

## ANSWERING REVIEWERS

Dear Editor,

Thank you for carefully reviewing our manuscript previously titled "*Contribution of the gut microbiota to the manifestation of hepatocellular carcinoma in patients with nonalcoholic steatohepatitis*" for possible publication in the World Journal of Hepatology. We are grateful to you and your reviewers for their constructive critique and valuable insights. We have revised the manuscript and attached point-by-point responses to the reviewers' comments below.

Thank you for your consideration and for further review of our manuscript. Please do not hesitate to contact us with any further questions or recommendations.

Yours Sincerely,

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Reviewer Comments:

***Reviewer #1: Interesting topic, well written***

**Response:**

Thank you for a good evaluation.

Reviewer #2:

***1. I suggest to reedit the Literature Search section as this methodology may not be able***

*to cover the overall cited references (135 references were cited in the main manuscript and only 6 articles were screened based on literature search criteria). Please provide the search strategy adopted for the selection of the publications by reporting the inclusion and exclusion criteria. A flow chart diagram would be helpful.*

**Response:**

Thank you for your insightful comment. We re-edited the Literature search section and provided literature inclusion and exclusion criteria.

A total of 1,730 articles and abstracts met the initial search criteria.

The titles, abstracts, and full papers were reviewed to identify the full text articles focusing on alterations in the gut microbiota in NASH/NAFLD - HCC compared to healthy controls, as well as animal model studies that discuss changes in the gut microbiota in NASH /NAFLD induced HCC (Supplement).

Inclusion criteria were: well-documented full-text articles written in English, presence of the following study groups - NAFLD/NASH with/without cirrhosis, NAFLD/NASH-HCC with/without cirrhosis, control group of healthy subjects.

Exclusion criteria after abstract and full text reviews were: articles written in other languages than English, no presence of NAFLD/NASH - HCC, no evaluation of the NASH / NAFLD - HCC microbiota, and evaluation between groups, no control group, no presence of full article text.

Following a comprehensive review of the current literature, we identified only six publications focusing on the gut microbiota in NASH/NAFLD induced HCC which were fully consistent with the inclusion criteria. Three selected articles were clinical studies, in which the microbiota composition of 86 patients with HCC induced by NAFLD was analyzed among others with NAFLD of different severity (Table 1). The other three publications included animal model studies in which mice with NAFLD and HCC microbiota were analyzed (Table 2).

The other cited articles were used to discuss current knowledge in the field. We provided a literature search flow chart as a supplement.

*2. Based on Literature search section and Figure content, it seems authors only summarized and updated 6 animal and human research in this review, but in fact the paper summarized and reviewed 135 references totally. Please correct/justify this logical coherence.*

**Response:**

Thank you for your observation. To clarify, we chose six well-documented clinical and experimental research on the role of the gut microbiota in the manifestation and promotion of HCC in NASH to emphasize one of the substantial imperfection of the presented research on this theme - absence of control group. The rest of the articles cited were reviews of the reviews of the literature and research, which we used to discuss current knowledge in the field. We point this out in the abstract and introduction. "In this review, we have evaluated well-documented clinical and experimental research on the role of the gut microbiota in the manifestation and promotion of HCC in NASH. Furthermore, a literature review of microbiota alterations and consequences of dysbiosis for the promotion of NASH-induced HCC and the advantages and limitations of the microbiota as an early marker of the diagnosis of HCC was carried out."

*3. Too many "et al"s were used in the main context, it affects the readability of the overall manuscript (For example, the sentence: "For instance, in Behary et al., Ponziani et al. and Loomba et al.'s studies, Bacteroidetes increased in advance NASH [51], while Sydor et al.'s and Mouzaki et al.'s studies showed that NASH patients possessed a lower abundance of Bacteroidetes[14, 69]" at page 13 Paragraph 1). Please adjust and reedit the manuscript following WJG manuscript style. Also, I suggest to provide more details about those studies reported.*

**Response:**

We are sorry for this inconvenience. We now edited and minimized the amount of et al's. The details of these studies are provided in the accompanying tables.

*4. Please use correctly if authors prefer to use "et al." style (at page 5 paragraph 2: Moreover, Huang DQ et al. forecasted the increase ..... ). Please, check and harmonize along the manuscript.*

**Response:**

We harmonized the style of "et al." along the manuscript and minimized the use of it.

*5. The sections "NASH-INDUCED HCC PATHOGENESIS ASSOCIATIONS WITH GUT MICROBIOTA" and "MECHANISMS OF MICROBIOTA CONTRIBUTION TO THE PERSISTENT LIVER INFLAMMATION AND HEPATOCARCINOGENESIS" are too long and redundant. I suggest to draw a summary graph and interpret it shortly.*

**Response:**

We have shortened the paragraphs.

*6. The manuscript writing needs to be improved with the proper structure following journal formatting requirements. Too many paragraphs with lack of logical order and transitions.*

**Response:**

Thank you for the comment. We edited the structure and improved the article.

*7. GENOTOXICITY section can be integrated with other sections as it conveyed little information relating to the manuscript's main theme.*

**Response:**

We agree with your comment. Therefore, we deleted this paragraph.

*Science Editor: A very detailed manuscript, which conducted a detailed clinical and experimental study on the role of intestinal microbiota in the performance and promotion of HCC in NASH. The innovation and urgency of the manuscript are not very high. The content of the manuscript is too much for mini review. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the peer-review/publication process, please revise your reference list accordingly.*

*Language Quality: Grade B (Minor language polishing)*

**Response:**

Thank You for your comments. We have shortened the manuscript and the reference list. We also resolved an accompanying issue with repeated references from the same journal.

Additional language polishing was performed.