Reviewer 1.

Minor comments:

Comment: Tables: - A title should be written for each table

Answer: Thank you for pointing this issue to us. Yes, indeed each table has a title but we have inserted it below the table. We now have placed them above/before the table and only the abbreviations are below.

Comment: Table 1: What is the difference you mean between "chronic HBV infection" and "chronic hepatitis B". The difference should be at least mentioned in a footnote of the table. There is disarrangement of the headings with repetition of the same titles "chronic hepatitis B"

Answer: Thank you very much for underlining this mistake. Indeed, we have not initially intended the first column to represent heading, just the type of infection. We now have corrected this mistake by rearranging the references and categories.

Comment: What is meant by stage 4 HCV infection?

Answer: We were referring to cirrhosis. We have added this in parentheses in the table.

Comment: Language: - Abstract: "….. highlight the influenced…"------- correct to "…..highlight the influence…" - Introduction: page 2, line 5: cytopenic or cytopathic? - Page 7, line 2: also, IL-22 in involved……. is involved - Page 7, heading 2.4.Flagellin: flagellin in involved…… is involved - Page 8, last paragraph: these protease…. these proteases - Page 11, under the title 5. The Gut Microbiota…… "It has been shown that there is a direct link between intestinal microbiota dysbiosis in patients with HBV or HCV-related liver disease"…… Please rephrase - Page 16, under the conclusion: determent……determinant Page 15: - Third paragraph: what is the difference between "symbiotic" and "synbiotic" ? Conclusion: - It is better to remove "as we have seen"

Answer: Thank you very much for pointing out these mistakes. While re-reading the manuscript we have corrected these and several others we have found.

Reviewer 2.

Comment: 1. This article focused on the gut-liver axis in viral B and C hepatitis, but the first half of the article mentioned the 'Microbiota and the immune system' can not

contact closely with viral B and C hepatitis. Thus, you’ d better to introduce the relationship of the microbiota and the immune system of hepatitis or hepatic carcinoma besides.

Answer: Thank you for your kind suggestion. We intended that paragraph for illustrating the various pathways by which the microbiota can influence the immune system (unrelated to hepatitis). In the Gut-Liver axis part we have detailed the pathways that were studied so far regarding hepatitis and liver diseases. We believe that this way the reader will first get an understanding of the possible mechanisms (some of which are not yet studied in direct relationship to hepatitis) and then will see which of these apply and were already studied. We have added a short text in order to connect the TLRs to HBV and HCV.

Comment: 2. The title of this article is ‘An overview of the gut-liver axis in viral B and C hepatitis’. As far as i know, the analysis of microbiota included not only the metabolome but also the metagenome, transcriptome and proteome, which did not mention in the article. In my opinion, you’d better change your title or provide the information of other analysis of microbiota in addition.

Answer: We did not talk about metagenome, transcriptome and proteome in the manuscript because we insisted on the microbiota not on the microbiome (the microbiome is the sum of microbes and their genomic elements in a given environment). We slightly changed the title to clarify this.

Ho H, Bunyavanich S. Role of the microbiome in food allergy. Curr Allergy Asthma Rep. 2018;18:27

Berg, G., Rybakova, D., Fischer, D. et al. Microbiome definition re-visited: old concepts and new challenges. Microbiome 8, 103 (2020).

Comment: 3. I have noticed the article named” Gut microbiome influences efficacy of PD-1‐based immunotherapy against epithelial tumors about microbiota” published in Science. Also, there are some articles about microbiota influences the efficacy of PD-1 based immunotherapy. Immunotherapy is one of the important treatment of hepatic carcinoma. Therefore, it is better to give more information about microbiome and immunotherapy in hepatic carcinoma.

Answer: Thank you very much for your suggestion. Indeed, we have considered also discussing the microbiome and its influence on HCC. This is however a very complex topic on its own and we believe we would not do it just adding it briefly in this review. We will consider this idea for a future article, but here we have decided to focus only on the liver inflammatory response in HBC and HCV infections.

Reviewer 3.

Comment: 1. In the "Microbiota and the immune system" part, clarify the relationship between products produced by microbiota, immune system and hepatitis B and C?

Answer: Thank you for your kind suggestion. We intended that paragraph for illustrating the various pathways by which the microbiota can influence the immune system (unrelated to hepatitis). In the Gut-Liver axis part we have detailed the pathways that were studied so far regarding hepatitis and liver diseases. We believe that this way the reader will first get an understanding of the possible mechanisms (some of which are not yet studied in direct relationship to hepatitis) and then will see which of these apply and were already studied. We have added a short text in order to connect the TLRs to HBV and HCV.

Comment: 2. In the "The Gut Microbiota-Viral B and C hepatitis" part, The treatment of hepatitis B or C influence the diversity and abundance of the intestinal microbiota. How to increase this diversity and abundance by interfering with microbiota to avoid the side effects of traditional treatment?

Comment: 3. In the process of interfering with intestinal microbial therapy, how to ensure that the anti-inflammatory effect of microbial components is enhanced, while the pro-inflammatory effect is weakened?

Answer for comment 2 and 3:

Restoring the balance of the intestinal microbiota by promoting the growth of good bacteria leads to beneficial effects of the healthy microbiota:

- antimicrobial protection ("One of the simplest mechanisms of antimicrobial protection is the presence of the two-tiered mucus layer, which keeps luminal microbes away from epithelial contact, predominantly in the large intestine" ; "induce synthesis of antimicrobial proteins (AMP) such as cathelicidins, C-type

lectins, and (pro)defensins by the host Paneth cells via a pattern recognition receptor (PRR) mediated mechanism" or "activate intestinal dendritic cells (DCs), which induces plasma cells in the intestinal mucosa to express secretory IgA (sIgA)"),

- immunomodulation: influences innate and adaptive immune systems ("gut associated lymphoid tissues (GALT), effector and regulatory T cells, IgA producing B (plasma) cells, Group 3 innate lymphoid cells, and, resident macrophages and dendritic cells in the lamina propria"
- Improvement of barrier function

Jandhyala SM, Talukdar R, Subramanyam C, Vuyyuru H, Sasikala M, Nageshwar Reddy D. Role of the normal gut microbiota. World J Gastroenterol. 2015;21(29):8787-8803.

Martina Antonini, Marta Lo Conte, Chiara Sorini, Marika Falcone. How the Interplay Between the Commensal Microbiota, Gut Barrier Integrity, and Mucosal Immunity Regulates Brain Autoimmunity; Front Immunol 2019;10:1937.

Sanders, M. E., Merenstein, D. J., Reid, G., Gibson, G. R. and Rastall, R. A. (2019) Probiotics and prebiotics in intestinal health and disease: from biology to the clinic. Nature Reviews. Gastroenterology and Hepatology, 16. pp. 605-616.

Elisavet Stavropoulou1and Eugenia Bezirtzoglou, Probiotics in Medicine: A Long Debate, Front. Immunol., 2020