Targeting the gut–lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection

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Abstract: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) 1 is a 2019 novel coronavirus, which only in the European area has led to more than 300,000 cases with at least 21,000 deaths. This manuscript aims to speculate that the manipulation of the microbial patterns through the use of probiotics and dietary fibers consumption may contribute to reduce inflammation and strengthen the immune system response in COVID-19 infection.

The reviews of this paper are available via the supplemental material section.

keywords: anti-inflammatory effects, COVID-19 infection, gut-lung microbiota aixs, high-fibre diet, probiotics, SARS-CoV-2

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[1] is a novel coronavirus first discovered in Wuhan, China, in December 2019, and is the seventh coronavirus species known to cause human disease. On 11 February 2020, the World Health Organization officially named the resulting illness corona virus disease-19 (COVID-19).[2] As of 19 May 2020, more than 225,886 cases of COVID-19 have been reported in Italy alone, with at least 32,007 deaths. Additional cases have been reported from all around the world.[3]

While many infected patients remain completely asymptomatic but yet fully capable of transmitting the virus,[4,5] other patients shows aberrant clinical manifestations such as fever, dyspnoea and cough, with less common symptoms including headache, sputum production and haemoptysis. Gastrointestinal symptoms, such as diarrhoea, nausea and vomiting, are rare.[6,7] In addition to these symptoms in patients with COVID-19, it has also been observed that aberrant pathogenic T cells and inflammatory monocytes are rapidly activated, producing a large number of cytokines and inducing an inflammatory storm.[8] Severe patients may develop acute respiratory distress syndrome, a decrement in the ratio of arterial partial pressure of oxygen (PO_2) to inhaled fraction of inspired oxygen (FiO_2) accompanied by development of bilateral infiltrates and hypoxaemia.[9] The majority of these patients require mechanical ventilation and tend to remain ventilator dependent for up to 2 weeks; sometimes they succumb to the disease.[10,11] To date, we understand little regarding the factors that govern either development or remission of severe disease. However, the most significant predictors of disease severity relate to either hyperactivation or dysregulation/suppression of the host immune response.[12]

COVID-19 is reported to be related to a group of SARS-like coronaviruses, with 89.1% nucleotide similarity.[13] Structural similarity is seen particularly in the domains binding to the angiotensin-converting enzyme-2 (ACE2) host receptor,[14,15] largely expressed in the epithelium of the lungs, liver and intestine. Specifically, expression of ACE2 has also been identified on the luminal surface of differentiated epithelial cells in the small intestine as well as in the colon and crypt cells.[16]

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The fact that ACE2 mutants exhibit altered gut microbial composition,[16] and patients with respiratory infections, including COVID-19 infection, may generally have gut microbial alterations and dysfunction, has led some researchers to link COVID-19 to the gut microbiota.[17] The involvement of the gastrointestinal milieu in COVID-19 is also supported by small case series showing that some patients have an altered gut microbiota composition, with depleted *Lactobacillus* and *Bifidobacterium*. However, we still need larger cohort studies to confirm this topic in the future.[18] Notably, the gut–lung axis, the crosstalk between the intestinal tract and the lungs, involves continuous bidirectional communication *via* the blood system, which is thus potentially able to modulate the local immunity of both the gut and the lungs, as well as their respective microbial patterns and composition.[19] Since the role of the microbiota is to maintain homeostasis and modulate local immune response, it is quite logical to expect that microbial alteration, known as dysbiosis, can contribute to the onset of disease. However, although it is clear that gut microbiota influences inflammation in the peripheral system, what happens in the lungs is still poorly understood.[20]

Numerous variables can affect lung microbiota, including bacterial composition, host immune response, lifestyle, diet, cigarette smoking and the use of certain drugs, such as antibiotics and corticosteroids.[21] As well as seeking to modify some of these habits whenever possible, we speculate that targeting the gut–lung microbiota axis by means of diet and dietary supplements may support COVID-19 management. Among dietary supplements, potential new treatments against COVID-19 infection could be based on probiotics,[17,22] which might not only reduce colonisation by pathogenic species but also increase commensal bacterial growth in the respiratory tract. Commensal bacterial species can suppress the growth of pathogens belonging to the same family or genus, suggesting the important role of bacterial interactions in maintaining homeostasis.[23,24] However, although probiotic treatment seems functional and promising, it has the disadvantage of inducing irritating side effects such as meteorism and flatulence due to a non-selective fermentation effect by gut bacteria.[25] To improve the therapeutic efficacy, 'prebiotics', with a specific fermentation, are also used. The term 'prebiotics' refers to food ingredients that are non-digestible and show beneficial effects on the host by stimulating the activity and growth of probiotics after colon fermentation.[25,26] Dietary supplements composed of both probiotics and prebiotics are also used and are called 'synbiotics'.[27]

