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REVIEW ARTICLE

Probiotics and COVID-19: is there any link?

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Significance and Impact of the Study: The role of probiotics in alleviation of the novel COVID-19 has not been established. This review provides an insight about the anti-inflammatory, antiviral effects of probiotics *in vitro*, animal models and human. The latter can provide an indirect evidence and/or hypothesis-driven approach to investigate the use of probiotics as adjunctive therapy in the prophylaxis and/or alleviation of COVID-19 symptoms.

Keywords
adjunctive therapy, anti-inflammatory, antiviral, COVID-19, microbiota, probiotics.

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Abstract

Understanding mechanisms of the novel SARS-CoV2 infection and progression can provide potential novel targets for prevention and/or treatment. This could be achieved via the inhibition of viral entry and/or replication, or by suppression of the immunologic response that is provoked by the infection (known as the cytokine storm). Probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host'. There is scarcity of evidence about the relationship between COVID-19 and gut microbiota. So, whether or not these supplements can prevent or ameliorate COVID-19-associated symptoms is not fully understood. The aim of this study is to provide an indirect evidence about the utility of probiotics in combating COVID-19 or its associated symptoms, through the review of its antiviral and anti-inflammatory properties *in vitro*, animal models and human trials.

Introduction

The novel coronavirus SARS-CoV-2 pandemic has emerged in late December of 2019 (Eurosurveillance Editorial 2020). To date, there is no established prevention or treatment protocol for this virus. Treatments are based on investigational repurposed drugs as well as symptoms alleviation. Small molecules that have shown to prevent viral entry or replication such as hydroxycholquine (Yazdany and Kim 2020) and remdesivir (Cao *et al.* 2020) are being studied in multiple clinical trials worldwide. Moreover, biologics such as tocilizumab and interferon-beta are being tested for their ability to suppress inflammation and the so-called 'the cytokine storm' (Liu *et al.* 2020). Indeed, COVID-19 patients who have had higher concentrations of pro-inflammatory cytokines and chemokines were more likely to be admitted to an Intensive care unit, namely, Granulocyte–colony stimulating factor (G-CSF), the human interferon-inducible protein 10 (IP-10/CXCL10), monocyte chemoattractant protein 1 (MCP-1) and tumour necrosis factor-alpha (TNF-α), in addition to elevated cytokines from T helper 2 cells such as interleukin (IL)-4 and IL-10 (Liu *et al.*, 2020).

According to World Health Organization (WHO), Food Agriculture Organization (FAO) and the International Scientific Association for Probiotics and Prebiotics (ISAPP), probiotics are defined as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' (Hill *et al.* 2014). The most commonly used micro-organisms are *Lactobacillus* sp., *Bifidobacteria* and *Saccharomyces* (Zendeboodi *et al.* 2020; Guimarães *et al.* 2020). They are available commercially as add-on to several food and dairy products, and supplements (de Almada *et al.* 2015; Kiousi *et al.* 2019; Roobab *et al.* 2020). Thereafter, the definition of the term probiotic has been modified and extended. Although the definition developed by WHO and FAO is generally conventional, new terminologies have emerged lately in

the literature such as 'paraprobiotics' (dead/inactivated cells of probiotics) and 'postbiotics' (healthful metabolites of probiotics) (Zendeboodi *et al.* 2020; Barros *et al.* 2020). In addition, there are prebiotics which are 'substrates that are selectively utilized by host microorganisms conferring a health benefit' (Neri-Numa *et al.* 2020). Most of the prebiotics are carbohydrate based, but that phenolic compounds and conjugated fatty acids can comply with the criteria of prebiotics as well. Prebiotics have also shown many health effects such as pathogen inhibitory effects and immune modulation, etc. (Neri-Numa *et al.* 2020). However, for the sake of this review will concentrate on probiotics.

