



PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 58113

Title: Role of gut microbiota *via* the gut-liver-brain axis in digestive diseases

Reviewer's code: 00009919

Position: Peer Reviewer

Academic degree: MD

Professional title: Professor

Reviewer's Country/Territory: Spain

Author's Country/Territory: China

Manuscript submission date: 2020-07-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2020-07-08 10:51

Reviewer performed review: 2020-07-10 12:36

Review time: 2 Days and 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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SPECIFIC COMMENTS TO AUTHORS

This is a cutting-edge and hot topic because of the high prevalence of liver diseases. Gut microbiota makes an important contribution and new strategies to modulate intestinal microbial composition of the host are emerging as potential therapeutic approaches. The manuscript provides information on the role of the gut microbiota on the irritable bowel syndrome, inflammatory bowel disease and functional dyspepsia, focusing on the potential mechanisms involved in gut-brain axis and their contribution to the treatment of those conditions. The paper is generally well written. However, 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. Thus, last year it was reported that neurobehavioral dysfunction in non-alcoholic steatohepatitis (NASH) is associated with hyperammonemia, gut dysbiosis, and metabolic and functional brain regional deficits (Higarza et al, Plos One 2019). Levels of short-chain fatty acids are increased in NASH and non-alcoholic fatty liver disease (NAFLD) (i.e. Porras et al. Free Radical Biol Med 2017) and this could contribute to inflammatory modulation and emotional processing and behaviors. Dysbiotic gut microbiota is also a source of secondary bile acids and changes in the network involving gut microbiota, circulating bile acids, and hepatic metabolism genes (Petrov et al, Mol Nutr Food Res 2019), contribute to metabolic endotoxemia and behavioral changes. The



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microbiota gut-liver-brain axis. Gut microbiota has also been reported to play a role in the neuroendocrine regulation of lipid metabolism (Wang et al. *Microorganisms* 2020). 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. Specific comments: Figure 1 should be modified to include liver-brain interactions and lacking microbial by-products need to be added. 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.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Reviewer's Country/Territory: Spain

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Reviewer chosen by: Pan Huang

Reviewer accepted review: 2020-09-04 09:24

Reviewer performed review: 2020-09-04 10:15

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

My previous comments have been reasonably answered. ONLY some minor changes



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would be required: 1) Language/formal mistakes should be corrected. i.e.: - Page 13 line 7. ③FMT?? - Page 21 section5. Should be "Polyphenols instead of "Polyphenol" - Final list of references. Only first word in title of articles should be a capital letter (see 151, 155 and others) 2) Page 20 section 3. In addition to effects found in ref. 119, other changes induced by FMT in HFD-mice have been reported (Porrás et al. Mol Nutr 2019). This should be cited.