



From: Dr. Chiranjib Chakraborty,
Professor, School of Life Science and Biotechnology,
Adamas University, Kolkata, India.

To,

Lian-Sheng Ma,
Editorial Office Director, Company Editor-in-Chief, Editorial Office
World Journal of Gastroenterology
Baishideng Publishing Group Inc.

Dear Sir,

Greetings!

Enclosed, please find our revision of the manuscript entitled, “*Altered gut microbiota patterns in COVID-19: Markers for inflammation and disease severity*” (Manuscript NO.: 73237, Review) by Chakraborty *et al.* This manuscript has been revised in accordance with the comments raised by the reviewers and editors. All changes are marked by the red color option of Microsoft word.

We want to thank the Editor and reviewers for the helpful comments and suggestions provided for our manuscript. This helped us to enrich the scientific quality of the manuscript. We have adequately addressed the comments raised by the Editor and reviewers. We hope to hear from you in the near future about the acceptability of our manuscript for publication in your esteemed Journal.

Lately, I have reviewed the article (Reviewer’s Code: 00503359, 23 October 2020) of your Journal. So I kindly request you a discount on the article processing charge (APC) for this article. Due to the financial crisis during the pandemic, the government is not releasing the research grant properly. At the same time, we are passing through an acute economic crisis. Therefore, we request you to kindly provide us with some discount on APC of the Journal. We can pay a maximum of USD 950 (with tax) for this article as APC.

Please note that we have corrected our MS through a professional editing service before the first submission and the certificate is attached herewith. Again, the revised version of the MS (R1 Copy) has been checked by a native English speaker who has checked the R1 copy of the MS thoroughly.

Please feel free to contact us in case you need any more clarifications.

I look forward to your kind response.

Thank you for your kind cooperation.

With best regards,



Chiranjib Chakraborty, Ph.D.

Professor, School of Life Science and Biotechnology,

Adamas University, Kolkata, India

Academic Editor: iScience (Cell press Journal) (IF= 5.458); Handling/Receiving Editor:

Infection ,Genetics and Evolution (IF=3.342); Associate Editor: Frontiers in Bioengineering and

Biotechnology (IF= 5.890); Associate Editor: Frontiers in Pharmacology (IF= 5.810)

Profile: <http://community.frontiersin.org/people/ChiranjibChakraborty/18716>

Google Scholar Id: 3m8rwpUAAAAJ

Point-by-point response to the comments of the reviewers and/or editors

We appreciate the encouraging comments of the Editor and reviewers on the current study. As suggested by the Editor and reviewers, we did our best to address the following points raised by the reviewers. We welcome the opportunity to clarify and revise our manuscript to make its scientific contributions more perceptible.

Response to Reviewer #1:

Thank you for the opportunity to review this informative article. I enjoyed reading it and I hope my comments would aid you in improving the research article.

1. Abstract: lacking in cohesiveness. It could be improved further by summarizing the key findings listed in the body of the article to attract the readers attention.

Answer: Thank you for the comment. We have revised the abstract and improved it by summarising the key findings. Please find the revised version (R1 copy) of the submitted manuscript.

2. Introduction: Lengthy and only discussed about gut microbiomes in brief. Many articles have already detailed COVID-19 symptoms and its management so I felt it was unnecessary to describe it at length instead of jumping straight into the topic at hand.

Answer: Thank you for the comment. We have revised the introduction section and corrected COVID-19 symptoms and their management as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

3. Body and conclusion : I strongly suggest to rewrite the conclusion to summarize and remind the link between the gut microbiota and covid-19. We should not be introducing new points like FMT etc. More discussion regarding the link between gut microbes and different demographic characteristics would improve the content (for example, you mentioned “elderly or co-morbid patients with certain medical conditions” in conclusion but did not describe in further detail why earlier, aside from one sentence)

Answer: Thank you for the comment. As suggested, we have corrected the conclusion section and removed the new point like FMT from ‘conclusion’. We have included more discussion regarding the link between gut microbes and different demographic characteristics.

At the same time, we have also added a new paragraph mentioning “elderly or co-morbid patients with certain medical conditions” in the conclusion section. Please find the revised version (R1 copy) of the submitted manuscript.

4. Some errors in references (eg. Upper case and lower case letters used inappropriately. Volumes quoted wrongly that need minor corrections.)

