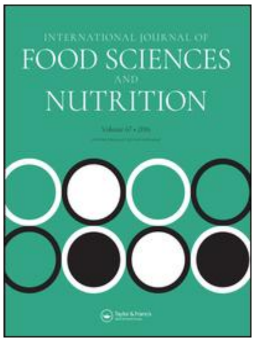

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ABSTRACT

Coronavirus disease 2019 (COVID-19) has become pandemic very rapidly at the beginning of 2020. In the rush to possible therapeutic options, probiotics administration has been proposed mainly based on indirect observation. Some evidence of COVID-19 effects on intestinal microbiota dysbiosis has been shown and probiotics have been considered for their efficacy in the management of respiratory tract viral infections. These observations could be reinforced by the more and more evident existence of a lung-gut axis, suggesting the modulation of gut microbiota among the approaches to the COVID-19 prevention and treatment. As different possible roles of probiotics in this extremely severe illness have been contemplated, the aim of this work is to collect all the currently available information related to this topic, providing a starting point for future studies focussing on it.

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Introduction

In December 2019 a viral outbreak referred to as COVID-19 (Heymann and Shindo 2020) has been reported from Wuhan, China. The viral agent has been recognised as a zoonotic beta-coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), similar to other SARS and MERS (Middle East Respiratory Syndrome) coronaviruses (Liu et al. 2020). COVID-19 causes a severe acute respiratory syndrome (SARS) named specifically SARS-CoV-2 with a lethality ranging from 2% in China (Xu et al. 2020) to 12% in certain region of Italy (Conticini et al. 2020). Post-mortem analysis on a patient died by SARS-CoV-2 conducted by these authors on lung, liver and hearth tissue that had shown severe damages at lungs with oedema and desquamation, evident symptoms of breath complications and fatigue. Some patients with COVID-19 showed intestinal microbial dysbiosis with decreased probiotics such as *Lactobacillus* and *Bifidobacterium*, suggesting the needing to assess nutritional and gastrointestinal function for all patients (Xu et al. 2020). Formerly, dysbiosis of the human gut microbiome has been linked to various health conditions, including respiratory tract infections (RTIs) through the gut-lung axis (Chan et al. 2020). Many studies, conducted on a variety of participant, with different ages, provenience and social extraction have explored the correlation between the ingestion of probiotics or symbiotics, in different forms and the onset of diseases, with a particular attention to RTIs (Auinger et al. 2013; Cohen et al. 2013; Gerasimov et al. 2016; Panigrahi et al. 2017). Nutritional support and application of prebiotics or probiotics were suggested also in COVID-19 infected patients, to regulate the balance of intestinal microbiota and reduce the risk of secondary infection due to bacterial translocation (Xu et al. 2020). Other authors have speculated that COVID-19 may be related to the gut microbiota, since some evidence highlighted a secondary gut infection or disfunction in patient with RTIs, probably due also to antibiotics which are not selective towards harmful bacteria. This suggest also a gut–lung crosstalk, and in some extent that the symptoms may be modulated by probiotics, altering in this way the gastrointestinal symptoms favourably and protecting also the respiratory system (Gao et al. 2020). Despite no treatment has been approved so far for the treatment or prevention of COVID-19 infections due to the lack of scientific evidences and clinical trials, an urgent need to find options to help these patients and preclude potential death is pushing the entire scientific community to focus on this topic (Kruse 2020). As a possible role of probiotics in COVID-19 prevention and treatment has been contemplated (Baud et al. 2020), the aim of this work is to collect all the currently

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available information related to this topic, providing a starting point for future studies focussing on it.

Role of probiotics in health and diseases

Probiotics are "live microorganisms which when administered in adequate amounts confer health benefits to the host" (FAO/WHO 2002). Their use to enhance human health has been studied since long, formerly as food ingredients and later also as cultures preparations (Timmerman et al. 2004; Collado et al. 2007; Kechagia et al. 2013). The application of probiotics has been primarily investigated for the prevention and treatment of gastrointestinal infections and diseases (Parvez et al. 2006), but other possible effects have been studied such as nutritional effects, prevention and treatment of oral infections, diarrhoea caused by several factors, irritable bowel syndrome, inflammatory bowel diseases, *Helycobacter pylori* infections, allergic diseases, antitumor effects and reduction of serum cholesterol (Lee and Salminen 2009; Cruz et al. 2020). Due to the reported ability of several probiotic strains to improve mucosal immunity against pathogens, possible effects also in the prevention and treatment of RTIs have been suggested. However, the efficacy and safety of probiotics are strain, dose, disease and possibly host dependent. Furthermore, despite the huge increase of *in vitro* studies regarding probiotic strains, the needing for *in vivo* studies, followed by animal studies and clinical trials on human studies, has been underlined (Collado et al. 2009). All this considered, as clinical data sustaining the use of probiotic in preventing COVID-19 are increasing, their use to reduce the burden and severity of this pandemic appears worthy of consideration (Baud et al. 2020).

