

**Cover letter with point-by-point responses to each of the reviewers' comments and a description of the changes made to the manuscript.**

Dear Reviewers,

Thank you for taking the time to provide thoughtful, detailed feedback. We are greatly appreciative of your time and have made the requested revisions. Below you will find your comments and our responses. We reference sections and line numbers for easier reading.

Thank you for your time and consideration,

Authors

**Reviewer' Comments to Authors:**

**Reviewer #1:** Dear authors: This is an very interested and important study. CRC development is of great complexity, and routinely been regarded as the results of adenomas or polyps advancement, while both of them have the complicated genetic background and signal regulations. As regarding the epigenetical mudulation, methylation is the hottest topic. However, what the mechanism of outer methyl donor can influence the methylation remaining uncertain, such as the efficacy of methyl uptake, transportation, and the final involvement in methyl related gene expression. Hence, this review seemingly has not resolved it commprehensively, though you provide the limitation of the research about this point, that is rather another issue. Quality of the manuscript is excellent, though lacking novel findings to extend the view of readers. Based on you work, the results and conclusion may be proper. Future works should strengthen the issues which mentioned above.

We included additional information in the Conclusions section, page 9, lines 7-10: "In any case, this review was not able to clarify which mechanisms underlie the influence of methyl donor nutrients on DNA methylation, as well as the efficacy of methyl uptake, transportation, and the final involvement in methyl-related gene expression".

**Reviewer #2:** Diet is a major factor in the aetiology of colorectal cancer (CRC). Dietary methyl donors might influence DNA methylation during carcinogenesis of CRC. This review attempts to discuss the relationship between the effects of methyl donor intake and polymorphisms. However, it is difficult for this review to explain the interaction between genetic and dietary data. The introduction and discussion sections of the manuscript are verbose due to lack of correlation between studies.

We appreciate the reviewer's comment. We introduced the following sentence in the manuscript: Discussion, page 9, lines 1-2: "Consequently, it is difficult for this review to explain the gene-diet interactions and their effects on the development of CRC."

**Language polishing requirements for revised manuscripts submitted by authors who are non-native speakers of English:** Previously we send a language certificate from a professional English language editing company. The revision process has resulted in a few changes, and the revised manuscript has been reviewed by a native English-speaking expert.

**Abbreviations:** We have removed abbreviations that did not appear at least two times in the text preceding the first usage.

**EDITORIAL OFFICE'S COMMENTS**

**Company editor-in-chief ' Comments to Authors:**

I have reviewed the Peer-Review Report, the full text of the manuscript, the relevant ethics documents, and the English Language Certificate, 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.

- Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file.

Please, find enclosed Figure 1 organized into a single PowerPoint file.

- Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content.

We have reviewed tables 1-5 and have placed them in accordance with the guidelines.

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- Before final acceptance, when revising the manuscript, the author must supplement and improve the highlights of the latest cutting-edge research results, thereby further improving the content of the manuscript. To this end, authors are advised to apply a new tool, the Reference Citation Analysis (RCA). RCA is an artificial intelligence technology-based open multidisciplinary citation analysis database. In it, upon obtaining search results from the keywords entered by the author, "Impact Index Per Article" under "Ranked by" should be selected to find the latest highlight articles, which can then be used to further improve an article under preparation/peer-review/revision. Please visit our RCA database for more information at: <https://www.referencecitationanalysis.com/>.

We applied the RCA tool and found a result: Kim et al. 2022. This article was published in September 2022, but we had located the online version ahead of print and included it in the review, numbered 34. We have updated this reference in the References section.