

20 January 2024

Dear Editor and Reviewer,

Thank you for reviewing our manuscript. Please find enclosed the revised version of our manuscript entitled “Impact of Microplastics and Nanoplastics on Liver Health: Current Understanding and Future Research Directions”. We feel that all the comments are very helpful in improving the legibility, objectivity, and scientific evaluation of the manuscript.

In the revised manuscript, in accordance with the valuable suggestions of the reviewers, we have made various modifications. All the revised parts are highlighted in red with Microsoft Word “Track Changes” function. The answers made are detailed, point-by-point, in a letter to the reviewer.

We hope that the revised manuscript will retain your attention, and that you will judge the revised manuscript to be suitable for publication in *WJG*.

Thank you.

Yours truly,
Tzung-Hai Yen

Reviewer #1:

Specific Comments to Authors:

The novel content is a serious but neglected problem facing mankind at present. I think the direction of analysis and elaboration chosen by the paper is also reasonable. However, I think it is still necessary for the author to add the following. 1. The theory of multiple blows is currently a recognized pathogenesis of MAFLD, and I think the author should elaborate it in the manuscript and link it with the pathogenesis of MPs. I think it can be derived from the inflammatory (activating macrophages -- pro-inflammatory cytokines ---- reactive oxygen species/oxidative stress) 2. The author mentions that intestinal flora is affected, and I think the literature should be supplemented to further clarify the effects of MPs on the diversity of intestinal flora and the abundance of some specific bacteria from the published articles 3. The section "Inflammation", I think, should be further specified as kupffer cells in the liver (macrophages in the liver) and look for the effect of MPs on the activation of kupffer cells. In addition, the activation of macrophages in the liver will affect lipid metabolism, activate the oxidation of free fatty acids, and then produce excess ROS, resulting in liver damage. This point should be reflected in the article. This is a very good research direction, because the research is a serious problem at present. We believe that "long-term uncontrolled inflammation" is the main cause of tumor induction. So I think this paper is very meaningful, but the author should elaborate on the above content in depth to provide guidance for other scholars' research.

Response:

Thank you for your constructive feedback on our manuscript. Below is our point-by-point response to your valuable comments:

1. The theory of multiple blows is currently a recognized pathogenesis of MAFLD, and I think the author should elaborate it in the manuscript and link it with the pathogenesis of MPs. I think it can be derived from the inflammatory (activating macrophages -- pro-inflammatory cytokines ---- reactive oxygen species/oxidative stress).

We sincerely appreciate your insight into the theory of multiple blows as a recognized pathogenesis of MAFLD. We agree with your suggestion and have incorporated a comprehensive elaboration of this theory in our manuscript. We have also highlighted the interconnected processes involving the activation of macrophages, pro-inflammatory cytokines, and reactive oxygen species/oxidative stress in the article. Please refer to page 6-7, line 87-112 of the revised manuscript.

2. The author mentions that intestinal flora is affected, and I think the literature should be supplemented to further clarify the effects of MPs on the diversity of intestinal flora and the abundance of some specific bacteria from the published articles.

Thank you for your thoughtful suggestion regarding the need for additional literature to clarify the effects of MPs on the diversity of intestinal flora and the abundance of specific bacteria. We did a thorough review of relevant published articles to supplement this section. Please refer to page 11, line 181-188 of the revised manuscript.

3. The section "Inflammation", I think, should be further specified as kupffer cells in the liver (macrophages in the liver) and look for the effect of MPs on the activation of kupffer cells. In addition, the activation of macrophages in the liver will affect lipid metabolism, activate the oxidation of free fatty acids, and then produce excess ROS, resulting in liver damage. This point should be reflected in the article

We appreciate your recommendation to further specify the "Inflammation" section, particularly with a focus on Kupffer cells in the liver. This crucial point is appropriately reflected and emphasized in the revised article. Please refer to page 9-10, line 150-154 of the revised manuscript.

Furthermore, we share your belief in the significance of our research direction, especially concerning the role of "long-term uncontrolled inflammation" as a primary cause of tumor induction. Your encouragement motivates us to enhance the depth of our manuscript. Please refer to page 12-13, line 202-210 of the revised manuscript.