It is well established that probiotics, mainly, the strains of lactic acid bacteria, can modulate the human gut microbiota via the suppression of opportunistic bacteria growth (Khaneghaha *et al.* 2020). Therefore, the administration as well as the stimulation of the growth and activity of probiotic strains in gut can be considered as a potential approach to control food-borne enteric pathogens. Moreover, there are many health benefits of probiotics beyond the gut; probiotics have shown to enhance the immunity, reduce the severity of certain allergic conditions, in addition to conferring some anticarcinogenic properties (Khaneghaha *et al.* 2020). There are scarce data available about the effect of COVID-19 on intestinal microbiota. A recent small study from China showed that patients with COVID-19 showed microbial dysbiosis with decreased *Lactobacillus* and *Bifidobacterium* counts (Xu *et al.* 2020). The same study proposed using prebiotics or probiotics as adjunctive therapy to regulate the balance of intestinal microbiota and reduce the risk of secondary infection in those patients. On the other side, animal studies (although not peer reviewed yet) indicated that *Lactobacillus acidophilus* and *Bacillus clausii* did not reduce coronavirus receptor expression in the murine small intestine compared with control and post-Salmonella infection models (Feng *et al.* 2020). It was reported that 58–71% of patients with COVID-19 in China were given antibiotics, and antibiotic-related diarrhoea occurred in 2–36% of patients (Mak *et al.* 2020). In those cases, supplementing the gut normal flora by using probiotics has been proposed to make COVID-19 patients less prone to secondary infections.

Human gut microbiota is a very diverse system and we should examine the efficacy of other types of beneficial bacteria, not only *Lactobacilli and Bifidobacteria,* in fighting COVID-19 or alleviation of the associated inflammation. To date, the rationale for using probiotics in COVID-19 patients can be merely extrapolated from an indirect hypothetical evidence (Mak *et al.* 2020; Baud *et al.* 2020). Therefore, we cannot draw any conclusions unless we have well-designed preclinical and clinical studies.

Of interest, studies have shown that probiotics can have potential anti-inflammatory and antiviral effects. Indeed, they act by suppressing cytokines production whether locally, i.e. on the intestinal mucosa level, or on extra-intestinal body organs (Kiousi *et al.* 2019). Several clinical trials have shown that the administration of probiotics to improve outcomes in immune system-related conditions, or viral infections, such as atopic dermatitis, rheumatoid arthritis and some allergic conditions, or respiratory tract infections (Kiousi *et al.* 2019).

Based on the above, it is plausible to assume that these anti-inflammatory, antiviral effects could potentially contribute, at least partially or in combination with other medications, in prevention and/or alleviation of COVID-19-related symptoms.

Results and discussion

Antiviral activity

It was shown that probiotics in adults or children were safe (Tapiovaara *et al.* 2016) and clinically effective (Wang *et al.* 2016) in reducing the severity and the duration of upper respiratory tract infections. These were confirmed via a review (Kanauchi *et al.* 2018) where the ability of different strains lactic acid-producing bacteria to ameliorate or prevent different viral infections was illustrated, such as decreasing titres of Ebola and cytomegalovirus, decreasing severity and duration of upper respiratory tract infection or gastroenteritis. The main focus of that review, however, was the anti-influenza activity of *L. lactis* JCM 5805, which has the potency to directly stimulate plasmacyotoid dendritic cells (pDCs) via toll-Like receptor 9 (TLR 9), which will in turn stimulate interferon production and control viral replication and spread. The activity of probiotic strain *B. subtilis* (Starosila *et al.* 2017) against the influenza virus *in vitro* and in animals was investigated. A new peptide, P18, produced by the probiotic strain was isolated, characterized and synthesized thereafter. Interestingly, while being nontoxic, P18 exhibited a complete inhibition of the influenza virus in vitro. Moreover, the antiviral effect of P18 in mice was comparable to that of oseltamivir phosphate (Tamiflu®). Recently, the effect *Lactobacillus gasseri* in prophylaxis against respiratory syncytial virus (RSV) infection was evaluated in mice (Eguchi *et al.* 2019). The RSV titre in the lung was significantly decreased, and the expression of pro-inflammatory cytokines in the lung was significantly diminished while interferons and interferon-stimulated genes were upregulated after the treatment. In clinical settings, a randomized, double-blind, placebo-controlled trial have shown that the administration of prebiotics and probiotics early in life of preterm infants resulted in a

significant lower incidence of viral respiratory tract infections, especially those caused by rhinovirus, even though viral RNA load was the same in the probiotic and the placebo groups (Luoto *et al*. 2014). Based on the above data, the alteration of gut microbiota with good choice of prebiotics and probiotics might offer a novel and cost-effective methodologies to reduce the risk of viral infections.

