



University of Nevada, Reno  
School of Medicine

March 17, 2021

ID: 02461118

Dear Editor,

We are resubmitting our review manuscript entitled "**Pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19**" by Jin, *et. al.* for your consideration for publication in *World Journal of Gastroenterology*.

We appreciate the reviewer and editor for their additional comments and suggestions to improve this manuscript. We revised the manuscript as per the comments and suggestions.

Please address all correspondence concerning this manuscript to me.  
Thank you very much for your consideration!

Sincerely,

A handwritten signature in black ink that reads 'Seungil Ro' with a stylized flourish at the end.

**Seungil Ro, Ph.D.**

*Associate Professor of Physiology and Cell Biology*  
University of Nevada, Reno School of Medicine

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Accept (General priority)

**Specific Comments to Authors:** COVID 19 emerges from Wuhan of China and is persistently spreading and reached almost every continent of the world. Most infected people will develop mild to moderate illness and recover without hospitalization. However, COVID-19 affects different people in different ways. In addition to respiratory symptoms, gastrointestinal (GI) symptoms have been widely observed in COVID 19 patients.

The authors of the submitted manuscript have summarized the GI symptoms and recapitulated potential mechanisms (impaired barrier function, gut inflammation, altered serotonin metabolism and gut microbiota dysbiosis) in COVID-19 patients. However, what's the different between your manuscript and the others (Ye et al. The mechanism and treatment of gastrointestinal symptoms in patients with COVID-19. Zhang et al. Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19; Gastrointestinal symptoms, pathophysiology, and treatment in COVID-19;)

**Response:** We appreciate the reviewer for the comment. We acknowledge that our paper and the two papers mentioned (Ye et al., Zhang et al.) include similar statistical numbers and expected pathophysiological mechanisms of gastrointestinal symptoms in COVID-19 patients. However, we would like to mention that there are two major differences compared to the two papers in providing the pathophysiological mechanisms. First, we clarified that serotonin metabolism may be a key pathophysiological mechanism in a subset of COVID-19 patients. Elevated serotonin levels in COVID-19 patients can directly cause diarrhea or intestinal inflammation, leading to GI symptoms. Second, we noted that persistent GI dysfunction caused by post-inflammatory functional GI disorders might also be present in COVID-19 patients. Additional information on this has been added to the conclusion (see changes marked with blue) in the revised manuscript.

*"To the best of our knowledge we are the first to propose altered serotonin metabolism in the pathogenesis of COVID-19 with diarrhea. This novel insight of serotonin metabolism might be a key player underpinning GI symptoms and severity in COVID-19 patients as altered serotonin signaling modulates the majority of pathological mechanisms in patients with FGIDs. Therapeutic modalities regulating serotonin signaling might offer potential treatment options in a subset of COVID-19 patients. Furthermore, we highlighted the important concept that there are post-SARS-CoV-2-FGIDs, which warrants future studies to dissect persistent GI symptoms after the clearance of SARS-CoV-2."*

#### LANGUAGE QUALITY

Please resolve all language issues in the manuscript based on the peer review report. Please be sure to have a native-English speaker edit the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, format, and general readability, so that the manuscript's language will meet our direct publishing needs.

**Response:** We have revised the manuscript to resolve all language issues. A native-English speaker, one of the co-authors of this review manuscript edited the manuscript for grammar, sentence structure, word usage, spelling, capitalization, punctuation, formatting, and general readability.

#### 5 EDITORIAL OFFICE'S COMMENTS

Authors must revise the manuscript according to the Editorial Office's comments and suggestions, which are listed below:

(1) Science editor:

1. Scientific quality: The manuscript describes a review of the pathophysiological mechanisms underlying gastrointestinal symptoms in patients with COVID-19. The topic is within the scope of the WJG. (1) Classification: Grade B; (2) Summary of the Peer-Review Report: The authors of the submitted manuscript have summarized the GI symptoms and recapitulated potential mechanisms in COVID-19 patients. However, what's the different between your manuscript and

the others. The question raised by the reviewer should be answered; and (3) Format: There is 1 table and 1 figure. (4) References: A total of 80 references are cited, including 63 references published in the last 3 years; (5) Self-cited references: There are no self-cited references; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately.

2 Language evaluation: Classification: Grade B.

3 Academic norms and rules: No academic misconduct was found in the Bing search.

4 Supplementary comments: This is an invited manuscript. No financial support was obtained for the study. The topic has not previously been published in the WJG.

**Response:** We appreciate the editor for the comments. We have revised the manuscript as per the peer-review report suggestions. We have appended all the formatting as per the journal style.

5 Issues raised:

(1) The "Author Contributions" section is missing. Please provide the author contributions;

**Response:** We have added the "Author Contributions" section in the revised manuscript.

(2) The authors did not provide original pictures. 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:** We have provided original figures in the revised submission. We have also stated that the figure is created using BioRender software. The arrows and text portions were created in PowerPoint so that the editor can make any necessary changes; however, only the overall size of the images can be adjusted and individual adjustments will not be possible because they were generated using BioRender.

(3) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

**Response:** We have revised the references throughout the revised manuscript as per the journal style recommendation.

(4) The column should be minireviews; and (5) Please obtain permission for the use of picture(s). If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200 ×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable. 6 Recommendation: Conditional acceptance.

**Response:** We agree with the editor and we have changed the column to minireviews. In this manuscript, we did not use a figure published elsewhere or that is copyrighted.