

Dear Lian-Sheng Ma,

I sincerely thank you for your prior acceptance of Manuscript NO: 80272 "Microbiota of the gastrointestinal tract. Friend or foe?" and reviewers for objective and important comments. It was very interesting for me to work on this document. However, this topic is so vast, it covers a variety of aspects of the functioning of the microbiome and its interaction with various body systems, that it is absolutely impossible to consider them in one article. For me personally, of particular interest was the interaction of the microbiome, as a separate organ in the human body, with various body systems, as well as mechanisms that can lead to disruption of its functioning and pathology, or, on the contrary, can contribute to recovery. It is these mechanisms that I tried to cover in more detail in this review article.

In accordance with the comments of the reviewers, I made the following corrections to the manuscript:

Reviewer #1.

1. Microorganism names are in italics.
2. I have edited the subheadings of the manuscript. New subheadings highlighted in yellow.
3. I reduced the number of paragraphs in the text by combining short paragraphs that have logically related content. In addition, I have rearranged some paragraphs for a more consistent presentation of the material.
4. I apologize for the typo. Corrected to "Mediterranean diet is ...."
5. I deleted the last sentence in Conclusion section.

Reviewer #2.

1. I agree with the reviewer that the submitted manuscript does not correspond to an editorial and for this reason will be presented as a review article.
2. The problem of the intestinal microbiome is so multifaceted that it cannot be considered in one article. The purpose of the presented manuscript is to discuss the mechanisms of interaction of the microbiome with various body systems, as well as mechanisms that can lead to disruption of its functioning and pathology, or, conversely, can contribute to recovery. Taking into account the comment of the reviewer, in the final part of the manuscript, more attention is paid to addressing the highly controversial issue of when to consider the gut microbiome as a friend and when as an enemy. This problem remains unresolved to date, and a clear answer to many questions has not yet been received.

3. I believe that a detailed consideration of the role of the microbiome in the development of specific diseases is impossible within the framework of one article and is not the goal of the submitted manuscript. In accordance with the reviewer's comment, I came to the conclusion that the above table is too superficial, contains unsystematized data and does not contribute to understanding the role of the microbiome in the development of these diseases. Given the above, I removed the table from the text, replacing it with Figure 1, which shows the relationship of intestinal dysbiosis with the development of various diseases in the form of a general scheme, and in the text of the manuscript I increased the number of references to the relationship of intestinal dysbiosis with specific diseases.
4. In the final part of the manuscript, I discuss in more detail the problem posed in the title of the manuscript, emphasizing that it is far from a final solution.
5. I changed the definition of dysbiosis and excluded categorical formulations from the conclusion, focusing on a large layer of unresolved problems that are open for discussion and subsequent research search.

Reviewer #3.

1. I agree with the reviewer that the submitted manuscript does not correspond to an editorial and for this reason will be presented as a review article. I have prepared Figure 1, which shows the relationship of intestinal dysbiosis with the development of various diseases in the form of a general scheme.
2. In the manuscript text, I increased the number of references to the association of intestinal dysbiosis with specific diseases, including the association with colorectal cancer. This problem is so interesting and multifaceted that it deserves consideration in a special article.
3. The role of trimethylamine N-oxide, hydrogen sulfide, and polyamines in health and disease is described in greater detail. The role of the microbiome in the biotransformation of a number of xenobiotics is also more correctly formulated.
4. I reduced the number of paragraphs in the text as much as possible by combining short paragraphs that have logically related content. In addition, I rearranged some paragraphs for a more consistent presentation of the material. The manuscript has been rechecked by professional proofreaders for grammar.
5. Microorganism names are in italics. "eg" have been to replace to "e.g.,".



#### Reviewer #4.

I agree with the reviewer that the submitted manuscript does not correspond to the editorial and for this reason it will be presented as a review article, the purpose of which is to discuss the mechanisms of interaction of the intestinal microbiome with various body systems, as well as mechanisms that can lead to disruption of its functioning and pathology or, conversely, may contribute to recovery. As for the problem of the microbiome - this is an "enemy" and "friend", this problem is no less debatable than the problem of "good" and "evil", and these questions have not yet received unambiguous answers. I have tried in the final part of the manuscript to pay more attention to the discussion of this problem, and, in addition, to focus on the existing unresolved problems and possible directions for finding answers to the most pressing questions, including the possibility of using postbiotics and/or antibiotics to regulate the microbiota.

Concerning the following remarks.

1. I corrected the outdated data on the ratio of the number of bacterial cells and cells of the human body, providing the appropriate reference.
2. The genus and the species names of bacteria are in italics.
3. I changed the definition of dysbiosis and excluded categorical formulations from the conclusion, focusing on a large layer of unresolved problems that are open for discussion and subsequent research search.
4. I removed the table from the text, replacing it with Figure 1, which shows the relationship of intestinal dysbiosis with the development of various diseases in the form of a general scheme, and in the text of the manuscript I increased the number of references to the relationship of intestinal dysbiosis with specific diseases.
5. A detailed consideration of the role of the microbiome in the development of specific diseases is not the goal of the submitted manuscript.

#### Reviewer #5.

1. I have more detail discussed the issue of using washed microbiota transplantation.
2. Updated information on the role of the microbiome in the metastasis of malignant tumors has been added to the review.
3. I have changed the term "microflora" to "microorganisms" or "gut microbiota" according to the context.

4. I reduced the number of paragraphs in the text by combining short paragraphs that have logically related content. In addition, I have rearranged some paragraphs for a more consistent presentation of the material.
5. For substantiate the role of the gut microbiome as friend or foe, I added to the manuscript information about the benefits of using FMT to treat serious infectious internal fistulas in patients with Crohn's disease.