

PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

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Title: Fecal microbiota transplantation for treatment of non-alcoholic fatty liver disease: Mechanism, clinical evidence, and prospect

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

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Reviewer's code: 05462152

Position: Peer Reviewer

Academic degree: MPhil

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

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Reviewer chosen by: AI Technique

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Review time: 4 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Novelty of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No novelty
Creativity or innovation of this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No creativity or innovation

Scientific significance of the conclusion in this manuscript	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Good <input type="checkbox"/> Grade C: Fair <input type="checkbox"/> Grade D: No scientific significance
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous
	Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

SPECIFIC COMMENTS TO AUTHORS

1. In the introduction, the mention of 25% global prevalence should mention that this is for the adult population. I looked back at the reference cited (Powell et al. 2021) and the reference that that article cited (Younossi et al. 2016) because 25% seemed high; both note that this number is prevalence among adults. 2. The following sounded strange; I think the last part of this sentence needs to be revised to say something like "sustain growth": "the population of NAFLD along with advanced liver disease is projected to sustain growing [2]." 3. There should be more references cited in the first paragraph of the subsection titled "Structure and Function of Gut-Liver Axis." For example, please include a reference for the "100 trillion" statistic. Also, in looking at Figure 1, I noticed that there are arrows to indicate increased or decreased signaling and presence of certain cells and bacteria; there should be more references and explanation for these specific mechanisms. This is a fascinating idea as to how FMT-related mechanisms work, but because FMT is still not widely accepted for indications besides *C. difficile* infections (at least here in the United States), I would recommend providing more detail since the underlying mechanisms that lead to the success of FMT for certain diseases are still

unclear. The mechanisms that regulate prevalence of firmicutes and other microbes especially should be noted since changes in microbes are emphasized regarding the effects of FMT. Also, please define TLR; the authors noted FXR but did not give the definition for TLR. 4. I like Figure 1. Visually, this figure looks well-done and is appealing. For publication though, please make this figure bigger as the print is very small in its current size in the Word document. 5. For Figure 1, the left panel in the picture is titled "Health." Please change this to "Healthy" to match the figure legend. 6. This sentence definitely needs references: "These issues have paved the road for FMT application in NAFLD treatment, which may (in theory) be safer than probiotics as it come directly from a healthy gut." I understand probiotics can lead to side effects, but despite being provided over-the-counter (at least in the US), I would not say FMT is safer. The US FDA put a hold on FMT clinical trials several years ago due to studies that used a fecal sample from a "healthy" donor who carried a pathogen that was not tested for in processing and led to the death of two patients (<https://www.fda.gov/vaccines-blood-biologics/safety-availability-biologics/safety-alert-regarding-use-fecal-microbiota-transplantation-and-risk-serious-adverse-events-likely>). Probiotics may be safer if they are made in a laboratory where all components of the treatments are known, as opposed to fecal material that may not be tested to understand what all those 100 trillion microbes are. I would like to believe that FMT is safer, but safety is still debatable, especially in individuals who are elderly and/or immunocompromised, which could describe many patients with NAFLD. FMT seems mostly safe, but please note that there can still be individuals who become severely ill. 7. This exclusion criterion is concerning: "2) participants had severe complications." Perhaps I am misunderstanding it though; this sounds like studies were excluded if participants had severe side effects from FMT. However, upon rereading this, I am wondering if this is talking about severe NAFLD or comorbidities. Could the authors

please clarify which of these interpretations is correct? If it is the former, that is concerning because studies that note severe side effects of FMT should be noted, and the severe side effects need to be discussed since this is crucial for making medical decisions.

8. I appreciated learning about use of FMT for NAFLD. It is disappointing that more significant results were not found, but I would be interested in seeing more studies comparing FMT to probiotics.