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# Letter to the Editor

## Are probiotics effective adjuvant therapeutic choice in patients with COVID-19?

*Dear Editor,*

we read very carefully the Editorial of Gao et al[1] about the effort needed to be put to patients with COVID-19 with an initial presentation of gastrointestinal symptoms.

On December 31, 2019, the Chinese health authorities announced the presence of an outbreak of febrile syndrome, associated with lungs of unknown origin[2]. The pathogen is a new β-coronavirus, called SARS-CoV-2, due to the genetic concordance (89.1%) with coronaviruses similar to SARS. The disease caused by the new virus was called COVID-19. The main symptoms are fever, cough and wheezing[3]. Patients in critical condition rapidly develop Acute Respiratory Distress Syndrome (ARDS), respiratory failure, multiple organ failure, even deaths[4]. Moreover, COVID-19 interact with GUT microbiota since about 5-10% of patients show diarrhea and gastrointestinal symptoms.

SARS-CoV peak S protein trimers bind a hydrophobic pocket of the extracellular catalytic domain of Angiotensin-Converting Enzyme 2 (ACE2), accounting the possible route for COVID-19[5]. ACE2 is expressed in endothelial cells of the vasculature and also in the epithelia of the lungs, intestine, and it plays a major role in acute lung injury and ARDS[6]. Following SARS-CoV entry, ACE2 increased Angiotensin II levels, providing a molecular explanation for the development of ARDS.

Given the presence of ACE2 in the intestine, there may be the possibility of a cross-talk between lung and gut. The presence of viral nucleic acids in the fecal samples and anal swabs of patients with COVID-19[7]], could explain the diarrhea (2%-10.1%) observed in COVID-19, related to a more serious clinical course of the disease. Moreover, ACE2 regulates amino acid transport in the intestine, and reduced tryptophan levels lead to reduced mTOR pathway activity in the small intestine[8]. The aberrant activation of mTOR causes an altered expression of antimicrobial peptides from small intestinal Paneth cells, which in turn alters the composition of the intestinal microbiota, with a vicious cycle.

As most patients had a good prognosis, while some were in critical condition, especially those with chronic underlying diseases, the immune response is essential for the control and resolution of COVID-19. It has been shown that rebalancing the gut microbiota can reduce enteritis and ventilator-associated pneumonia[9]. In different pathological situations, including COVID-19, the loss of homeostatic equilibrium between TREG cells (IL-10) and Th17 cells (IL-17) was observed. Therefore, it is possible to hypothesize the therapeutic use of probiotics and their metabolites, such as propionic acid, to restore the innate and adaptive immunity[10].

It is conceivable to use probiotics, as *Lactobacillus rhamnosus* and *Bifidumbacterium lactis* HN019, that exhibit anti-inflammatory effects, to maintain the balance of intestinal microecology and prevent secondary bacterial infection in patients with COVID-19. Moreover, as hypo-nutrition aggravates the impaired immunity in COVID-19, we suggest for a correct immunomodulation a prebiotic, probiotic, postbiotic, polyphenols, and zinc supplementation, that are able to restore innate and adaptive immunity and may be an adjuvant therapeutic choice of COVID-19.

**Conflict of Interest**

The Authors declare that they have no conflict of interests.



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## References


1) Gao QY, Chen YX, Fan JF. 2019 Novel coronavirus infection and gastrointestinal tract. J Dig Dis 2020; 21: 125-126. 10.1111/1751-2980.12851.
2) Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, Hu Y, Tao ZW, Tian JH, Pei YY, Yuan ML, Zhang YL, Dai FH, Liu Y, Wang QM, Zheng JJ, Xu L, Holmes EC, Zhang YZ. A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265-269.
3) Wang D, Hu B, Hu C, Zhu F, Liu X, Zang J, Wang B, Xiang H, Cheng Z, Yong Xiong, Zhao Y, Li Y, Wang X, Peng Z. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323: 1061-1069.
4) Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, Zhang L, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo L, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395: 497-506.
5) Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, Wang W, Song H, Huang B, Zhu N, Bi Y, Ma X, Zhan F, Wang L, Hu T, Zhou H, Hu Z, Zhou W, Zhao L, Chen J, Meng Y, Wang J, Lin Y, Yuan J, Xie Z, Ma J, Liu WJ, Wang D, Xu W, Holmes EC, Gao GF, Wu G, Chen W, Shi W, Tan W. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395: 565-574.
6) Imai Y, Kuba K, Ohto-Nakanishi T, Penninger JM. Angiotensin- converting enzyme 2 (ACE2) in disease pathogenesis. Circ J 2010; 74: 93-100.
7) Zhang W, Du RH, Li B, Zheng XS, Yang XL, Hu B, Wang YY, Xiao F, Yan B, Shi ZL, Zhou P. Molecular and serological investigation of 2019-nCoV infected patients: implication of multiple shedding routes. Emerg Microbes Infect 2020; 9: 386-389.
8) Hashimoto T, Perlot Y, Rehman A, Trichereau J, Ishiguro H, Paolino M, Sigl V, Hanada T, Hanada R, Lipinski S, Wild B, Camargo SM, Singer D, Richter A, Kuba K, Fukamizu A, Schreiber S, Clevers H, Verrey F, Rosenstiel P, Penninger JM. ACE2 links amino acid malnutrition to microbial ecology and intestinal inflammation. Nature 2012; 25; 487: 477-481.
9) Bradley KC, Finsterbusch K, Schnepf D, Crotta S, Llorian M, Davidson S, Fuchs SY, Staeheli P, Wack A. Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection. Cell Rep 2019; 28: 245-256.e4.
10) Soldati L, Di Renzo L, Jirillo E, Ascierto PA, Marincola FM, De Lorenzo A. The influence of diet on anti-cancer immune responsiveness. J Translat Med 2018; 16: 75-92.



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