Probiotic effects on immune responses

Boosting immune responses during the incubation and non-severe stages of Covid-19 infection, to eliminate the virus and preclude disease progression to severe stages, have been proposed as extremely important. In the gastrointestinal tract (GIT), known as one of the most microbiologically active ecosystems playing a crucial role in the working of the mucosal immune system, probiotics stimulate the immune system and induce a network of signals mediated by the whole bacteria or their cell wall structure (Maldonado Galdeano et al. 2019). Many probiotic effects are mediated through immune regulation, particularly through balance control of proinflammatory and anti-inflammatory cytokines (Isolauri et al. 2001). Another important effect exerted by probiotics is to enforce and maintain the integrity of junction between enterocytes, in this way entrance of SARS-CoV2 is reduced, as well as the risk to develop COVID-19 (Baud et al. 2020). During recent years, the connection between gut microbiota and general health have been demonstrated. Diet can modulate the functionality of the intestinal microbiome which uses nutrients from ingested foods, releases harmful or beneficial metabolites and regulates the immune system (De Filippis et al. 2016; De Angelis et al. 2020). The gut mucosal surface is a principal site of entry of pathogens into the human body but in healthy subjects, intestinal epithelium and its microbiota provide an efficient barrier to invading microorganisms (Fava et al. 2015). Gut is involved in immunity as dendritic cells of the intestinal lumen are the first cells of the mucosal immune system to encounter commensal and pathogenic bacteria (Tang et al. 2009). Dysbiosis, meaning imbalances in the composition and function of the intestinal microbes, is associated with various human diseases (Illiano et al. 2020). Thus, manipulation of the intestinal microbiota has been proposed as a potential alternative approach for maintaining health and preventing and/or treating diseases (Yan and Polk 2011). This can be done by stimulating beneficial bacteria colonising the GIT through the diet (Bottari et al. 2017) or by the administration of probiotics. Probiotics able to assist in restoring unbalanced microbiota and maintaining gut immune homeostasis have been defined also as immunobiotics, i.e. microorganisms which possess the ability of improve innate immune response. Some studies have shown that this stimulation is exerted by intra and extra cellular molecules like peptidoglycan, phospho-polysaccharides lipoteichoic acid or DNA. Specifically, the ability to modulate the innate immune system is attributed to membrane molecules of probiotics that can communicate and signalling with the epithelial cells of gut, exerting in this way the probiotic effect (Villena et al. 2008). Modulation activity of immune system is also fundamental since it has been proven that an excessive immune response can cause as much damages as the pathogenic infection itself. Restoring gut microbiota has been shown to improve resistance to virus or pathogenic attacks also at the respiratory mucosa level (Racedo et al. 2009; Zelaya et al. 2016). In different trials, it has been demonstrated that probiotics, such as *L. rhamnosus* GG, can help improving intestinal and lung barrier and homeostasis, by increasing regulatory T cells, ameliorating anti-viral defense, and decrease pro-inflammatory cytokines in systemic and respiratory infections. These immunomodulatory benefits are especially important to individuals who have developed, or are at risk of developing, COVID-19 (Campbell 2020). The gut and lungs are anatomically distinct, but potential anatomic communications and complex pathways involving their respective microbiota have reinforced the existence of a gut–lung axis, which can shape immune responses and interfere with the course of respiratory diseases. Probiotic strains could be used to manipulate these microbiota, offering new perspectives in the management of respiratory failures (Enaud et al. 2020) which is one of the leading causes of death due to COVID-19 infection (Hor et al. 2018).