Answer: Thank you for the comment. We have rechecked and corrected all the references as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

5. There still exist some grammatical errors and some sentences could be improved by rephrasing, but this is tolerable. (eg. Tocilizumab has been used to treat disease severity. Toci is used in severe disease is more accurate. Another example, in Fig 1. Did you mean gut virome in the last frame?)

Answer: Thank you for the comment. We have corrected and removed all grammatical errors and shorten the sentences suggested by the reviewer.

We have corrected the spelling mistake in the last frame of Fig 1 and corrected as gut virome. Please find the revised version (R1 copy) of the submitted manuscript.

6. There is a lack of novelty in the article as it has been discussed in several platforms with few studies already performing large meta-analysis (eg Yamamoto et al doi.org/10.1371/journal.pone.0253293).

Answer: Thank you for the comment. We have revised our manuscript in view of the novelty. There are very few publications about the Gut-brain-lung axis, which we have included in our manuscript. Hypoxia in COVID-19 and gut microbiota also has been discussed in a separate section. We also added a new table (table 3) about the Clinical trials to understand gut microbiota's role in COVID-19 and its therapeutic implications. Also, we have added some new sections that are novel: Gut microbiota in elderly and co-morbid COVID-19 patients with certain medical conditions; Gut microbiota based on usage or non-usage of antibiotics in

COVID-19 patients; Future perspective; and also added a new table (table 4). Please find the revised version (R1 copy) of the submitted manuscript.

I feel the article would have been more interesting if the scope is more well defined; for example, discussion about dysbiosis and severity in detail, or about probiotics like Kurian et al. Probiotics in Prevention and Treatment of COVID-19: Current Perspective and Future Prospects. doi:10.1016/j.arcmed.2021.03.002.

Answer: Thank you for the comment. We have corrected the section as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

Response to Reviewer #2:

This review paper investigated the role of gut microbiota alterations in COVID-19 disease as markers for hyperinflammation and disease severity, and discussed the possibility of using probiotics, prebiotics and synbiotics to restore gut microbiota as therapeutic strategies for COVID-19 treatment. The study presented in this review on the role of changing human microbiome as a COVID-19 therapy is very timely, comprehensive, and pioneering, and would be a big contribution to COVID-19 treatment if it can be published after the authors make the following minor revision to the typos and grammatical errors:

1) Page 2, in Abstract, line 12, “Inflammation” should be “Augmented inflammation”. Localized acute transient inflammation is a protective immunological response to tissue damage [1,2], and will be resolved in one or two days. It helps to remove the injurious stimuli like infections and trauma, and initiate tissue regeneration. Only the uncontrolled hyperinflammation has detrimental effect on health and contributes to disease severity.

Answer: Thank you for the comment. We have corrected the sentences in Abstract, line 12, as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

2) Page 7, line 16, “compostion” should be “composition”

Answer: Thank you for the comment. We have corrected the stated word as “composition” at page 7, line 16. Please find the revised version (R1 copy) of the submitted manuscript.

3) Page 18, reference 13, the authors’ list should be “Perisetti A, Gajendran M, Mann R, Elhanafi S, Goyal H.”; and the volume and issue of this reference is 66(9).

Answer: Thank you for the comment. We have added the complete authors' list as suggested by the reviewer (page 18, reference 13). Please find the revised version (R1 copy) of the submitted manuscript.

4) Page 20, Reference 29, please use capital letters for the initials of the authors, and use “et al.” after “Hui DS”, as the authors’ list is not complete.

Answer: Thank you for the comment. We have corrected the initials for the authors and use et al. after “Hui DS” (reference 29) as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

5) Page 21, Reference 36, please use capital letters for the initials of the authors, and include “Yan J-B” after “Li P,” in the authors’ list.

Answer: Thank you for the comment. We have used capital letters for the authors’ initials in reference 36, as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

6) Page 29, reference 107, please use capital letters for the initials of the authors. Reference: 1. Yang A, Wu Y, Yu G, Wang H (2021) Role of specialized pro-resolving lipid mediators in pulmonary inflammation diseases: mechanisms and development. *Respir Res* 22, 204. DOI: 10.1186/s12931-021-01792-y 2. Costantini S, Sharma A and Colonna G (2011). The Value of the Cytokinome Profile, *Inflammatory Diseases - A Modern Perspective*, Dr. Amit Nagal (Ed.), ISBN: 978-953-307-444-3, InTech, Available from: <http://www.intechopen.com/books/inflammatory-diseases-a-modern-perspective/the-value-of-the-cytokinome-profile>.

