1 Peer-review report

Reviewer #1: Dear Editor-in-chief, The manuscript I had the pleasure to review by Ya-Peng Yang is a review article on the open issues regarding fecal microbiota transplantation. The Authors give a general overview on the available evidence about safety, standardization ed effectiveness evaluation of FMT. Moreover, in this review, the Authors propose a new model based on germ-free mice to assess the safety and the effectiveness of FMT. The content of the paper is certainly of interest and the language in generally good; however, is quite hard to understand the aim of the manuscript. It seems that the authors want to give a clear review of the state-of-art but, at the same time, wants to give a very personal interpretation of the matter. Furthermore, it isn't clear whether Authors did use the presented model or just propose it. Since the structure of the manuscript it's quite confounding to the reader, I would recommend clarifying its aim and structure. If the Authors wants to propose a new animal model for FMT assessment I would recommend modifying the chosen article type (e.g. Field of Vision, Opinion Review, Letter to the Editor). Moreover, I would recommend providing experimental data about the use of the proposed model by the Authors themselves or by other research groups. On the other side, if the Authors prefers focusing on a review article, I would recommend some modifications: • Authors should present how the performed the review of the literature. • The paper should strongly benefit from a summarizing table about presented articles. • I would suggest rephrasing the subtitles. It would be preferable that Authors' personal comments, which are certainly very valuable, should be at the end of the dissertation and not the main topic of the review; otherwise, it would become a 'viewpoint' rather than a 'narrative review'. • I would also suggest expanding the comment about safety since this represent the major ethical issue to consider in future for very needed randomized studies (e.g. PMID: 29592876, 32574415, …).

1. Thanks for the constructive comments, we have modified the manuscript type to "Opinion Review" and clarified the aim and structure of the manuscript.
2. Thanks for the constructive comments, we have supplemented the experimental conclusions of other research groups using the proposed model （PMID: 26060932）.
3. Thanks for the constructive comments, we have modified the manuscript type to "Opinion Review".
4. Thanks for the constructive suggestion, we have expanded the comment about safety as required.

Reviewer #2: The review by Yang et al. aims to review the advantage of germ-free animals as a tool to improve the safety, effectiveness in FMT. The idea is novel, but fails to meet the clinical expectations. Unfortunately, I may need to disagree on

multiple aspects of introduction including safety, standardization. Several international guidelines are available that provide highly standardized protocols on FMT in C. difficile (by the way it call Clostridioides difficile). The experience of the past years clearly shows that with appropriate indication FMT has no issues with acceptability. If performed at high (minimal) quality standards FMT is a safe method. Therefore the great question is if germ free mice would provide any benefit in this regard in particular for CDI. Going through the review, I was not convinced by the scientific discussion and rationale. There are multiple limitations related to xenograft microbiota studies.

1. Thanks for the constructive comments. Several international guidelines are available that provide highly standardized protocols on FMT. However, the causal relationship and mechanism of FMT efficacy need to be clarified, and thus a Germ-free animal disease model is urgently needed to analyze the causal relationship mechanism of FMT efficacy.
2. Thanks for the constructive comments. Recent investigation of doctors, medical students, donors and patients has shown that FMT is less acceptable compared with traditional treatment methods, especially fecal bacterial suspension prepared by the rough method(PMID: 31919742, 24719899, 28569156).
3. Thanks for the constructive comments. With the increase in the strictness of donor screening and the development of clinical technology, the safety of FMT has gradually declined. However, FMT has not been approved as a new drug, which is primarily due to the lack of preclinical safety studies. Our purpose is to dig out the functional bacteria that play a major role in FMT, and develop a safe, controllable, standard, and effective formula of FMT, which therefore needs to be explored on the basis of Germ-free animals.
4. Thanks for the constructive comments. Humanized flora animals (mouses, pigs) have been widely used in experimental exploration (PMID: 26060932, …).

RE-REVIEW:

Dear Editor in Chief, the Authors have addressed all the raised issues. The paper now provides a complete Authors' viewpoint. I believe the publication as an "Opinion Review" is more appropriate.

we are willing to change the manuscript type to "Opinion Review" according to the re-reviewer opinion.

2 Editorial Office's comments

1) Science Editor: The authors have strong opinions on the subject of fecal microbiota transplnatation, and could discuss issues in an "Opinion Review".
Language Quality: Grade C (A great deal of language polishing)
Scientific Quality: Grade D (Fair)

Thanks for the constructive comments, we have revised the manuscript as required to be more rigorous and scientific. And we have modified the manuscript type to "Opinion Review".

2) Editorial Office Director: I recommend the manuscript to be published in the World Journal of Meta-Analysis.

Thanks, we have transferred the manuscript to World Journal of Meta-Analysis.

3) Company Editor-in-Chief: I recommend the manuscript to be published in the World Journal of Meta-Analysis.

Thanks, we have transferred the manuscript to World Journal of Meta-Analysis.