

Dear Editors,

Thank you for the opportunity to submit a revision and for your continued consideration of our manuscript titled "MicroRNAs in Hepatocellular Carcinoma Treatment: Charting the Path Forward." for publication in the World Journal of Gastroenterology.

We are also grateful to the reviewers who have volunteered their time and expertise to provide valuable feedback and suggestions for the improvement of our manuscript. We have made grammatical and format corrections, incorporated most of the suggestions, and made changes according to reviewer feedback. Please see below for our line-by-line response to each comment and we have highlighted relevant changes in a copy of the manuscript itself.

Warm Regards,
The Authors

Reviewer 1:

- 1) While the introduction provides a general understanding of the importance of HCC, it could further emphasize the specific significance of the research to spark reader interest. Consider introducing one or two specific research questions or challenges.

Added sentences on additional research questions and limitations with current knowledge [lines 106-110].

- 2) No figures or illustrations are provided in the manuscript, which may impact reader comprehension of complex concepts. Adding some diagrams or flowcharts would help visualize the author's points.

Thank you for this suggestion. A figure (Table 1) has been added listing examples of specific miRNAs associated with tumor suppression, tumor promotion, and those that may serve dual roles.

- 3) The conclusion section summarizes current knowledge and provides outlook, but it might be too general. Suggest incorporating specific recommendations or directions in the conclusion to stimulate further research considerations.

Agreed with this suggestion. Added additional directions and recommendations for future research in the conclusion section. We also addressed some limitations of prior studies and suggested ideas for overcoming these [lines 199-208, 210-216, 222-227].

- 4) When discussing treatment possibilities, the manuscript does not explore other treatment methods or challenges with existing treatments that are relative to miRNA treatment. Including this discussion can make the manuscript more comprehensive.

Thank you for this suggestion and we agree that this would make the article more comprehensive. We added comments regarding the limitations of current treatment modalities as well as thoughts on the relevance of adding miRNA therapy in the introduction section [lines 78-85] and referenced this later in the conclusion [lines 222-227].

- 5) When contemplating the application of miRNA in therapy, the significance of targeted delivery systems cannot be overstated, as they play a crucial role in mitigating potential harm to other organs and tissues. The manuscript additionally addresses and highlights concerns related to targeting precision, toxicity, and the durability of carriers in the sixth and seventh paragraphs under the section titled "Significance of microRNAs." While the manuscript articulates compelling viewpoints, it seems somewhat unprepared for potential counterarguments. Strengthening the manuscript's persuasiveness could be achieved through a more comprehensive examination of potential opposing opinions.

Appreciate this suggestion. Added sentences addressing the concerns regarding exosome therapy as well as options for ameliorating possible risks in their future use [lines 186-195].

Reviewer 2:

1. It is suggested appropriately increase the current clinical application of the interactions between miRNAs and protein in hepatocellular carcinoma.

Added additional areas of clinical application in the conclusion section [lines 222-227, 210-216]. Also added discussion regarding the importance of interactions between miRNAs and other proteins such as lncRNAs and ccRNAs [lines 205-208].

2. Some more information on the limitations and future perspectives of interactions between miRNAs and hepatocellular carcinoma could be mentioned.

Added additional perspectives regarding use of miRNAs with current HCC therapies [lines 222-227] and future directions for miRNA research [lines 202-208, 210-216, 222-227].

3. It is suggested to add a supplementary figure with a graphic abstract which could better clarify the significance of this study.

Thank you for this suggestion. We added a table providing a brief outline of miRNAs associated with HCC as well as their postulated role [line 120].

4. Some important studies regarding the miRNAs in hepatocellular carcinoma. should be cited and discussed. For example, PMID: 37744274, PMID: 37105392, PMID: 35858900.

We appreciate these interesting articles. We have added discussion of these miRNAs [lines 142-146] in the body as well as their interactions with H19 and circGPR37B in the conclusion [lines 205-208].

Revision reviewer

Comment: If feasible, incorporate a graphic abstract in the form of a figure rather than a table to vividly illustrate the significance of this study. Doing so has the potential to elevate the overall impact of the research on the reader.

Response: Thank you for this suggestion in addition to the earlier assistance. Our goal with this manuscript and table was to provide a clinical overview of other microRNAs that are known to be involved with hepatocellular carcinoma. I have attempted creating figures in lieu of the table, but these attempts have resulted in diagrams that are either too technical to clinical readers or too generalizing. Given that some of these microRNAs also have multiple roles, they would also require multiple schematics to fully describe and these types of figures can already be found in some of the cited literature that study specific microRNAs.