Reply to the Reviewer/Editor.

Dear Respected Editor/Reviewer

Good day

Thank you very much for the comprehensive review and the precious time you spent reviewing this study. We did the advised changes and answered the queries. All the changes were marked in red for easy tracking by the reviewer. The manuscript looks much better with these changes, and we tried to improve the language as we could. Thank you again for your precious assistance.

Here we are replying point by point:

Reviewer 1:

Thank you very much for your positive feedback and helpful suggestions.

This work proposes an extensive review on the role of gut microbiota in various childhood disorders. It is an important and novel topic. This review provides a large amount of detailed information for the researchers in the related areas. However, there are also several problems that need major revision:

1) The manuscript has no page or line number, making it difficult to point out the details.
Our Reply: we added the page and lines number

2) In page 5, the "FUNCTION OF GUT MICROBIOTA" part is not well organized. It seems only the role of microbiota derived SCFAs was described. Other important mechanisms should be added. For instance, bile acid and neurotransmitters.

Our Reply: This section has been updated. The changes were highlighted in red.

3) In page 11, the authors mentioned that microbiota plays an essential role during brain development through its effects on serotonin synthesis. Since both the brain and microbiota system can produce synthesis serotonin, authors should convince readers of the specific function of microbiota-derived serotonin. Related references should be provided.

Our Reply: we added the following information to the text (highlighted in red):

About 95% of the body's serotonin is formed by the gut microbiota, affecting mood and gastrointestinal activity. However, scientists found that serotonin can not cross the blood-brain barrier. So, it works mainly on the peripheral enteric nervous system and works as a hormone affecting different tissues, including those regulating metabolic homeostasis (). However, the beneficial role of probiotics in alleviating the manifestation of many psychiatric disorders such as depression and anxiety could be related to their ability to secrete serotonin, a significant player in many psychiatric disorders (). Meanwhile, animal studies showed that probiotic use might cause rising plasma tryptophan levels, decreased serotonin concentrations in the frontal cortex and decreased cortical dopamine metabolites, thus improving the depressive symptoms ().

Gao K, Mu CL, Farzi A, Zhu WY. Tryptophan Metabolism: A Link Between the Gut Microbiota and Brain. Adv Nutr. 2020 May 1;11(3):709-723. PMID: 31825083. DOI: 10.1093/advances/nmz127.

Evrensel A, Ceylan ME. The Gut-Brain Axis: The Missing Link in Depression. Clin Psychopharmacol Neurosci. 2015 Dec 31;13(3):239-44. PMID: 26598580. DOI: 10.9758/cpn.2015.13.3.239.

Huang R, Wang K, Hu J. Effect of Probiotics on Depression: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Nutrients. 2016 Aug 6;8(8):483. DOI: 10.3390/nu8080483. PMID: 27509521; PMCID: PMC4997396.

4) In the "GUT MICROBIOTA IN COMMON PEDIATRIC DISORDERS" part, the authors summarized the altered gut microbiota composition in various childhood disorders. However, the deeper mechanisms were not described. This review will be more helpful for the researchers in a related field if some specific metabolic and molecular mechanisms are added.

We added the mechanisms in most disorders. The changes are highlighted in red.

5) In Figure 1, the different gut-microbiota-axes were shown. However, it is not clear enough. Authors should show more details of the mechanism underlying the interaction of gut microbiota and host--may need more figures--so that the study results are clear to the readers.

Our Reply: The figure is a collective figure and summarizes the six axes. Adding more description will complicate it. The details are well-elaborated in the manuscript.

6) Please note the format of the tables. For instance, the fonts need to be unified.
Our Reply: Table formating was corrected

Reviewer 2:

Very nice review on gut microbiota, the current profile of both basic and clinical science. It systematically discussed the application in childhood diseases. If it could describe something of epilepsy, it would be better.

Our Reply:

Thank you very much for the precious time you spent reviewing the article. Also, we appreciate your supportive comments.

We added a section about the Gut microbiota and epilepsy under the (**Gut Microbiota and Child Neurodevelopment section)**

The word heart was corrected

The one in bacterial translocation1 removed

LANGUAGE POLISHING:

Native English-speaker did language polishing

ABBREVIATIONS

The basic rules on abbreviations were strictly followed

EDITORIAL OFFICE'S COMMENTS:

All the editorial instructions were followed in finalizing this manuscript.

On behalf of all authors, we thank editors and reviewers for their support during the publication of this manuscript.

Many thanks

Professor Mohammed Al-Biltagi