

**Title: Intestinal microbiota in the Treatment of Metabolically Associated Fatty Liver Disease**

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Dear Editor and Reviewers,

Thank you so much for your valuable comments and suggestions on our manuscript. We thank the reviewers for the time and effort that they have put into reviewing the previous version of the manuscript. Their suggestions have enabled us to improve our work. Based on the instructions provided in your letter, we uploaded the file of the revised manuscript. Enclosed please find out the responses to the referees. We sincerely hope this manuscript will be acceptable to publish on World Journal of Clinical Cases.

Thank you all for all your help and looking forward to hearing from you soon.

***RESPONSE TO THE EDITOR:***

**EDITOR COMMENT:** I recommend the manuscript to be published in the World Journal of Clinical Cases. 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/>.

**Responses :** Thank you for coordinating the review process. We have agreed that the manuscript would be published in the World Journal of Clinical Cases. As

suggested, we have used the RCA to complement the latest cutting-edge research results.

***RESPONSE TO REVIEWER #1:***

**Comment 1:** Pay attention to the use of “microbiota” & “microbiome”, there is subtle differences between these two terms.

**Response:** We are very sorry for our negligence of the use of “microbiota” & “microbiome”. In the revised version, these two terms are updated.

**Comment 2:** The significant limitation of the paper is its duplicative nature. The authors should more clearly indicate how the present review differs from those already published.

**Response:** Thank you for pointing this out. Recent animal studies and Clinical researches have been presented. The treatment options mentioned in the article, such as antibiotics, specific doses and duration of use can provide more help for clinicians in choosing treatment options.

**Comment 3:** The authors best to draw a systematic map to show the relationship between intestinal microbiome and NAFLD.

**Response:** We have added the Figure 1, which show the relationship between intestinal microbiome and MAFLD.

**Comment 4:** The references cited by the author are not up to date, which means the summarization is not new.

**Response:** As suggested, literature review is updated substantially with many new references. (ref. 101-105, etc.)

**Comment 5:** Please follow the rule of abbreviations in the text. For the first time, use both a full and abbreviated form, next time, just use an acronym.

**Response:** It is really true as Reviewer suggested that follow the rule of abbreviations in the text. Both a full and abbreviated form have been updated in the revised version.

**Comment 6:** In the whole text, “in vivo” & “in vitro” should be italicized.

**Response: The “in vivo” and “in vitro” have been italicized in the revised version of the paper.**

**Comment 7:** The format of the references should be unified according to the journal’s policy (ref. 95, etc.).

**Response: We have checked and attest that all formatting and style requirements have been met.**

**Comment 8:** The treatment options mentioned in the article, such as antibiotics, lack specific doses and duration of use cannot provide more help for clinicians in choosing treatment options, as well as the absence of side effects.

**Response: The Table 2 and Table 3 have added doses and duration of use to help with future treatment.**

#### ***RESPONSE TO REVIEWER #2:***

**Comment 1:** One important recent change has occurred in the terminology of NAFLD. I recommend using “Metabolic Associated Fatty Liver Disease” instead of “NAFLD”.

**Response: We agree with the Reviewer. We now have changed it to Metabolic associated fatty liver disease or MAFLD throughout the manuscript.**

**Comment 2:** Please define the effect of Small intestinal bacterial overgrowth on MAFLD and cite the following articles: a. Wijarnpreecha K, Lou S, Watthanasuntorn K, Kroner PT, Cheungpasitporn W, Lukens FJ, Pungpapong S, Keaveny AP, Ungprasert P. Small intestinal bacterial overgrowth and nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Eur J Gastroenterol Hepatol.* 2020 May;32(5):601-608. doi: 10.1097/MEG.0000000000001541. PMID: 31567712. b. Ivana Mikolasevic, Bozena Delija, Ana Mijic, Tajana Stevanovic, Nadija Skenderevic, Ivan Sosa, Irena Krznaric-Zrnica, Maja Abram, Zeljko Krznaric, Viktor Domislovic, Tajana Filipec Kanizaj, Delfa Radic-Kristo, Aleksandar Cubranic, Aron Grubestic, Radislav Nakov, Ivana Skrobonja, Davor Stimac, Goran Hauser. Small intestinal bacterial overgrowth and non-alcoholic fatty liver disease diagnosed by transient elastography and liver biopsy.