Probiotics used for prevention and treatment of respiratory tract infections

In recent years' probiotic strains have been increasingly considered as a powerful ally in fighting and prevent RTIs. Treatments with probiotics bacteria have been shown to reduce both upper and lower respiratory tracts infections (Campbell 2020). Probiotic lactic acid bacteria (LAB) have been administered both directly in the respiratory tract or integrated in the diet to improve the immune response and fight viral infections (Barbieri et al. 2017). In that study the author evaluates the effect of *L. rhamnosus* CRL1505 in modulating the immune response of malnourished mice towards inoculated *Streptococcus pneumoniae* (Barbieri et al. 2017). Mice supplemented with *L. rhamnosus* CRL 1505 showed an ameliorated response to *S. pneumoniae* infections mediated by myeloid cells and lymphocytes B. In another study by Perdigón (Perdigón et al. 2001), mice infected with *S. pneumoniae* were administrated with 1 of 3 different probiotic LAB strains, *Lactobacillus casei* CRL 431, *Lactococcus lactis* NZ9000, *L. rhamnosus* CRL1505 or a probiotic fermented yoghurt produced by *Lactocbacillus delbrueckii* subsp. *bulgaricus* CRL 423 and *Streptococcus termophilus* CRL 412. In all cases, several beneficial effects were recorded in treated mice such as the reduction of pathogen present in lungs and blood, an increase of neutrophil count in blood and higher level of IgA, known for the anti-pneumococcal activity, in the intestine and in the aerial ways (Perdigón et al. 2001; Le Loir et al. 2005; Racedo et al. 2009). Probiotic LAB have been used also as antiviral agent to fight or prevent respiratory infections both in human and animals, administrated locally or involved in food preparation (Al Kassaa et al. 2014; Barbieri et al. 2017). They have been described for their ability to inhibit virus by directly interacting with them with a mechanism similar to phagocytosis. As an example, *Lactobacillus plantarum* YU, isolated from fermented Japanese food, showed a very high interleukine-12-inducing activity *in vitro*, inducing activity in mouse peritoneal macrophages. The probiotic strain suppressed antigen-specific Immunoglobulin E production by activation of Th1 immune responses in mice and enhanced natural killer cell activity and IgA production *in vitro*, proving a protective effect against influenza A virus infection *in vivo* (Kawashima et al. 2011). More recently lactobacilli isolated from healthy human noses have been shown to have probiotic effects in the form of nasal spray (De Boeck et al. 2019). Other lactobacilli are able to avoid the attack of viral particles to mucosal cells, this open also the possibility of employment of probiotics in nasal spray to ameliorate immune system and avoid respiratory tract infections (Campbell 2020). Further mechanisms that *Lactobacillus* species exert against respiratory viruses have been proposed such as the production of proteinaceous or non- proteinaceous inhibitors factor like H_2O_2, lactic acid and bacteriocins (Al Kassaa et al. 2014), being the mechanisms of action of these latter against viruses non fully understood (Wachsman et al. 2003). A combination of *L. rhamnosus* GG and *Bifidobacterium animalis* subsp. *lactis* BB12 was shown to inhibit the incidence of diseases caused by respiratory viruses and needing for antibiotics of about 50% in the group who was administered with probiotics with respect to placebo group (Rautava et al. 2009). Influenza virus H1N1 titres in lungs of infected mice have been decreased by the oral daily administration of *L. plantarum* L-137, a strain with proinflammatory activity. Moreover, *L. rhamnosus* CRL 1505 had shown the ability to stimulate immune system by secretion of IFN-γ and IL in 3 weeks-old mice, reducing viral load in lungs tissue injuries after the challenge with respiratory syncytial virus, without the help of antibiotics (Salva et al. 2011; Chiba et al. 2013). The administration of probiotic fermented drinks and probiotics such as *L. casei* Shirota showed to increase antibody responses to influenza virus vaccination in the elderly and accelerate innate immune response of respiratory tract and protect against various respiratory infections in newborns, infants and children, groups at higher risks of respiratory infections (Yasui et al. 2004; Boge et al. 2009). Furthermore, probiotic oral administration has been shown to influence inflammatory cytokine production