Answer: Thank you for the comment. We have corrected reference 107 as suggested by the reviewer. Please find the revised version (R1 copy) of the submitted manuscript.

Response to Reviewer #3:

The article of " Altered gut microbiota patterns in COVID-19: Markers for inflammation and disease severity" is an interesting review article which compiles all the major studies and observations related to effect of COVID19 on gut microbiota. Though the article specifies various mechanisms of the alteration of the gut microbiota in this condition beautifully I feel there are certain aspects which need to be highlighted

1) Patients with respiratory illness/ pneumonia are generally given antibiotics either empirically or to treat superimposed bacterial infections-is there any literature that reports on differences in gut microbiota based on usage or non- usage of antibiotics in COVID-19 patients.

Answer: Thank you for the comment. We have added a separate section about gut microbiota based on usage or non-usage of antibiotics in COVID-19 patients. Please find the revised version (R1 copy) of the submitted manuscript.

2) Also, is a particular population more predisposed to it - namely elderly, racial groups, comorbidities, nursing home residents etc. In the various studies specified it will be more helpful if you could describe the demographics of the study populations as a passing reference as well.

Answer: Thank you for the comment. We have added the demographics of the study populations in tables (table 1, 2, and 3) within the revised manuscript. Please find the revised version (R1 copy) of the submitted manuscript.

3) At certain places in the article I felt statements made should be supported by relevant references e.g 1st line of 3rd para of introduction, 1st line of 3rd para of topic "GI symptoms in COVID-19 patients" etc. You have mentioned about some trials for therapeutic implications - are there any observational studies, reports of usage of regular probiotics which have shown benefit in this situation.

Answer: Thank you for the comment. We have added the by relevant references in 1st line of 3rd para of the introduction, and 1st line of 3rd para of the topic "GI symptoms in COVID-19 patients" as suggested by the reviewer.

Yes; most of the trials for therapeutic implications are observational; we have included in table 3.

Please find the revised version (R1 copy) of the submitted manuscript.

Response to Reviewer #4:

This is a detailed review and extensive literature search on what is so far known regarding the role of gut microbiota in COVID 19 infection. including gastrointestinal symptoms in COVID 19, the severity of disease, and the cross-talk between various organ systems of the human body when infected with the virus. Figures and tables are self-explanatory. However, there are many aspects of the subject which remain to be studied. For example, it will be interesting to know whether there is a difference in gut microbial as far as the different COVID variants are concerned.

Answer: Thank you for the comment. We have added a new section about the gut microbiota and different COVID-19 variants as suggested by the reviewer. Also, we have added some new sections, which are as follows: Gut microbiota in elderly and co-morbid COVID-19 patients with certain medical conditions; Gut microbiota based on usage or non-usage of antibiotics in COVID-19 patients; Future perspective; and also added a new table (table 4). Please find the revised version (R1 copy) of the submitted manuscript.

Response to Reviewer #5:

Understanding the role of the gut microbiota in immune system modulation during SARS-CoV-2 infection may aid advances in therapeutic strategies for COVID-19 treatment. Chiranjib etc. reviewed several significant factors affecting the microbiota in COVID-19 patients. Generally speaking, this review was well written. However the following questions need to be addressed:

1, The part of Abstract should highly summarize the content of this article, however, in this version, it does not meet the criteria, it is better to improve.

Answer: Thank you for the comment. We have carefully revised and improved the abstract section based on novelty and summarized the article content. Please find the revised version (R1 copy) of the submitted manuscript.

2, The part of conclusion is too general, it is better to substantively refine the field of these studies.

Answer: Thank you for the comment. We have rewritten a more focused conclusion and substantively refined these studied' fields with novelty. We also added a new section 'Future perspective', within the manuscript. Please find the revised version (R1 copy) of the submitted manuscript.

