease (NAFLD) is a condition of excess fat accumulation in the liver without significant alcohol consumption, and it consists of liver damage, ranging from steatosis to steatohepatitis, advanced fibrosis and cirrhosis. Obesity, hypertriglyceridemia, hyperglycemia, and type 2 diabetes are the best-known risk factors for NAFLD^[1,2]. Besides these risk factors, plus-size clothing fashion and sleep shortage may also be associated with NAFLD^[3].”

(Page5 line 2 to line 7)

(2) The papers you recommended are valuable for us, and we have cited one of them in introduction section and refresh the reference list section.

3 **Trovato FM**, Martines GF, Brischetto D, Catalano D, Musumeci G, Trovato GM. Fatty liver disease and lifestyle in youngsters: diet, food intake frequency, exercise, sleep shortage and fashion. *Liver Int* 2016; 36: 427-433 [PMID: 26346413 DOI: 10.1111/liv.12957].

(3) To strengthen and improve the conclusion, we have added following

sentences in our manuscript.

“We provide the basis for clinical use of Si-Ni-San freeze-dried powder and some underlying mechanisms of its action. Although more in-depth research is needed in the future, Si-Ni-San freeze-dried powder may also be a clinical option for NAFLD treatment.”

(Page14 line 28 to line 30 page 15 line1)

Reviewer’s code: 03478516

Comment: Dealing with the pandemic of obesity the link of the metabolic syndrome with HCC, via NAFLD, is clearly reported in the following article, i.e., Could metabolic syndrome lead to hepatocarcinoma via non-alcoholic fatty liver disease? World J Gastroenterol. 2014 Jul 28;20(28):9217-28. Not all the reports clearly emphasise the role of gut flora modifiers as evident in.....Systematic review on intervention with prebiotics/probiotics in patients with obesity-related nonalcoholic fatty liver disease. Future Microbiol. 2015;10(5):889-902. Authors repeatedly refer to IL-6, but they should present data on the serum level of this cytokine. In case of lack of availability of these data, Authors should put this aspect as limitation to study. Authors are kindly requested to present their data as mean plus/minus SD and not SEM, because readers are interested in the dispersion of values and not to the precision of the mean, due to the paucity of observation for each group (8). Authors are recommended to strictly follow these advices.

Response: We are very appreciated for your comment. Based on your valuable suggestions, we have revised our manuscript as follows.

(1) The papers you recommended are valuable for us, and we have cited one of them in introduction section.

9 **Scalera A, Tarantino G.** Could metabolic syndrome lead to hepatocarcinoma

via non-alcoholic fatty liver disease? *World J Gastroenterol* 2014; 28; 20: 9217-9228
[PMID: 25071314 DOI: 10.3748/wjg.v20.i28.9217]

(2) Because lack of the data of IL-6, we have listed this aspect as a limitation of our study.

“Fourth, the change in some cytokines, such as IL-1 and IL-6, was not detected in the present study.”

(Page14 line 20 to line 22)

(3) We present our data as mean \pm SD to replace mean \pm SEM.