Manuscript ID: World Journal of Gastroenterology-86246

Response to Editors' and Reviewers' comments

We would like to sincerely thank the reviewers. We are pleased that the reviewers have provided valuable comments and the Editor has given us the opportunity to address these comments and resubmit the revised manuscript for further consideration. Following are the details of the comments and the specific changes that we have made in the revised manuscript.

Editor-in-Chief comments:

I have reviewed the Peer-Review Report, the 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. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them 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. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. 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/.

Response:

We thank the Editor for the comments. We have amended the figures and figure legends accordingly. We have included the figures in a single PowerPoint file and the

updated figure legends in the revised manuscript. We have amended the tables into standard three-line tables and included them in a single file.

We reviewed the latest highlight articles and have added several recent references in the revised manuscript. We also clarified the reference PMID and DOI. We added an "Article Highlights" section to the revised manuscript. We have ensured that our running title is no more than 6 words via word count. Lastly, we have examined the guidelines and format for manuscript revision and have attempted to address all comments carefully in the revised manuscript.

Response to Reviewer 1

Specific Comments to Authors: Probiotics have shown promise in alleviating symptoms of diarrhea-predominant irritable bowel syndrome (IBS-D); however, certainty of evidence is low. Well-powered randomized controlled dose-ranging trials are warranted on promising single-strain candidates. It is not an interesting manuscript. Authors cannot succeed to present their idea in a clear way adding information to the existing literature. What are the original findings of this manuscript? What are the new hypotheses that this study proposed? What are the new findings of this study? What are the new concepts that this study proposes? What are the future directions of the topic described in this manuscript?

We thank the reviewer for the comments. We have attempted to highlight the original findings in the Discussion of the revised manuscript. We believe this study is unique in showing dose-ranging efficacy of a probiotic candidate strain in diarrhea-predominant IBS in a well-powered randomized controlled trial. We have updated the introduction, including additional review of the literature, the need for well-powered studies in IBS-D and proposed hypotheses. We have also added future directions on the study of probiotics for IBS-D in the Discussion. We believe multi-omics studies will play an important role in elucidating mechanisms of action going forward.

Response to Reviewer 2

Specific Comments to Authors: A randomized controlled trial to assess one strain (L. plantarum Lpla33) in two doses versus placebo for the treatment of IBS-D. Well done study that is comprehensively described and nicely written. A few minor comments should be addressed.

1. Introduction, 3rd paragraph. When discussing the results of reference #13 (Wang Y 2022), the authors state "…probiotic strain selection likely a key limitation for single strain studies." Please clarify what you mean by this. Were separate sub-groups of identical strains assessed in Wang 2022 or not? Were there insufficient numbers of studies with the same single strain to analyze? Why is a single strain a limitation?

We thank the reviewer for the comment and agree that strain specificity is of importance when designing and differentiating studies. The Wang et al. meta-analysis differentiated multi and single strain studies but did not report in detail on strain specificity. We have amended the section for clarity and removed the sentence in question. We have also added background by referencing the McFarland et al. meta-analysis that accounted for strain-specificity.

2. In Study design and procedures. Please describe how subjects were recruited? This is often not well described in trials. Was the study advertised? Did physicians enroll patients during clinic visits? Etc.

Thank you for the comment. We have specified how participants were recruited for the study in the Study design and procedures section of the revised manuscript.

3. In Results. Study parameters. Please provide attrition rate.

We have provided the attrition rate in the Study parameters section of the revised manuscript. Over the intervention period, study attrition rates were 5 (4.8%), 2 (1.9%) and 4 (4.0%) for the placebo, *L. plantarum* 1B and *L. plantarum* 10B groups, respectively.

4. In Discussion, 3rd paragraph. Please discuss other important meta-analysis of IBS which assessed 14 different probiotic types (McFarland LV 2021 in Eclin Med). Otherwise, good review of other strains with dose-responses.

Thank you for the suggestion. We have revised the 3rd paragraph of the Discussion. Specifically, we have added the McFarland et al. meta-analysis along with additional discussion pertaining to probiotic strain specific dose-responses for IBS. We have also updated all doses mentioned in the Discussion to scientific units for consistency.

5. References. Reference #14 is not a valid reference, as it is an internal document and not published. Authors should cite this source within the text. Reference #16. Provide a more complete description of this source, Authors? Title? Etc. not just url address. Reference #27. Missing title. Reference #33. Missing authors.

We thank the reviewer for the note. We removed Reference #14 (instead including source within the text) and amended References #16, 27 and 33.

6. Figure 1 and 2. Nicely done. 7. Tables. Clear and well done.

Thank you.