

Dear Editor,

Thank you very much for your letter and the reviewer's comments on our research article manuscript entitled "**Role of gut microbiota via the gut-liver-brain axis in digestive diseases**" (ID: 58113). These comments are all valuable and very helpful to revise and improve our manuscript. After carefully considered these comments, we have made corrections on the previous manuscript. We hope this revision meets your and reviewer's requests. The revised portions are marked in red in the paper. Our point-by-point responses to the reviewer's and Science Editor's comments are listed below.

#### **Responds to Reviewer's Comments:**

##### **Reviewer :**

**Comment 1:** I think that the focus should be modified, because which is really important is the gut-liver-brain axis. In most cases organ dysfunction is linked to a dysbiotic gut microbiota and to harmful microbial by-products, such as ammonia, short chain fatty acids, secondary bile acids and different endotoxins. Increased concentrations of these toxic metabolites together with the inability of the diseased liver to clear such products is thought to play an important patho-ethiological role. Therefore, I suggest the manuscript to be modified considering this three-components axis. The gut-liver axis has been recently reviewed in an interesting paper by Milosevic et al (Int J Mol Sci 2019). Additionally, there are some gastrointestinal pathologies that are lacking and should be included in the review.

**Response 1:** We thank the reviewer for this valuable suggestion. We have studied these comments and tried our best to revise the manuscript accordingly. Some lack of gastrointestinal pathologies have been included in the review. (References 20, 21 and 22)

**Comment 2:**I suggest to add a section on NASH/NAFL and discuss all the above mentioned aspects and their impact in future therapeutic strategies. Another condition that should be analyzed in a section separated from alcoholic liver disease is cirrhosis, which has a multifactorial origin, and its complications, such as hepatic encephalopathy. See to this respect the reviews by Mancini et al (Food Funct 2018) (this one is already cited in the manuscript) and Campion et al (World J Hepatol 2019) or articles on the beneficial effects of rifaximin (i.e. Kaji et al. Antibiotics 2020). A section covering those aspects also need to be added.

**Response 2:** We thank the reviewer for this helpful suggestion. According to the reviewer's suggestion, we have added two sections, one is non-alcoholic fatty liver disease, the other is cirrhosis and hepatic encephalopathy. The potential mechanism involving the gut-liver-brain axis and its treatment of these diseases have been mentioned.

**Comment 3:**Figure 1 should be modified to include liver-brain interactions and lacking microbial by-products need to be added.

**Response 3:**We thank the reviewer for this valuable suggestion. In Figure 1, we have added liver-brain interactions and microbial by-products such as ammonia, short-chain fatty acids and tryptophan.

**Comment 4:**Table 1 requires lacking information on the treated-diseases to be added, Authors should also reconsider if all the mentioned treatment really involve the gut-brain axis. Change the title of the article to include liver in the axis.

**Response 4:**We thank the reviewer for this helpful suggestion. Table 1 has added treatment disease information, and treatments that do not involve the

gut-liver-brain axis have been deleted. Also the title of the article has been changed.

**Responds to Science Editor Comments:**

**Comment 1:** Summary of the Peer-Review Report: This is a cutting-edge and hot topic because of the high prevalence of liver diseases. The paper is generally well written. However, the reviewer thinks the focus should be modified, because which is really important is the gut-liver-brain axis. Figure 1 should be modified to include liver-brain interactions and lacking microbial by-products need to be added. Change the title of the article to include liver in the axis. The questions raised by the reviewers should be answered;

**Response 1:** Thank you very much for your notice. We have carefully addressed to the reviewer's comments point-by-point.

**Comment 2:** I found no "Author contribution" section. Please provide the author contributions.

**Response 2:** We have added author contributions (page 30).

**Comment 3:** I found the authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s)

**Response 3:** We have uploaded the funding agency copy of approval document(s) on the above demand.

**Comment 4:** I found the authors did not provide the original figures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor.

**Response 4:** We have uploaded the original figure documents.

Thanks again for spending your valuable time to help us revise the review manuscript.

Best regards,

Dr. Xie Rui, MD, PhD  
Zunyi Medical University