

To the Editor

As requested, we modified our manuscript according to the suggestions and corrections received. We are now sending you the revised document within the 1-month period granted to us in your last e-mail dating 12th April 2019 (*From: "z.m.gong" <z.m.gong@wjgnet.com> To: carloalessandria <carloalessandria@libero.it> Bcc: Date: Fri, 12 Apr 2019 17:50:58 +0800 Subject: Manuscript NO: 47485 can be accepted for publication for free in the World Journal of Hepatology - "Please inform us within 1 week whether you are interested in our offer to publish your manuscript in WJH; a 1-month grace period will then be allotted for the revisions to be completed"*). All the changes made in the manuscript are highlighted in red, as per journal instructions, and hereafter you will find the answers to the reviewers' comments.

Kind regards,

The Authors

Answers to the reviewers' comments

Reviewer #1: This manuscript is an excellent review about pathogenesis of HE and possible dietary approaches to therapy of HE. For the reader not so familiar with this topic it would be desirable to design some cartoons or tables that better visualize the different aspects of pathogenesis and therapeutic approaches. E.g. NH₃-metabolism; Inflammation in HE; Leaky gut ... One could easily adhere to the order of the chapters of the manuscript I admit this would require some additional work for the authors, but it would improve the quality and readability of the manuscript.

ANSWER: according to the reviewer's suggestion, we added Table 1 (describing current available therapies, mechanisms of action, and corresponding levels of evidence; page 57) and Figures 1, 2 and 3 (illustrating the pathogenesis of hepatic encephalopathy, the mechanisms underlying the development of leaky gut, and the role and mechanisms of action of the different possible dietary approaches; pages 53-56).

Reviewer #2: This is a interesting manuscript reviewing the efficacy of dietary measures to prevent and to treat the hepatic encephalopathy in patients with cirrhosis. The manuscript is well written and the review is extensive including recent advances on the topic. I consider that the content of this review may be useful for the clinician who treats cases of hepatic encephalopathy daily. To improve the readability of the review it would be good to include a

figure that summarizes the pathogenesis of hepatic encephalopathy and a table that describes the scientific evidences and clinical utility of different dietary therapeutic strategies.

ANSWER: as for Reviewer number 1, following reviewer 2 input, we added Table 1 (describing current available therapies, mechanisms of action, and corresponding levels of evidence; page 57) and Figures 1, 2 and 3 (illustrating the pathogenesis of hepatic encephalopathy, the mechanisms underlying the development of leaky gut, and the role and mechanisms of action of the different possible dietary approaches; pages 53-56).

Reviewer #3: To the authors, This is a well-written and interesting manuscript however, this manuscript DOES NOT focus on nutritional or dietary management, the manuscript is focused, as the authors mention on the gut microbiota and its effect on hepatic encephalopathy. In a small section EASL and ESPEN guidelines for nutritional management are mentioned, but this review does not add any information different from what we already know and has been published in several other reviews (calories, macronutrients, some micronutrients, BCAAs). I do not believe this adds anything different or was missing in the literature to send to a journal such as WJG. Fecal microbiota transplantation is for sure an interesting therapeutic option but has nothing to do with nutritional management and it is included in dietary approach. Although the authors included an exceptional amount of references they left out important and classic references which is also noted in the manuscript as they mentioned several prebiotics and probiotics, and they left out information on VSL#3. My suggestion is to change the title to gut microbiota or something similar instead of dietary approach and maybe try WJH.

ANSWER. Following Reviewer 3 comments:

1. We changed the title of the chapter including fecal microbiota transplantation from "DIETARY APPROACH AND GUT-LIVER AXIS" to "DIETARY APPROACH, INTESTINAL MICROBIOTA MODULATION AND GUT-LIVER AXIS"
2. In the chapter dealing with probiotics, we included two references about the use of VSL#3 in HE (references 209 and 216)
3. Review title was changed from "Dietary approach in cirrhotic patients with chronic hepatic encephalopathy" to "Dietary approach and modulation of gut microbiota in cirrhotic patients with chronic hepatic encephalopathy".

Reviewer #4: The authors presented an excellent review describing the principles of treatment of chronic hepatic encephalopathy in cirrhotic patients. They paid special attention to the dietary approach. Obviously, adequate nutrition is of paramount importance for cirrhotic patients. All of them must pass a nutritional assessment, especially patients with

hepatic encephalopathy. I would like to draw the attention to deficiency publications over the past five years (68 - 33,2 %).

ANSWER: following Reviewer 4 suggestions, the proportion of publications over the last five years has been increased from 33,2% to 46% (108/233 references).

Reviewer #5: In my opinion, the manuscript is an excellent and comprehensive review regarding dietary approach for cirrhotic patients with chronic hepatic encephalopathy. I made some proofreading for few spelling and comma error.

ANSWER : all spelling and comma errors have been corrected.