Anti-inflammatory activity

In vitro/ex vivo studies

A recent paper (Yu *et al*. 2019), evaluated the anti-inflammatory potential of *Weissella cibaria* (JW15) against lipopolysaccharide (LPS) stimulation in RAW 264.7 cells. Treatment with heat-killed JW15 decreased nitric oxide and prostaglandin E2 production via downregulation of the inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). In addition, treatment with heat-killed JW15 suppressed the expression of pro-inflammatory cytokines, IL-1β, IL-6 and TNF-α. The anti-inflammatory properties of treating with heat-killed JW15 were associated with mitogen-activated protein kinase (MAPK) signalling pathway-mediated suppression of nuclear factor-κB (NF-κB). These results indicated that JW15 possesses anti-inflammatory potential and provide a molecular basis regarding the development of functional probiotic products.

Moreover, the effect of potential probiotic strains on early gingivitis was evaluated in an ex vivo model (Schmitter *et al*. 2018). Human monocytes were stimulated by bacterial LPS. Strains *Lactobacillus paracasei* and *Lactobacillus plantarum* induced statistically significant and dose-dependent reductions in the release of multiple inflammatory mediators including IL-6, IL-8 and prostaglandin E2 *vs* placebo.

The effects of two strains of *L. rhamnosus, L. rhamnosus GG and GR-1* in modulating production of TNF-α in human monocytic cell-line THP-1 and mouse macrophages were investigated. (Kim *et al*. 2006). In C57BL/6 mouse, bone marrow–derived immortalized macrophages (BMDIM) and THP-1 cells, both strains, suppressed the production of *E. coli*- and LPS-induced TNFα production. This in vitro study showed that this suppression was likely mediated through downregulation of TNF-α mRNA expression and a paracrine effect of G-CSF, as G-CSFR–/– macrophages produced similar amounts of TNF-α as wild-type cells. G-CSF induced the activation of Signal Transducer and Activator of Transcription 3 (STAT3) protein, which in turn prevented JunN-terminal kinases (JNK) activation and consequently resulted in suppression of TNF-α production in LPS- or E. coli-activated macrophages. A comprehensive review (Plaza-Diaz *et al*. 2017) summarized five *in vitro* studies which assessed the anti-inflammatory role of antibiotics in intestinal diseases. Pretreatment of Caco2 cells or dendritic cells with several probiotics decreased production of several inflammatory chemokines and cytokines, such as IL-22, IL-8 and TNF-α, and downregulation of MAPK and NF-κB pathway or even ameliorated enterocyte apoptosis in intestinal epithelial cells.

Animal models

Two strains of *Lactobacillus* (*mucosae and fermentum*) were assessed for anti-inflammatory properties (Ayyanna *et al*. 2018) in acute and chronic Freund's adjuvant-induced inflammation model. The two probiotic strains were administered orally along with feed to the Wistar albino male rats as whole cell as well as micro-encapsulated form. Both forms of the probiotics lead to a significant decrease in paw oedema. Percentage of inhibition in paw thickness of micro-encapsulated probiotic bacteria, un-encapsulated strains was revealed as 85 ± 13 and $77 \pm 25\%$ respectively. In addition, there was an upregulation of anti-inflammatory cytokine genes and levels (IL-10) and downregulation of proinflammatory cytokine genes and levels (IL-6 and TNF-α) in probiotic-treated rat. The paw tissues of the probiotic-treated rats have also exhibited the low level of lipid peroxides formation and higher anti-oxidant activities when compared to the control. The anti-inflammatory role of probiotics in various animal models in different forms of colitis was reviewed (Plaza-Diaz *et al*. 2017), and it was found that the administration of probiotics ameliorated these conditions as evidenced through histological improvement, reduction in disease severity index or decline in the levels of inflammatory markers such as myeloperoxidase activity, iNOS, COX-2, NF-κB, TNF α, IL-6 and phosphorylated Akt, while increasing IL-10 expression in colonic tissue (Plaza-Diaz *et al*. 2017). In animal models of multiple sclerosis (Morshedi *et al*. 2019), it was shown that giving probiotics reduced T-cell autoreactive cell response, production of pro-inflammatory cytokines and increased levels on anti-inflammatory markers such as IL-10 and nitric oxide.

Human studies

In two clinical studies, the administration of probiotics resulted in reduction in IL-6, C-reactive protein, while there was increased levels of IL-10 in the sera of the multiple sclerosis patients (Morshedi *et al*. 2019). One clinical study (Plaza-Diaz *et al*. 2017) showed that probiotics administration reduced the systemic pro-inflammatory biomarkers in both gastrointestinal and nongastrointestinal conditions in colitis patients after 6–8 weeks of treatment.