Response to Science editor:

The role of intestinal microorganisms in the regulation of the immune system may contribute to the therapeutic strategy of covid-19 treatment. The manuscript is well, concisely and coherently organized and presented and the style. There are several small suggestions:

1 The summary should be more specific and attractive.

Answer: Thank you for the comment. We have revised the manuscript and made it more specific and attractive. Please find the revised version (R1 copy) of the submitted manuscript.

2. It would be better to emphasize some special and interesting ideas and distinguish them from relevant manuscripts.

Answer: Thank you for the comment. We have now emphasized some special, novel, and interesting topics in this manuscript. There are very few publications about the Gut-brain-lung axis, which we have included in our manuscript. Hypoxia in COVID-19 and gut microbiota also has been discussed in a separate section. We also added a new table (table 3) about the Clinical trials to understand gut microbiota's role in COVID-19 and its therapeutic implications. Also, we have added some new sections that are novel: Gut microbiota in elderly and co-morbid COVID-19 patients with certain medical conditions; Gut microbiota based on usage or non-usage of antibiotics in COVID-19 patients; Future perspective; and also added a new table (table 4). Please find the revised version (R1 copy) of the submitted manuscript.

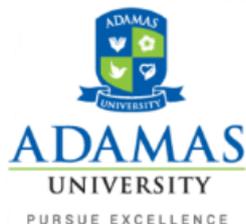
3. **Differences between different virus subtypes.**

Answer: Thank you for the comment. There is no study has been noted about different virus subtypes related to gut microbiota till date. Therefore, we have not included about the different virus subtypes in our submitted manuscript.

Response to editor-in-chief:

I have reviewed the Peer-Review Report, the full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors. Before final acceptance, uniform presentation should be used for figures showing the same or similar contents; for example, "Figure 1 Pathological changes of atrophic gastritis after treatment. A: ...; B: ...; C: ...; D: ...; E: ...; F: ...; G: ...". Please provide decomposable Figures (in which all components are movable and editable), organize them into a single PowerPoint file. Please authors are required to provide standard three-line tables, that is, only the top line, bottom line, and column line are displayed, while other table lines are hidden. The contents of each cell in the table should conform to the editing specifications, and the lines of each row or column of the table should be aligned. Do not use carriage returns or spaces to replace lines or vertical lines and do not segment cell content. In order to respect and protect the author's intellectual property rights and prevent others from misappropriating figures without the author's authorization or abusing figures without indicating the source, we will indicate the author's copyright for figures originally generated by the author, and if the author has used a figure published elsewhere or that is copyrighted, the author needs to be authorized by the previous publisher or the copyright holder and/or indicate the reference source and copyrights. Please check and confirm whether the figures are original (i.e. generated de novo by the author(s) for this paper). If the picture is 'original', the author needs to add the following copyright information to the bottom right-hand side of the picture in PowerPoint (PPT): Copyright ©The Author(s) 2022. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published; and correctly indicating the reference source and copyrights. For example, "Figure 1 Histopathological examination by hematoxylin-eosin staining (200×). A: Control group; B: Model group; C: Pioglitazone hydrochloride group; D: Chinese herbal medicine group. Citation: Yang JM, Sun Y, Wang M, Zhang XL, Zhang SJ, Gao YS, Chen L, Wu MY, Zhou L, Zhou YM, Wang Y, Zheng FJ, Li YH. Regulatory effect of a Chinese herbal medicine formula on non-alcoholic fatty liver disease. World J Gastroenterol 2019; 25(34): 5105-5119. Copyright ©The Author(s) 2019. Published by Baishideng Publishing Group Inc[6]". And please cite the reference source in the references list. If the author fails to properly cite the published or copyrighted picture(s) or table(s) as described above, he/she will be subject to withdrawal of the article from BPG publications and may even be held liable.

Answer: Thank you for the comment. We have corrected and reformatted the figures as suggested by the editor-in-chief. All submitted figures are original and developed by co-authors, with no such part of the figures having any copyright issue. Tables are also formatted as suggested, followed by the journal guidelines. Please find the revised version (R1 copy) of the submitted manuscript.



From: Dr. Chiranjib Chakraborty,
Professor, School of Life Science and Biotechnology,
Adamas University, Kolkata, India.

To,

Lian-Sheng Ma,
Editorial Office Director, Company Editor-in-Chief, Editorial Office
World Journal of Gastroenterology
Baishideng Publishing Group Inc.

