

Faecal microbiota transplantation for the treatment of irritable bowel syndrome: A systematic review and meta-analysis

Point-by-point response to Editor and Reviewers

We would like to thank the editors and the three reviewers for the constructive comments, which we feel have contributed to substantially improve our protocol.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This review combined findings from eight randomised clinical trials that assessed the efficacy of FMT in 465 IBS patients demonstrating no significant difference in the improvement of symptoms in the FMT group compared to the placebo group, the authors did not find evidence to support the use of FMT for IBS patients outside of clinical trials in this systematic review and meta-analysis. There are still some questions: 1. In the review, participants were diagnosed with IBS according to a physician's opinion or accepted symptom-based diagnostic criteria, e.g., Rome III or IV criteria). Whether different diagnose standards and paths have an impact on the results ?

Answer: Thank you for your suggestion. We share the same view on this matter. Most of the patients in the included trials had moderate-to-severe IBS and were diagnosed according to Rome III criteria. The newest Rome IV criteria are more rigorous, and it is not clear whether the consequentially increased homogeneity of IBS study populations will affect the efficacy of FMT.

The diagnosis criteria for the included trials has been described in the results section - study design and setting: "All participants in the trials were diagnosed with IBS by a physician and according to accepted, symptom-based diagnostic criteria (e.g., the Rome criteria)[5]. Participants in the Lahtinen et al[58] trial were diagnosed by a gastroenterologist, Aroniadis et al[59], Halkjær et al[43], Holster et al[61], Holvoet et al[44], Johnsen et al[62] and Singh et al[63] all used the Rome III criteria; El-Salhy et al[60] used the Rome IV criteria."

By exclusively analyzing studies that employ the ROME III criteria and by excluding the investigations conducted by Lahtinen and El-Salhy in the evaluation of treatment efficacy on the primary outcome, no significant difference emerges in the overall findings, which remain non-significant. It is plausible to contend that the most substantial improvement in the Irritable Bowel Syndrome Severity Scoring System (IBS-SSS) occurs in El-Salhy's study after three months. The strict inclusion criteria used in El-Salhy's study, specifically the Rome IV criteria, could account for this finding. However, such an explanation is speculative, and our subgroup analysis indicates that numerous other factors could explain the augmented effect observed in El-Salhy's study.

2. In the review, Eight RCTs (a total of 502 participants) with different FMT types, quantity of FMT given, route of administration, type of donor, frequency of administration participants with IBS classified according to subtype, were included. Whether these factors lack of coherence have an impact on the results of investigating the effectiveness of FMT compared to placebo (including autologous FMT) in IBS ?

Answer: We agree with the reviewer that these factors lack of coherence could have an impact on the results. The most relevant results and Figures regarding subgroup analysis are presented in the result section (Figure 6) and all additional analysis are attached as appendices (Appendices 8-13). In addition, it is discussed in the discussion section: "In general, the results from trials used for this review were characterised by high heterogeneity. Therefore, it is possible that the lack of a positive overall effect is simply the result of how different the trials were from one another. When comparing the trials there were pronounced differences in the selection processes for participants and donors, the route of administration, the transplant quantity, and frequency of administration. These differences make it difficult to draw conclusions regarding FMT as a treatment for IBS." We have added the following marked sentence to the discussion "Despite the subgroup analyses we conducted as part of this review, firm conclusions cannot be drawn due to the small number of events and participants in the trials. Nonetheless, the results do suggest a possible beneficial effect in delivering FMT by endoscopy (colonoscopy or gastroscopy) over other routes. to clarify the most important results."

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (General priority)

Specific Comments to Authors: This manuscript is written in a standardized manner with a clear and appropriate methodology. It is recommended to add investigation of the causes of heterogeneity and sensitivity analysis.

Answer: We appreciate your input and concur that the heterogeneity observed in this review and meta-analysis is noteworthy. We delved into the variations in the study designs and scrutinized their quality, as illustrated in Figure 6 + Appendices 8-13. Our subgroup analysis divulged that the distinct processing and administration methods of fecal microbiota transplant (FMT), including its mode of delivery, may contribute to the observed heterogeneity.