On the other hand, diet also has a strong impact on microbiota. For those patients with COVID-19 that are able to follow their own diet, such as asymptomatic patients and patients with mild symptoms or in quarantine, it is advisable to pursue a healthy balanced diet, rich in cereals, whole grains, legumes, fruits and vegetables. The reason for emphasising this kind of diet is the inverse correlation between the consumption of dietary fibre and the serum levels of C-reactive protein, Interleukin (IL)-6, IL-18 and tumor necrosis factor-alpha (TNFα) which are strong inflammatory cytokines. In addition, high-fibre diets are associated with lower glucose concentrations and higher plasma concentrations of adiponectin, an insulin-sensitising adipocytokine with anti-inflammatory properties.[28–32] The pathogenesis of SARS-CoV-2 is accompanied by a massive release of pro-inflammatory cytokines including IL-6, TNFα and IL-12. These considerations have prompted the clinical community to test immunosuppressive drugs against the coronavirus, including tocilizumab, which is an anti-IL-6 receptor drug that has shown efficacy in reducing C-reactive protein, alleviating symptoms and improving oxygen intake.[33] It is thus clear that the anti-inflammatory effects of dietary fibre can strongly support the action of antiviral and immunosuppressive drug therapies.

The anti-inflammatory mechanisms promoted by these complex carbohydrates may derive from their soluble nature, which enables them to be fermented by certain species of intestinal bacteria, producing several metabolites, of which the most widely recognised are short chain fatty acids (SCFAs). SCFAs are physiologically active bioproducts mainly composed of acetate, propionate and butyrate, able to regulate host metabolism, immune system and cell proliferation.[34] The major species that produce SCFAs are *Bacteroides* spp., *Bifidobacterium* spp. and *Prevotella* spp., but also *Streptococcus* spp., Firmicutes, *Clostridium* spp. and many others.[34–36] These products of microbial activity can have one to six carbon atoms (C1–C6). Acetate has two carbon atoms (C2) and emerges from acetyl-CoA or by the reductive acetyl-CoA pathway.[37] Propionate has three carbon atoms (C3) and derives from the

succinate pathway or from the lactate as precursor and simple sugars substrates in the acrylate pathway. Propionate is also formed *via* the propanediol pathway with fucose and rhamnose as substrates.[36] Butyrate is synthesised as a result of the reduction of acetoacetyl-CoA to butyryl-CoA and to butyrate by butyrate kinase and transbutyrylase.[38] Butyryl-CoA may also form butyrate through butyryl-CoA transferase-acetate Co-A.[39,40] These molecules are absorbed into the blood stream and transported to peripheral tissues where they are able to regulate the immune system and host metabolism, and reduce inflammation.[34,41–43] These bacterial products promote anti-inflammatory mechanisms by acting as signalling molecules, producing anti-inflammatory cytokines while reducing chemotaxis and immune cell adherence.[34,44] It has also been shown that SCFAs may enhance the haematopoiesis of dendritic cell precursors from bone marrow, activating T_H2 effector cells in the lung and thus providing a humoral response to extracellular bacteria, parasites and toxins.[20] Furthermore, the intake of whole grains is reported to have a beneficial effect on lung injuries and to reduce chronic respiratory disease mortality.[45–47] A healthy balanced diet, mainly characterised by high consumption of fruits, vegetables, wholegrains, plant oils and fish, low alcohol consumption (preferably wine), and avoidance of high-saturated fat foods, refined sugar, red meats and sugar-containing beverages, would be recommended, along with physical exercise.

All these findings support the hypothesis that prebiotics, probiotics and a higher intake of dietary fibre may constitute a valuable supportive medical treatment, promoting anti-inflammatory effects and augmenting immune response. Specifically, all these strategies can be adopted in asymptomatic patients and patients with mild symptoms or in quarantine who can follow their own diet in order to prevent and reduce systemic inflammation and also specifically to improve alveolar-capillary function and lung permeability. In addition, this strategy can be also used in the acute phase of COVID-19 to prevent worsening of pulmonary interstitial lesions and to mitigate postinfection complications, including fibrotic outcomes.

In conclusion, the most common therapeutic options for viral infections are directed at either blocking viral entry and replication or promoting durable cellular and humoral immunity for the uninfected population *via* vaccination.[12] Since there is no vaccine or specific efficacious clinically proven therapies available at the moment, preventing SARS-CoV-2 infection by maintaining high hygiene by washing our hands, avoiding contact with infected people and reinforcing the immune system are the best strategies. Although there is no clinical evidence that targeting the gut–lung microbiota axis would play a therapeutic role in COVID-19 infection, we believe that the manipulation of microbial patterns through the use of probiotics, prebiotics and a high-fibre diet may help to reduce cell inflammation, maintain a healthy gut microbial diversity and strengthen the immune system. However, an enormous effort to find new antiviral and anti-inflammatory therapies for this fatal infectious disease is still required.

Author contribution(s)

Luana Conte: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing-original draft; Writing-review & editing.

Domenico Maurizio Toraldo: Conceptualization; Methodology; Supervision; Writing-review & editing.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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