Oct. 13th, 2015

Dr. Lian-Sheng Ma
President and Company Editor-in-Chief
Baishideng Publishing Group Inc

Re: Revision of ***World Journal of Gastroenterology***, **ESPS Manuscript NO: 20154:** "**Chemoprevention of obesity-related liver carcinogenesis by using pharmaceutical and nutraceutical agents**"

Dear Dr. Lian-Sheng Ma,

Thank you for your letter dated Aug. 31st, 2015, regarding our manuscript: **ESPS Manuscript NO: 20154**. We are grateful to you and the reviewers for the helpful comments on our manuscript. We have taken all these comments into account and hereby submit a revised version of our paper. We have addressed all the comments by reviewers #00032933, #00182548 and #00004157, as indicated and we hope that the explanations and revisions of our work are satisfactory.

We would like to thank you and the reviewers again for your helpful comments, and hope that the revised manuscript can again be considered for publication in ***World Journal of Gastroenterology***.

Respectfully yours,

Hiroyasu Sakai, M.D., Ph.D.

ESPS Manuscript NO: 20154

Answering reviewers

Thank you for your valuable comments concerning our manuscript entitled, "**Chemoprevention of obesity-related liver carcinogenesis by using pharmaceutical and nutraceutical agents"**. We hereby submit our revised manuscript according to the reviewers' comments. All revised sentences in the new version are explained as listed below, and all changes have been underlined in the main manuscript.

Reviewer #00032933:

Comment No.1. Please give a section to discuss weight reduction as one of the therapeutic policy.

As indicated by reviewer #*00032933*, there are increasing evidences that indicate the beneficial effects of weight reduction in the prevention or treatment of NAFLD/NASH. Therefore, we have added a section in the text, and reviewed this topic by citing recent publications (Page 10, line 25-28 ~ Page 11, line 1-15). We appreciate your valuable comment.

Comment No.2. The authors recommended Green tea catechins (GTCs), Branched-chain amino acids (BCAA) and Acyclic retinoid (ACR) to be potential agents in management of NASH or NASH-related HCC. Please discuss the rational of long-term use with these agents in human.

As demonstrated in the main text, our clinical studies reported that the administration of ACR or BCAA significantly prevented the development of HCC in patients with liver cirrhosis (Page 14, line 17-19) (Page 16, Line 11-26) (Page 18,

line 16-18). Besides, as shown by our experimental studies, these agents have a potential to improve metabolic abnormalities, including insulin resistance and chronic inflammation. In addition, the safety of these agents in human has been demonstrated in recent clinical studies (Page 18, line 12-13) (Page 18, line 17-18). Therefore, we assume that the long-term use of ACR or BCAA might be effective in management of obesity (NASH)-related HCC.

Actually, there are no clinical studies that evaluate the chemopreventive effects of GTCs on obesity-related HCC in humans. However, several clinical studies showed its chemopreventive effects in several human malignancies (Page 13, line 20-28 ~ Page 14, line 1-2). Besides, a potential to improve metabolic abnormalities, as well as the safety of GTCs in human are described in the text (Page 12, line 17-28 ~ Page 13, line 1-19) (Page 18, line 12-13). Based on these evidences described in our manuscript, we believe that the long-term use of GTCs might also be effective in management of obesity (NASH)-related HCC.

Reviewer #00182548:

Comment No.1. As the authors write on the etiology and pathogenesis of obesity, they must mention and explain the role of heredity and the microbiome composition.

As indicated by reviewer #*00182548*, the involvement of either heredity or microbiome composition in the development of obesity-related HCC have been highlighted in recent publications. We have addressed these topics by citing recent publications (Page 9, line 22-28 ~ Page 10, line 1-6) (Page 10, line 8-23). We appreciate your valuable comment.

Comment No.2. I suggest to make small corrections, as: "In this review, we demonstrated the possibility…" –In this review, we highlighted the possibility…; at Conclusions chapter the last sentence is again: "In conclusion…"

We have revised our manuscript according to the reviewer's suggestion (Page 4, line 8) (Page 18, line 4-6) (Page 18, line 25). We appreciate your kind suggestion.

Reviewer #00004157:

Comment No.1, 2. Genetic risk factors play also a major role in the predisposition towards hepatic carcinogenesis in NAFLD, and should be highlighted: this has recently been reviewed by Dongiovanni et al. in this journal. In particular, PNPLA3 I148M variant is a common strong risk factor for HCC in NAFLD and obesity, independently of its effect on predisposition towards progressive fibrosis and cirrhosis (reviewed by Dongiovanni, WJG2013).

As indicated by reviewer #*00004157*, the involvement of genetic risk factors in the development of obesity-related HCC have been highlighted in recent publications. We have addressed this topic by citing recent publications (Page 9, line 22-28 ~ Page 10, line 1-6). We appreciate your valuable comment.

Comment No.3. It should be cited that retinol reduced HCC incidence in a secondary prevention trial in patients with HCC. The cited paper of Muto and the original published in NEJM in 1999 should be highlighted.

As suggested by reviewer #*00004157*, we highlighted the chemopreventive effects of acyclic retinoid for recurrence or secondary HCC after curative treatment by citing indicated publications (Page 16, line 13-20) (Page 18, line 16-17).

Comment No.4. In contrast, there is no experimental demonstration that the other

approaches (GTCs and BCAA) proposed in the manuscript may be effective in humans. This extremely important fact, and the need for larger studies in the field, should be stressed in the manuscript.

As described in our manuscript (Page 14, line 17-19), the long-term oral administration of BCAA was associated with a reduced incidence of HCC in obese cirrhotic patients. That is, this result suggests that BCAA treatment may be effective in humans. In contrast, there are no clinical studies that evaluate the chemopreventive effects of GTCs on obesity-related hepatocarcinogenesis in humans. We discussed these points in the following section (Page 13, line 20-28 ~ Page 14, line 1-2). Beside, we have added a description that indicates the necessity for further investigations in the main text (Page 14, line 1-2) and "Conclusion section" (Page 18, line 28 ~ Page 19, line 1-2).

Comment No.5. A very important mechanism linking obesity to hepatic carcinogenesis that has not been addressed by the authors is senescence of hepatic stellate cells due to obesity-induced gut microbial metabolite, inducing a senescence secretome (Yoshimoto, Nature 2013). This needs to be cited.

As indicated by reviewer #*00004157*, recent publication indicates that the activated hepatic stellate cells due to obesity-induced gut metabolites are associated with the hepatocarcinogenesis via the secretion of various tumor-promoting factors in the liver. We have addressed this topic by citing recent publications (Page 10, line 8-23).

Comment No.6. Minor language editing: e.g. in the core tip, inhibition of hepatic carcinogenesis or HCC development, not HCC;

We have revised our manuscript according to the reviewer's suggestion (Page 4, line 7). We appreciate your kind suggestion.