

We sincerely thank the Reviewer for evaluating our manuscript and providing the valuable comments. These comments are very helpful for improving the quality of our manuscript, and leading us with preciseness in research.

#### Responses to Comments:

##### Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

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.

**Response: Thanks for your preciseness. We have revised it to “a global prevalence of about 25% in adult population”.**

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]."

**Response: Thanks for your suggestion. We have changed it to "the population of NAFLD along with advanced liver disease is projected to sustain growth [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.

**Response: Thanks for your comments. We have cited more references, and provided more detail on explanation for the specific mechanisms of NAFLD-related gut-liver axis in section "MECHANISM OF FMT FOR NAFLD". Such as "Some of these components are agonists of Toll-like receptor (TLR) signal pathway, which result in enhanced hepatic expression of inflammatory cytokines, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 $\beta$  (IL-1 $\beta$ ), thus promoting inflammation and fibrosis."**

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.

**Response: Thanks for your comment. We have increased the resolution and size of the Figure 1.**

5. For Figure 1, the left panel in the picture is titled "Health." Please change this to "Healthy" to match the figure legend.

**Response: Thanks for your comment. We have changed "Health" to "Healthy" in revised Figure 1.**

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.

**Response: Thanks for your comment. We agree with you on this point, and this sentence is not a rigorous statement. Indeed, as you said, probiotics can lead to side effects, while FMT also arises safety concern. Currently it is hard to say which one is safer. We have changed it to "These issues have paved the road for FMT application in NAFLD treatment, which is expected to yield better clinical efficacy and less side effect", to avoid conveying wrong message.**

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.

**Response: We are sorry for this misunderstanding. Here, the word "severe complications" refers to "severe comorbidities from NAFLD". We have clarified it in revised manuscript.**

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.

**Response: Thanks for your comment. Because FMT is an emerging therapeutic strategy for NAFLD, currently available data on this topic is limited. As the advancement and improvement of FMT, it is believed that more significant results could be seen in future studies, and the comparison of efficacy between FMT and probiotics will be conducted in more clinical trials.**