**Response: We have added a few sentences regarding MAFLD and Small intestinal bacterial overgrowth. And we have cited these references (ref. 22,23).**

**Comment 3:** Please define the role of helicobacter pylori on MAFLD and cite the following articles: a. Jamali R, Mofid A, Vahedi H, Farzaneh R, Dowlatshahi S. The effect of helicobacter pylori eradication on liver fat content in subjects with non-alcoholic Fatty liver disease: a randomized open-label clinical trial. *Hepat Mon.* 2013 Dec 6;13(12):e14679. doi: 10.5812/hepatmon.14679. PMID: 24358044; PMCID: PMC3867002. b. A Jamali, S Karbalai, G Tefagh, A Ahmadi, R Jamali. The Effects of Helicobacter Pylori Eradication on Liver Function and Metabolic Profile in Non-diabetic Non-alcoholic Steatohepatitis: A 5-year Randomized Clinical Trial. *Middle East Journal of Digestive Diseases (MEJDD)* 14 (1), 85-95.

**Response: We have added a few sentences on this and included the reference provided by the reviewer.**

### ***RESPONSE TO REVIEWER #3:***

**Comment 1:** The reviews on this topic regularly appear in various scientific journals, I believe that the introduction should indicate how this review differs from those published earlier.

**Response: Thank you for pointing this out. The introduction has indicated how this review differs from those published earlier in the revised version. Recent animal studies and Clinical researches have been presented. The treatment options mentioned in the article, such as antibiotics, specific doses and duration of use can provide more help for clinicians in choosing treatment options.**

**Comment 2:** Currently prefer the term "metabolically associated fatty liver disease" rather than "non-alcoholic fatty liver disease"; if you insist on the old terminology, explain your choice.

**Response: We agree with the Reviewer. We now have changed it to Metabolic associated fatty liver disease or MAFLD throughout the manuscript.**

**Comment 3:** A table should be provided with data from published studies on changes in the intestinal microbiota in MAFLD and MASH.

**Response: We agree and have added table 1 to list changes in the intestinal microbiota in MAFLD and MASH.**

**Comment 4:** The claimed figure 1 is not presented.

**Response: In the revised version, a few sentences regarding figure 1 has been deleted.**

**Comment 5:** An additional schemes of disorders of the gut-liver axis in MAFLD and the points of application of the drugs described in the article should be presented.

**Response: We have not only added specific doses and duration of drugs in the Table 1 and Table 2, but also intestinal microbiota can promote the progression of NAFLD through several mechanisms.**

**Comment 6:** The pathology of the gut-liver axis in MAFLD should be described more fully.

**Response: We have added intestinal microbiota can promote the progression of NAFLD through several mechanisms in the revised version of the paper.**

**Comment 7:** The authors write "The impaired intestinal barrier allows bacteria and their products, including pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), into the circulatory system", but the term "damage-associated molecular patterns" is usually used for macroorganism molecules that are released when its tissues are damaged, so justify the use of this term in relation to bacteria.

**Response: We agree with the Reviewer. We now have corrected and removed "damage-associated molecular patterns (DAMPs)".**

**Comment 8:** The authors use both the terms "lipopolysaccharide" and "endotoxin" without specifying that these are synonyms. Clarify this and use only 1 term.

**Response: Clarify the terms "lipopolysaccharide" and "endotoxin" are synonyms by the reference (Zhang X, Cui X, Jin X, Han F, Wang J, Yang X, Xu J, Shan C, Gao Z, Li X, Zuo M, Yang J, Chang B. Preventive Role of Salsalate in Diabetes Is Associated With Reducing Intestinal Inflammation Through Improvement of Gut Dysbiosis in ZDF Rats. Front Pharmacol. 2020 Mar**

**19;11:300. doi: 10.3389/fphar.2020.00300. PMID: 32265702; PMCID:  
PMC7096544.).**