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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastroenterology*

Manuscript NO: 76864

Title: Gut Microbiota Alteration and Modulation in HBV-related Fibrosis and Complications: molecular mechanisms and therapeutic inventions

Provenance and peer review: Unsolicited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 00052947
Position: Peer Reviewer
Academic degree: MD
Professional title: Director, Professor
Reviewer's Country/Territory: Germany
Author's Country/Territory: China

Manuscript submission date: 2022-04-04

Reviewer chosen by: AI Technique

Reviewer accepted review: 2022-04-05 15:47

Reviewer performed review: 2022-04-10 17:04

Review time: 5 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

General comment The interaction between gut bacteria and the effects of advanced liver disease is well known since many decades. With the increasing knowledge of the gut microbiota, the problems created by the gut bacteria in patients with severely reduced liver function can be better understood and new approaches in diagnosis and therapy are under study. The authors have collected and reviewed the respectable number of 136 papers dealing with this important topic. Unfortunately, the text does not satisfy the expectations raised in the title. a) The title mentions explicitly "HBV-related fibrosis and complications", but HBV is heavily neglected. It could have been very interesting to describe and discuss the effect of the potentially immunomodulatory role of HBeAg and other HBV products on the gut microbiota and to follow the effect of increasing HBV-related immune pathogenesis from the low inflammatory, highly replicative phase to the highly active CHB on the gut microbiota and vice versa. The authors miss that point completely, although they mention the immune stimulatory effect of the bacterial components like LPS and many others. Among the 136 cited papers only ca. 30 mention HBV in the title and even most of these do not really deal with the immune biology of HBV. b) Currently, the paper deals predominantly with the effect of the gut microbiota on the biochemical and clinical sequelae of end stage liver disease with or without decompensation irrespective of the original cause of the liver disease. This is acceptable, but the title and the entire text should be revised accordingly. c) The English is very faulty and needs thorough editing from a native speaker. d) The layout and design of the tables should be improved. Minor points 1. Title. Replace HBV by hepatitis B virus in the title, but see above. 2. L44. Though the authors do not discuss this primarily,

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hepatocellular carcinoma is a major outcome of chronic hepatitis B and may be related to gut microbiota. 3. L73-78. The authors should read, cite here and apply the definitions of the phases of CHB from international associations like EASL (in addition refs. 71, 76,84), APASL or AASL. The reason for tissue repair is chronic inflammation, mainly driven by immune pathogenesis. Ref. 2 is not optimal to inform about the phases and courses of HBV infections. 4. L225. CCl4 may read likeC14 and may be deleted here unless written correctly CCl4. 5. L300. NAs like tenofovir are DAAs. 6. Table 2 is very difficult to read. 7. Table 3. The table should be divided into two parts: 1. Studies in mice (6, including ref.114). 2. Studies in humans (11).

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Reviewer's code: 06195980
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: China

Author's Country/Territory: China

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Reviewer accepted review: 2022-04-09 13:44

Reviewer performed review: 2022-04-17 13:18

Review time: 7 Days and 23 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [Y] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
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Re-review	[Y] Yes [ ] No

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Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This review systematically described the alterations of gut microbiota in HBV-related liver fibrosis, and summarized the advanced therapeutic strategies targeted microbiota, mainly gut microbiota alteration and immunity reaction of HBV-related liver fibrosis initiation and progression, gut microbiota dysbiosis in liver fibrosis complications, therapeutic strategies towards fibrosis and complications up to date. There are some limitations. Major: 1.The article mentioned that the relationship between liver and gut microbiota was mainly through portal vein and biliary system, however, only summarized the relationship between bacterial translocation and liver through portal vein, lack of the concentration on the role of biliary system, for example, regulation of basal metabolism, gastrointestinal hormone release and immune response by the gut-liver axis which was mediated by bile acids and gut flora. 2.When liver fibrosis progressed to the compensated and decompensated stages of cirrhosis, the alterations or/and characteristics in gut microbiota were not specifically described. 3.The gut microbiota dysbiosis associated with hepatic encephalopathy has been extensively studied, but the authors have not paid much attention to it. Minor: 1.Table 2 is meaningless, since the gut microbiota of patients in different studies may be significantly different due to diet, region, living habits, etc. It is inappropriate to forcibly piece together these results in different studies. Table 1 is enough. 2.The author should check the full text carefully to avoid spelling mistakes, grammar mistakes and other problems. Such as, page 10, line 270, “gut-brain- axis” (gut-liver-brain axis or gut-brain axis?); page 4, line 87, “Actinobacteri” (Actinobacteria ?)”. 3.References cited did not support some conclusions of the paper. Such as, page 13, lines 337-339 (the original: While infections

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with enterococci and Escherichia coli accounted for 72% of positive ascites cultures in patients without any prophylaxis, none of these bacteria were identified in the ascites of patients taking rifaximin. In contrast, 75% of the micro-organisms detected in the ascites of patients treated with rifaximin were klebsiella species), and lines 357-358 (the original: Lactulose and probiotics are effective for secondary prophylaxis of HE in patients with cirrhosis).