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ANSWERING REVIEWERS

Name of journal: World Journal of Gastroenterology

Manuscript NO: 54060

Title: Natural products that target macrophages in treating non-alcoholic steatohepatitis

Reviewer's code: 02861277
Position: Editorial Board
Academic degree: MSc, PhD
Professional title: Academic Fellow, Doctor, Postdoctoral Fellow, Senior Postdoctoral Fellow
Reviewer's country: Italy
Author's country: China

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Reviewer chosen by: Jin-Zhou Tang
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Reviewer performed review: 2020-01-16 10:11
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SPECIFIC COMMENTS TO AUTHORS

In the manuscript titled "Natural products that target macrophages in treating non-alcoholic steatohepatitis", the authors provided an overview about the role of macrophages in the pathogenesis of NAFLD/NASH together with the effect of several natural compounds on their recruitment, polarization and metabolic status. The topic reviewed by the authors is extremely interesting taking into account the urgent need to set a validated therapeutic approach for NAFLD/NASH. Comments Macrophages (and in general innate immunity) have a prominent role in the pathogenesis of

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NAFLD/NASH. However, macrophages act also as antigen-presenting cells (APCs) mediating the stimulation of T lymphocytes that, in their turn, mediate the activation/polarization of macrophages. Recently, the adaptive immune responses have been recognized as a key player in NAFLD/NASH progression. Based on these premises, I think that the role of adaptive immunity should be mentioned (giving some hints in the introduction) to provide to the readers an overall picture of inflammatory responses in the pathogenesis of NAFLD/NASH. Moreover, I think that the authors should give some comments about the several natural compounds to which they refer. The authors should reply to some questions related to those products such as: which are the more promising on the base of the experimental results? Which is the most studied (if any)? Which are the missing point in this research field? Which are the critical issues (if any) related to the use of those compounds? Are there human studies for some products (e.g. curcumin)? To my opinion, the reply to these questions will give much more appeal to the manuscript. Moreover, I think that the authors should give some comments about the several natural compounds to which they refer. The authors should reply to some questions related to those products such as: which are the more promising on the base of the experimental results? Which is the most studied (if any)? Which are the missing point in this research field? Which are the critical issues (if any) related to the use of those compounds? Are there human studies for some products (e.g. curcumin)? To my opinion, the reply to these questions will give much more appeal to the manuscript.

Re: We appreciate the reviewer's comments and suggestions.

Macrophages are innate immune cells, but also modulate adaptive immunity through T/B lymphocytes. We added the related discussion in "INTRODUCTION" section, 2nd paragraph:" Macrophages are versatile innate immune cells. As scavengers, they engulf worn-out cells and debris. As secretory cells, they produce a wide array of powerful

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chemical substances, such as enzymes, complement proteins. In addition, macrophages can present antigens, and along with dendritic cells to initiate adaptive immune response...”; 3rd paragraph:” In addition, high titers of immunoglobulin G exist in 40% adult NAFLD/NASH patients, 60% pediatric NASH patients, and in diet-induced NASH animals, suggesting that adaptive immune responses also take active part in NASH development...”

As for the suggestion for giving comments on related natural compounds, we provided the information in “SUMMARY AND PERSPECTIVES” section, the inserted paragraph:” There are plenty of reports about natural products in treating liver-related diseases, and on the base of the available experimental results, curcumin, berberine, flavonoids, sparstolonin B, baicalin, emodin are among the most promising agents in NASH treatment. Actually, several natural products are already under clinical investigation. Curcumin is currently in phase II/III clinical trials, expecting to improve liver steatosis, fibrosis and liver inflammatory mediators in NAFLD patients. Administration of berberine plus lifestyle intervention has been proven to reduce body weight, hepatic fat content, serum lipid profiles, improve insulin sensitivity, and increase brown adipose tissue mass in NAFLD patients.”; and we also discussed the issue in the last paragraph:”… The variance of patient choice and adherence, dosing methods, as well as test cycle may cause inconclusive results, and large-scale, multicenter random control trials are needed. In addition, many natural products show low bioavailability, strategies in promoting drug utilization or improving dosage form (nano-particle, biological vector) need to develop…”.

We rechecked the manuscript, and highlighted the revision.