

February 14th, 2021

Re: Manuscript No. 61946

Dear Editor,

thank you for your letter and the possibility to submit our revised opinion review titled "How far along are we in revealing the connection between metformin and colorectal cancer?" for publication in the World Journal of Gastroenterology.

We have carefully considered the reviewers' comments, and have revised the manuscript accordingly. The changes are marked in **red** in the revised version of the manuscript. Please find below, the answers to specific reviewers' comments.

*Reviewer #1: First - the interesting comparison of data from various studies, Second - the researchers suggested the role of metformin in the prevention of development of CRC, Third-no randomized trials.*

Thank you for your kind comment.

*Reviewer #2: Overall, this is a well-written article, with the major topics discussed regarding colorectal cancer and metformin use. General: Is there any consideration given to performing a systematic review instead of a scoping review?*

Thank you for the suggestion, but we believe that a short and concise form of opinion review is more suitable for our proposed concept on this subject.

*1. Could the authors provide more scientific evidence regarding the proposed mechanism that metformin reduces the risk of colorectal cancer. The mTOR pathway is mentioned, but more details need to be given regarding specific pathways, and also, to non-basic science readers, they may not understand this significance of the mTOR pathway so it should really be explicitly spelt out.*

We appreciate this valuable suggestion, as mTOR pathway plays a role in coordinating cell growth and proliferation in colorectal carcinogenesis. We have included more detailed and explicit description of the mTOR pathway involvement in CRC carcinogenesis, as well as the potential role of metformin within the pathway.

*2. Would the authors consider some diagrams? I could suggest one to delineate the mechanism.*

Thank you for the suggestion. We have added a diagram simplifying metformin's mode of action to make it clearer to readers.

3. *It would also be good to summarise the papers which discuss metformin as chemoprevention and adjuvant treatment in tables to make it clearer to readers and to break the monotony of paragraphs of words.*

Thank you for the comment, but we prefer not to repeat the same studies in the table as this is a short and concise form.

4. *A lot of focus is given to discussing the good effects of metformin. Are there any side effects? In particular, would you give metformin to patients who are non-diabetics as chemoprevention?*

Thank you for the comment. We have included potential side effects of metformin, and also data on the use of metformin in the chemoprevention of CRC in non-diabetic patients.

We corrected several typos and additionally revised manuscript for grammar and language.

In conclusion, we thank the reviewers for recognizing the presented manuscript as a good scientific effort, as well as for the useful and constructive comments, which made us think more critically about the presentation of our work. We hope that we have improved the consistency, clarity and interpretation of data in the revised manuscript and that the revised manuscript will meet the reviewers' and editors' requirements and be suitable for publication in *World Journal of Gastroenterology*.

Thank you again for the privilege of submitting our work to *World Journal of Gastroenterology*.

Sincerely,

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