

Review of: "Proposal to Explain the Cause of Long COVID Based on the Concept of Host Factor Variants"

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Potential competing interests: No potential competing interests to declare.

The paper titled **"Proposal to Explain the Cause of Long COVID Based on the Concept of Host Factor Variants"** aims to explain the cause of long COVID through the host factors variants concept, which involves cellular variants and major histocompatibility complex (MHC) polymorphism.

I think that this work is very interesting but I suggest a major revision as some aspects have to be considered in the light of the research done during the Covid 19 pandemic. This will allow the authors to update the state of the art and at the same time clarify their hypothesis and support it more. The paper should be integrated considering the following aspects:

- It is important to read and quote the following very recent paper: Interplay between Multisystem Inflammatory Syndrome in Children, Interleukin 6, Microbiome, and Gut Barrier Integrity <https://doi.org/10.3390/immuno4030015>
- The COVID-19 pandemic has sparked a surge in research on microbiology and virology, shedding light on overlooked aspects such as the infection of bacteria by RNA virions in the animal microbiome. Studies reveal a decrease in beneficial gut bacteria during COVID-19, indicating a significant interaction between SARS-CoV-2 and the human microbiome. I suggest the authors to read and quote this article: DOI 10.3390/microorganisms12040643
- The early use of antibiotics seems to be crucial to inhibit disease progression—to prevent viral replication in the gut microbiome, and control toxicological production from the human microbiome. It has been studied the impact of specific antibiotics on recovery from COVID-19 and long COVID (LC). I suggest the authors to read and quote this article: 10.1002/jmv.29507
- The introduction needs to be expanded with the following new papers, because it should also mention that it is possible to detect SARS-COV2 in fecal specimens from patients with Covid's pneumonia findings on CT but negative to multiple RT-PCR testing of SARS-CoV-2 on oropharyngeal and nasopharyngeal swab specimens. For this purpose, it is best to read and cite the following work: doi: 10.3390/medicina57030290.
- In addition, it is important to report that SARS-CoV-2 could have Bacteriophage Behavior or Induce the Activity of Other Bacteriophages doi: 10.3390/vaccines10050708 and its mechanism: 10.3390/ijms24043929; 10.3390/microorganisms12040643.
- I suggest reading and citing the following recent works: Detection of recombinant Spike protein in the blood of individuals vaccinated against SARS-CoV-2: Possible molecular mechanisms: 10.1002/prca.202300048; A retrospective cohort study on early antibiotic use in vaccinated and unvaccinated COVID-19 patients. 10.1002/jmv.29507.

- In addition, there have been several investigators who have studied the relationship between the gut microbiota and COVID19. For example, it was shown that people with COVID- 19 had toxin-like peptides, which were almost identical to the toxic components of animal venoms, such as conotoxin, phospholipases, phosphodiesterases, zinc-metal proteinases, and bradykinins, in both blood, feces, and urine. (Toxin-like Peptides from the Bacterial Cultures Derived from Gut Microbiome Infected by SARS-CoV-2-New Data for a Possible Role in the Long COVID Pattern) [10.3390/biomedicines11010087](https://doi.org/10.3390/biomedicines11010087)
- In addition, spontaneous replication of SARS-CoV-2 was observed in bacterial cultures of patients' feces for up to 30 days and beyond [10.1080/19490976.2023.2244718](https://doi.org/10.1080/19490976.2023.2244718).
- I suggest the authors to read and quote this review article focuses on medical biochemistry, proteomics and deutenomics principles that explain the persisting spike phenomenon in circulation with organ-related functional damage even in asymptomatic individuals: [10.1002/prp2.1218](https://doi.org/10.1002/prp2.1218)
- The authors should make a little effort to make the work comprehensible to a broader spectrum of readers
- I believe that to make the article more appealing you should include a nice color image that summarizes the results, the molecular mechanism and the message the authors want to give
- Define the major limitation of this work