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: The current meta-analysis has the potential, however, there are some issues before publication as follows: 1- It is mentioned that "We exclude trials with quasi-random designs and cluster randomised controlled trials"; it is better to include also these studies and by performing a subgroup analysis only separate RCTs from non-RCTs.

Answer: We concur that such studies hold significant interest. Nevertheless, adhering to good scientific practices, we opted to adhere to the approved protocol to avert any potential bias that may arise from any post-protocol findings. Additionally, the review and meta-analysis were carried out in accordance with the Cochrane Handbook standards, thereby enhancing the credibility, dependability and accuracy of our review and meta-analysis.

2- Subgroup and sensitivity analysis should move before that statistical analysis section.

Answer: We agree with the reviewer and have moved the section as proposed.

3- Data collection and analysis needs citation and you can add the following citations: 10.1093/ptj/pzab144; and also 10.1016/j.joim.2023.01.003

Answer: Thank you for your comment. We have carefully examined the suggested articles, we have found that they do not have a direct connection to the subject matter of our manuscript, as they belong to a different field of research, and have therefore decided not to include them.

Rahmati M, Gondin J, Malakoutinia F. Effects of Neuromuscular Electrical Stimulation on Quadriceps Muscle Strength and Mass in Healthy Young and Older Adults: A Scoping Review. Phys Ther. 2021 Sep 1;101(9):pzab144. doi: 10.1093/ptj/pzab144. PMID: 34106246.

Rahmati M, Molanouri Shamsi M, Woo W, Koyanagi A, Won Lee S, Keon Yon D, Shin JI, Smith L. Effects of physical rehabilitation interventions in COVID-19 patients following discharge from hospital: A systematic review. J Integr Med. 2023 Jan 20:S2095-4964(23)00003-1. doi: 10.1016/j.joim.2023.01.003. Epub ahead of print. PMID: 36717302; PMCID: PMC9851951.

Instead, we have referred to the Cochrane Consumers and Communication Review Group's data and results template (reference 70).

4- Instead of GRADE criteria, Cochrane risk of bias tool should be performed to assess the quality of RCTs. Although, in the method section Cochrane risk of bias tool is mentioned, in the abstract not.

Answer: We have used the Cochrane risk of bias tool to assess the quality of the RCTs. A sentence has been added to the abstract: "The Cochrane risk of bias tool were used to assess the quality of the trials."

5- In statistical section: " Heterogeneity was evaluated based on visual inspection of forest plots, expressing heterogeneity as I² values using the following thresholds: 0% to 40% (unimportant), 40% to 60% (moderate), 60% to 80% (substantial), and >80% (considerable),

and the P value for the chi-squared test.” This needs citation and you can add the following citations: 10.1016/j.physio.2021.04.005

Answer: ref: Thank you for your comment. We have carefully examined the suggested article, we have found that it does not have a direct connection to the subject matter of our manuscript, as it belongs to a different field of research, and have therefore decided not to include it.

Rahmati M, Malakoutinia F. Aerobic, resistance and combined exercise training for patients with amyotrophic lateral sclerosis: a systematic review and meta-analysis. *Physiotherapy*. 2021 Dec;113:12-28. doi: 10.1016/j.physio.2021.04.005. Epub 2021 Apr 27. PMID: 34555670

Instead, we have referred to our published protocol for this review and meta-analysis (reference 66).

6- Data synthesis should be also move before that statistical analysis section.

Answer: We agree with the reviewer and have moved the section as proposed.

(1) Science editor:

The manuscript has been peer-reviewed, and it's ready for the first decision.

Language Quality: Grade A (Priority publishing)

Scientific Quality: Grade B (Very good)

Answer: Thank you very much.

(2) 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. Before final

acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological 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/>.

Answer: Thank you. The Figures are organized into a single PowerPoint file and the tables have been conducted according to your standards. Highlights have been written and added to the final manuscript.