

We thank the reviewers and editors for their critical and insightful evaluation of our manuscript. The raised concerns are certainly of major importance, and we have tried to answer them accordingly. We believe the excellent reviewers' suggestions contributed to a much-improved presentation of our findings. Please note, that in addition to a point-by-point response to comments (answered below), we have additionally included minor formatting edits throughout the manuscript.

Comments from the Editors and Reviewers:

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: Dear editor, I appreciate the chance to review the manuscript, which focused on an interesting topic: Repurposing metformin for the treatment of gastrointestinal cancer. I have some questions listed as below.

#1. The part of the mechanism of metformin as an anti-cancer agent is too long. The author should better shorten it.

As suggested, we shortened this review part by taking out the following sentences:

"Metformin restores the multifunctionality of CD8+ TILs by displacing central memory T-cells to effector memory T-cells, providing resistance to re-exposure to the same tumor cells ^[63]."

"Metformin stimulates AMPK, which leads to suppression of the Ras/Raf/ERK/MAPK pathway, resulting in reduced expression of the SNAI family (which is linked to increased HDAC inhibitor recruitment). As a result, driving the hypomethylation of the E-cadherin promoter, which has a crucial role in initiation of epithelial-to-mesenchymal transition (EMT) in any form of cancer ^[71]."

#2. Some clinical trials were mentioned in the manuscript to demonstrate that metformin showed anti-cancer agent. What are the clinical features of these trials, such as inclusion criteria, prospective or retrospective study.

We added a new column detailing this information in tables 1 and 2.

#3. The overall survival is influenced by many factors, such as types of tumours, differentiation of the type, neoplasm staging and treatment. It is difficult to demonstrate that metformin plays roles in it.

We added an entire new session (Perspectives – page 16 and 17) to better discuss this important point:

We also included the following phrase in discussion (Page 18).

"Given that the survival outcomes are affected by a multitude of factors, including type of tumors, differentiation, staging and treatment"

4. If the author could make a meta-analysis for the cohort studies, it may be more convincing.

We are aware that a meta-analysis would be more convincing; however, the present manuscript was previously commissioned by the editor to "describes an opinion review of the repurposing metformin for the treatment of gastrointestinal cancer" as highlighted by the Science editor.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: The authors review the rationale of metformin as a drug repurposed for cancer treatment along with the clinical research about metformin in GI cancers. For me, the review is well-organized and interesting. It provides a comprehensive summarize of clinical research about metformin in GI cancers. However, some concerns should be addressed before acceptance.

#1. There are numerous papers that have focused on the roles of metformin in cancer and GI cancers. The authors should highlight the novelty of this review and provide some new opinion on this field.

#2. The section for outlook or perspective of the metformin in GI cancers is limitetd. Please give more examples in detail.

To better address these points, we included a perspective section (Pages 15 and 16):

We also highlighted some ongoing clinical trials, as following:

Page 11: "Furthermore, there are ongoing trials evaluating the role of metformin in CRC. We highlight, in adjuvant setting, a phase 3 trial (NCT02614339) with high-risk stage II and stage III CRC that aims to evaluate the impact of metformin for 48 months on disease free survival. In refractory CRC setting, there is an interesting phase 2 trial is recruiting patients to explore the combination of the immune checkpoint inhibitors, such as nivolumab and metformin (NCT03800602)."

Page 12: "Unfortunately, there are few clinical trials that are ongoing to analyze this question. An interesting phase 2 randomized trial (NCT04114136) are ongoing to evaluate the synergistic effect of metformin, rosiglitazone and anti-PD-1 on the treatment of refractory solid tumors including GC. Metformin could reduce tumor oxygen consumption creating a less hypoxic T cell environment leading to restore its anti-tumor cell function. The trial NCT04033107 analyze the combination of metformin and vitamin C in DS tumors including GC."

