

RESPONSES TO REVIEWERS' COMMENT:

Combined use of lactoferrin and vitamin D as a preventive and therapeutic supplement for SARS-CoV-2 infection: Current evidence

Cipriano M *et al.* Lactoferrin and vitamin D against SARS-CoV-2 infection

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Reviewer #1:

- This is a review paper, highlighting the use of lactoferrin and vitamin D as a preventive and therapeutic supplement for SARS-CoV-2 infection. Therefore, I suggest to revise the title to give clear view that this is a review paper.

Response: Given that this is an opinion review we understand that the title of the article is appropriate for the text.

- There were only 11 papers being cited in this manuscript. And only last 3 papers discuss on the use of combination of LF and vitamin D in SARS-CoV-2 (animal study). Thus, I suggest for the authors to define the method how the search for previous related published research being conducted.

Response: Given that this is an opinion review, we understand that the description of the methodology used is not mandatory. We chose relevant articles (according to the study objective) indexed in the main databases including PubMed, Web of Science and Scopus.

- Usual format for review including narrative review is to start with introduction segment, followed by the discussion. I still suggest for the authors to follow the format.

Response: Suggestion accepted. The article has the following sections: introduction, discussion (divided into subsections) and conclusion.

Reviewer #2:

- This review proposed LF as a potential treatment for COVID-19, which is an interesting topic. However, the follow points need to be refined. 1. the mechanism of LF on

preventing COVID-19 were not specific on SRAR-Cov-2. Its anti-virus function were general instead of specific.

Response: We have included new insights in this regard.

- 2. The issue also exists for Vit D.

Response: We have included new insights in this regard.

- 3. LF induced neonatal MDSC, which alleviated the necrotizing enterocolitis in neonates. Besides, LF induced MDSC relieved inflammatory complications of certain medicines. LF induced MDSC presented anti-infection function, which was opposite to MDSC in pathologic conditions. Meanwhile, MDSC was found to hazard the prognosis of COVID-19 patients. This should be discussed.

Response: We have included new insights in this regard.

- 4. LF was the major ingredients of breast milk. Does LF protected infants? 5. The physiological and pathological role of LF shall be mentioned.

Response: We have included new insights in this regard.

Reviewer #3:

- This is an interesting hypothesis and with recent studies suggesting low vitamin D levels to be associated with Covid severity, the potential of lactoferrin in enhancing vitamin D's immunomodulatory effects, besides lactoferrin's proposed beneficial effects, needs to be investigated.

Response: We have included new insights in this regard.

The authors are grateful for the comments and suggestions of the three reviewers.

Best regards,
Marcos Roberto Tovani-Palone