The functional properties of eight *Lactobacillus* strains from infant showed probiotic potential as well as ability to resist acidic pH and bile salts (Oh *et al*. 2018). These isolate included various lactobacillus species: *L. reuteri 3M02*

and 3M03, L. gasseri 4M13, 4R22, 5R01, 5R02 and 5R13, and L. rhamnosus 4B15, which were evaluated for anti-oxidation, inhibition of α-glucosidase activity, cholesterol-lowering and anti-inflammatory activity. Particularly, two strains of *L. rhamnosus, 4B15 (4B15)* and *L. gasseri 4M13 (4M13)* showed considerably higher anti-oxidation, inhibition of α-glucosidase activity and cholesterol lowering, and greater inhibition of nitric oxide production than other strains. Moreover, the aforementioned strains substantially inhibited the release of inflammatory mediators such as TNF α, IL-6 and IL-1β, but increased IL-10 in LPS-stimulated RAW 264.7 macrophages.

Regarding the effect of probiotics in respiratory illnesses, two randomized controlled trials showed that critically ill patients on mechanical ventilation who were administered probiotics (*Lactobacillus rhamnosus GG, live Bacillus subtilis* and *Enterococcus faecalis*) had significantly less ventilator-associated pneumonia compared with placebo (Morrow *et al*. 2010; Zeng *et al*. 2016). Accordingly, it can be speculated that COVID-19-related pneumonia could be alleviated in the same manner.

No published studies so far evaluated the use of probiotics as add-on therapy for the management of COVID-19, so their role is not yet established. However, according to a recent science blog by IASPP, many researchers all over the world are studying the relationship between microbiome and susceptibility to COVID-19 as well as assessing the ability of various probiotics strains to reduce the viral load via different mechanisms of action (International Scientific Association of Probiotics and Prebiotics board of directors 2020). Currently a research team in Belgium is exploring the potential of specific strains of *lactobacilli* in the nasopharynx and oropharynx to reduce viral activity via the barrier-enhancing and anti-inflammatory effects, and reduce the risk of secondary bacterial infections in COVID-19 (International Scientific Association of Probiotics and Prebiotics board of directors 2020). In the United Kingdom, there is an ongoing Phase II randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of oral live biotherapeutic MRx-4DP0004 (two capsules) in addition to standard supportive care for hospitalized COVID-19 patients for 14 days. In the United States, a multicenter, randomized, double-blind, phase 2 trial using a commercial product of *Lactobacillus rhamnosus GG* (20 billion CFU) *vs* placebo is conducted to see its ability to decrease infections and improve outcomes. The same team is in the process of developing protocols to study prevention and treatment of COVID-19 in a range of other at-risk populations including hospitalized patients and healthcare workers.

In lieu of their antiviral and anti-inflammatory activity, although very early to judge, it is tempting to assume that probiotics can potentially be among the rational adjunctive options for the treatment and prophylaxis of viral infections including COVID-19 infection. In a preprint paper by Feng *et al*. (2020), RNA sequencing results showed that the coronavirus receptors, including angiotensin-converting enzyme 2 (ACE2) for SARS-CoV and SARS-CoV2, were highly expressed in human enterocytes. Interestingly, these potential target cells that have constant expression in the small intestine are constant while being continuously changed in lung tissues. Therefore, enterocytes may act as a conserved cell reservoir for coronaviruses, a fact that should draw the attention of health researchers to this site of SARS-CoV2 infection.

In conclusion, until there is more evidence about the novel coronavirus pathogenesis and its effect on gut microbiome, the use of conventional probiotics for COVID-19 cannot be liberally recommended. Although gut dysbiosis has been suggested in the pathogenesis of certain respiratory conditions (Li *et al*. 2021), more targeted and novel approaches are warranted. Although the modulation of gut microbiota is expected to be one of the promising therapeutic approaches to alleviate COVID-19 and/or its associated inflammatory complications, still the utility of probiotics as add-on therapy may need to be further studied in well-designed randomized controlled clinical trials to establish their efficacy and safety.

Materials and methods

Search was done using the different database including Google Scholar and PubMed using the following MeSH terms: COVID-19, probiotics, novel coronavirus, respiratory tract infection, anti-inflammatory and antiviral.

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Conflict of Interest

The author has no conflict of interest to declare.

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