Page 13: "Results of ongoing clinical trials recently completed are expected with substantial interest. NCT01666730 explores overall survival improvement of metformin associated with modified FOLFOX6 in metastatic patients, NCT02005419 evaluates DFS at 1 year with the combination of metformin and gemcitabine in resected subjects and NCT02048384 analyses safety of metformin with or without rapamycin after disease stabilization on first line chemotherapy in metastatic individuals."

#3. The content are well-performed. However, for "3.1 Intrahepatic Cholangiocarcinoma (ICC) and Gallbladder Cancer (GBC)", it may be confusing to express the original meaning.

We reformulated this session to make it clearer, please see the changes in page 15 and 16.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: In this manuscript, the authors aim to reviews the current findings on the anti-cancer mechanisms of metformin and its apparatus from pre-clinical and ongoing studies in gastrointestinal (GI) malignancies. The review article has certain scientific significance and application value. However, there are several concerns for this manuscript is needed for improvement.

#1. I think the word "gastrointestinal tumors" may change into "digestive system tumors".

As suggested, we changed "gastrointestinal tumors" to "digestive system tumors"

#2. The manuscript lack their insights/comments about studies on this field in future. What's their ideas about roles of metformin in development/diagnosis/clinica treatments of gastrointestinal tumors.

#3. The manuscript should provide information about shortage of current studies on metformin and cancers. I am not sure if the authors are doing researches on this field or just write a review about this topic.

To better address these points, we included a perspective section (Pages 16 and 17):

We also highlighted some ongoing clinical trials, as following:

Page 11: "Furthermore, there are ongoing trials evaluating the role of metformin in CRC. We highlight, in adjuvant setting, a phase 3 trial (NCT02614339) with high-risk stage II and stage III CRC that aims to evaluate the impact of metformin for 48 months on disease free survival. In refractory CRC setting, there is an interesting phase 2 trial is recruiting patients to explore the combination of the immune checkpoint inhibitors, such as nivolumab and metformin (NCT03800602)."

Page 12: "Unfortunately, there are few clinical trials that are ongoing to analyze this question. An interesting phase 2 randomized trial (NCT04114136) are ongoing to evaluate the synergistic effect of metformin, rosiglitazone and anti-PD-1 on the treatment of refractory solid tumors including GC. Metformin could reduce tumor oxygen consumption creating a less hypoxic T cell environment leading to restore its anti-tumor cell function. The trial NCT04033107 analyze the combination of metformin and vitamin C in DS tumors including GC."

Page 13: "Results of ongoing clinical trials recently completed are expected with substantial interest. NCT01666730 explores overall survival improvement of metformin associated with modified FOLFOX6 in metastatic patients, NCT02005419 evaluates DFS at 1 year with the combination of metformin and gemcitabine in resected subjects and NCT02048384 analyses safety of metformin with or without rapamycin after disease stabilization on first line chemotherapy in metastatic individuals."

Reviewer #4:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a very excellent review that should be published. Acceptance in WJG is highly recommended.

(1) Science editor:

1 Scientific quality: The manuscript describes a opinion review of the repurposing metformin for the treatment of gastrointestinal cancer. The topic is within the scope of the WJG. (1) Classification: Grade B, Grade A, Grade C and Grade C; (2) Summary of the Peer-Review Report: The authors review the current findings on the anti-cancer mechanisms of metformin and its apparatus from pre-clinical and ongoing studies in gastrointestinal (GI) malignancies. It is well-organized and interesting. However, some questions raised by the reviewers should be answered; and (3) Format: There are 2 tables and 1 figure. A total of 179 references are cited, including 20 references published in the last 3 years. There are 4 self-citations, which are related to this review. 2 Language evaluation: Classification: Grade B, Grade B, Grade A, and Grade B. 3 Academic norms and rules: No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an invited manuscript. The topic has not previously been published in the WJG. 5 Issues raised: (1) The "Author Contributions" section is missing. Please provide the author contributions; (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; and (3) 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 ×).

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 Re-Review: Required. 7 Recommendation: Conditional acceptance.

We added a the "Author Contributions" section and reviewed the text according to reviewers' comments.

(2) Editorial office director:

(3) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.