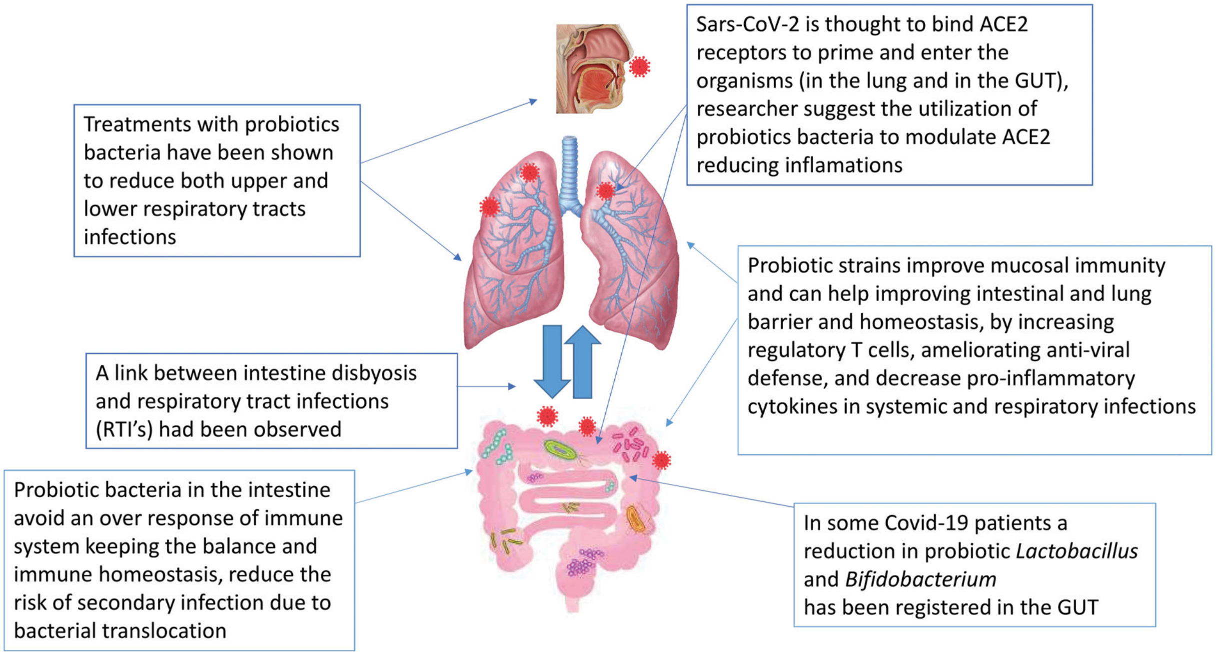

Figure 1. Clues suggesting a possible application of probiotics in reducing burden and severity of Sars-CoV-2 infections.

in the lungs, which has been linked with Covid-19 lethality (Mehta et al. 2020).

Probiotics ACE inhibitory effect

Similar to other SARS coronaviruses, SARS-CoV-2 is thought to bind, through its surface spikes proteins with the angiotensin-converting-enzyme 2 (ACE2) receptor for intracellular invasion and utilise cellular serine protease TMPRSS2 to prime and replicate in infected organisms (Li et al. 2003; Gurwitz 2020; Hoffmann et al. 2020). On the other hand, the mechanism for acute lung injury during infection has been postulated to be mediated through activation of renin angiotensin system (RAS), in which ACE2 produces several protective effects (Cole-Jeffrey et al. 2015). The expression of ACE2, which is expressed by epithelial cells of the lung, intestine, kidney, and blood vessels, is substantially increased in patients treated with ACE inhibitors (Wan et al. 2020). For these reasons, some researchers suggested that ACE inhibitors might benefit patients with Covid-19 by reducing pulmonary inflammation (Meng et al. 2020), although others argued that ACE inhibitors might enhance viral entry by regulating ACE2 levels. Several probiotics, particularly LAB, have been reported as able to produce peptides with ACE inhibitory effect (Ettinger et al. 2014). Indeed, some media sources have recently called for the administration of probiotic food and drugs, both prophylactically and in the context of suspected Covid-19. However, due to the still controversial debate on the effect of ACE-inhibitors in the Covid-19 progression (Tignanelli et al. 2020), the potential role of probiotic in modulating ACE2 level is to be critically considered when they are proposed as an adjunctive therapeutic option (Fuglsang et al. 2003). Further, following the demonstration of a non-catalytic role for ACE2 in amino acid transport in the gut, a recent work speculated that a therapeutic effect of ACE2 can be mediated, in part, by its actions on the gastrointestinal tract and/or gut microbiome. This is consistent with emerging data supporting the existence of a link between the gut and lungs and suggesting that dysbiosis of the gut and lung microbiomes is associated with cardiopulmonary disease (Cole-Jeffrey et al. 2015). In this optic, a possible role of probiotic in shaping the evolving role for gut and lung microbiota in the onset of SARS-CoV2 infection' symptoms should be assessed.

Conclusion

On the basis of the available evidence, the possible benefits of probiotic administration in the framework of Covid-19 infection (Figure 1), may be due, principally, to their effects on innate and adaptive immunity. Probiotic actions such as influence on cytokines production by intestinal epithelial cells, IgA secretion stimulation to improve mucosal immunity, activation of phagocytosis and macrophage production, modulation of levels and function of regulatory cells, and induction of dendritic cells maturation, likely affect systemic inflammation. Furthermore, increasing evidence supports a link between the gut and lungs, thus, further studies should be addressed to investigate a potential role of probiotic in attenuating Covid-19 either through immunomodulatory actions on systemic inflammation or by direct interaction with the lungs. However, not all probiotics are likely to be the same, thus a more targeted approach through the characterisation of specific properties of probiotic bacteria at strain level during the development of potential application in COVID-19 and its comorbidities.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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