

Dear editor,

We deeply appreciate all the comments made by the editors and reviewers. We revised the manuscript very carefully according to the comments as following:

1. The certificate of the funding agency for the grant has been provided.
2. We provided the original editable figures in PowerPoint format.
3. We have not used any copyrighted figures.

We thank once again for the attention and comments from the editors and reviewers to improve our manuscript.

We are looking forward to your kind reply.

Sincerely yours,

Balasubramaniyan Vairappan

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Answering reviewers

Name of Journal: *World Journal of Clinical Cases*

Manuscript NO: 68058

Title: Role of Zonula Occludens in gastrointestinal and liver cancer

Author: Amit Kumar Ram, Balasubramaniyan Vairappan

We would like to thank the reviewers for their fruitful comments to improve our manuscript further. The point-by-point replies to all the comments raised by the reviewers are given below.

Response to Reviewer #1:

S. No.	Comments	Response
1	The review covers most pertinent aspects of the ZO proteins in cell proliferation and their expression in (GI) cancer and HCC. However, the section of “THERAPEUTIC APPROACH TARGETING ZO PROTEINS FOR PREVENTION OF GASTROINTESTINAL CANCER AND HCC” appears to be underdeveloped. More relevant	We deeply appreciate and thank the reviewer for this suggestion. As per the suggestion of the reviewer the section of “THERAPEUTIC APPROACH TARGETING ZO PROTEINS FOR PREVENTION OF GASTROINTESTINAL CANCER AND HCC” has been revised and elaborated in our revised manuscript.

	<p>information should be presented. A published review on this subject could be cited and could help expand this topic (Zeisel M B, Dhawan P, Baumert T F. Tight junction proteins in gastrointestinal and liver disease. Gut. 2019, 68(3): 547–561. doi:10.1136/gutjnl-2018-316906.).</p>	<p>We have also cited the reference “Zeisel M B, Dhawan P, Baumert T F. Tight junction proteins in gastrointestinal and liver disease. Gut. 2019, 68(3): 547–561. doi:10.1136/gutjnl-2018-316906” Ref. #7 as suggested.</p>
2	<p>The authors discuss many studies about expression of ZO proteins in (GI) cancer or HCC. However, too many examples are listed, it would be useful to summarize them and reorganize. For example, The authors list the relationship between ZO proteins expression and tumor cell differentiation, liver metastasis, high tumor grade, poor outcome, its expression in Caco-2 and T84 cell lines, intestinal permeability in one section. I suggest that the authors should reorganize them again.</p>	<p>As per suggestion, we have summarized and reorganized the section about the expression of ZO proteins in (GI) cancer or HCC in our revised manuscript.</p>
3	<p>The authors claim that further studies are needed to develop inhibitors or peptide modulators to examine the</p>	<p>We thank the reviewer for this comment. As ZO proteins have a dual function, one in maintaining the intact epithelial and</p>

	<p>specific regulation of the PDZ domain of ZO proteins which can be implemented for cancer therapy, and cerebral ischemia brain injury model is list here. Does ZO proteins function the same in cerebral ischemia brain injury and cancer therapy? Other parts also have similar problems, please check.</p>	<p>endothelial cells and the other in the signal transduction. In the brain it forms a blood-brain barrier and prevents cerebral injury while in epithelial cells it maintains cell polarity and keeps it intact, thus preventing epithelial to mesenchymal transition of the cell which is a hallmark feature of cancerous cells.</p> <p>We have included other examples of inhibitors or peptide modulators targeting PDZ domain in cancer (Pancreatic cancer and Breast cancer) conditions in our revised manuscript. Ref. #101 and 102</p>
4	<p>Manuscript could use to be revised for grammatical and spelling errors.</p>	<p>We appreciate the reviewer for the suggestion. The revised manuscript has been proofread and corrected for grammatical and typo errors.</p>