Dear Sir,

Greetings!

Enclosed, please find our revision of the manuscript entitled, “*Altered gut microbiota patterns in COVID-19: Markers for inflammation and disease severity*” (Manuscript NO.: 73237, Review) by Chakraborty *et al.* This manuscript has been revised in accordance with the comments raised by the reviewers and editors. All changes are marked by the red color option of Microsoft word.

We want to thank the Editor and reviewers for the helpful comments and suggestions provided for our manuscript. This helped us to enrich the scientific quality of the manuscript. We have adequately addressed the comments raised by the Editor. We hope to hear from you in the near future about the acceptability of our manuscript for publication in your esteemed Journal.

Lately, I have reviewed the article (Reviewer’s Code: 00503359, 23 October 2020) of your Journal. So I kindly request you a discount on the article processing charge (APC) for this article. Due to the financial crisis during the pandemic, the government is not releasing the research grant properly. At the same time, we are passing through an acute economic crisis. Therefore, we request you to kindly provide us with some discount on APC of the Journal. We can pay a maximum of USD 950 (with tax) for this article as APC.

Please feel free to contact us in case you need any more clarifications.

I look forward to your kind response.

Thank you for your kind cooperation.

With best regards,



Chiranjib Chakraborty, Ph.D.

Professor, School of Life Science and Biotechnology,

Adamas University, Kolkata, India

Academic Editor: iScience (Cell press Journal) (IF= 5.458); Handling/Receiving Editor:

Infection ,Genetics and Evolution (IF=3.342); Associate Editor: Frontiers in Bioengineering and

Biotechnology (IF= 5.890); Associate Editor: Frontiers in Pharmacology (IF= 5.810)

Profile: <http://community.frontiersin.org/people/ChiranjibChakraborty/18716>

Google Scholar Id: 3m8rwpUAAAAJ

Point-by-point response to the comments of the editors

We appreciate the encouraging comments of the Editor and reviewers on the current study. As suggested by the Editor and reviewers, we did our best to address the following points raised by the reviewers. We welcome the opportunity to clarify and revise our manuscript to make its scientific contributions more perceptible.

Response to Reviewer #1:

We are very pleased to receive your revised manuscript (No.73237). However, there are some questions that need to be addressed. -----

1. I want to confirm whether all figures are original. If an author of a submission is re-using a figure or figures published elsewhere, or that is copyrighted, the author must provide documentation that the previous publisher or copyright holder has given permission for the figure to be re-published. Please provide the permission certificate.

Answer: Thank you for the comment. All submitted figures are original and developed by co-authors, with no such part of the figures having any copyright issue. Please find the revised version (R2 copy) of the submitted manuscript.

-----2. Further language polishing is required in order to meet the publication requirement (Grade A). Now, you are requested to send the revised manuscript to a professional English language editing company or a native English-speaking expert to polish the language further. When you submit the subsequent polished manuscript to us, you must provide a new language certificate along with it.-----

Answer: Thank you for the comment. Please note that we have corrected our manuscript by a professional editing service and the certificate is attached herewith. Again, the revised version of the manuscript (R2 Copy) has been checked by a native English speaker who has checked the R2 copy of the manuscript thoroughly.

3. Please mark the specific position of “figure 4-7” in your manuscript.

Answer: Thank you for the comment. We have mark the specific position of “figure 4-7” in our submitted manuscript. Please find the revised version (R2 copy) of the submitted manuscript.

----4. Please delete duplicates in references and renumber them. It is unacceptable to have more than 3 references from the same journal. To resolve this issue and move forward in the publication process, please revise your reference list in the attached file “73237 ref”.

Answer: Thank you for the comment. We have deleted all duplicate references and renumbered it. Please note that the cited references are very text and content specific. Therefore, we are unable to delete or replace the reference because, if we change the reference the flow of the manuscript text and scientific specificity will be lost. Please find the revised version (R2 copy) of the submitted manuscript.

----5. We request that the first author make an audio file describing your final core tip. Acceptable file formats: .mp3, .wav, or .aiff. Maximum file size: 10 MB.----Please revise in the attached file “73237_Auto_edited” and reply within two weeks, thank you!

Answer: Thank you for the comment. We have prepared the audio file as per the instructions. Please find the revised version (R1 copy) of the submitted manuscript.