Opinion

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Can Probiotics Play an Important Role Against COVID-19?

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ABSTRACT

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Introduction

Probiotics are live microorganisms, which if administered at adequate amounts, confer beneficial physiological effects [1]. Previous study underscored the positive impact (whether directly or indirectly) of probiotics on the ACE enzymes [2]. During the process of food fermentation, probiotics make bioactive peptides which interfere with the ACE enzymes through blocking the active sites [3,4]. The debris of the dead probiotic cells can also work as inhibitors to ACE [1], suggesting that probiotics are possibly potential blockers to the ACE receptors, which act as gateway for SARS-CoV-2 to attack gastrointestinal cells. Imai and colleagues reported that ACE blockers could be used to decrease respiratory distress syndrome [5]. The prebiotics are defined as 'substrates that are selectively utilized by host microorganisms conferring a health benefit' [6]. Similar to probiotics, prebiotics can be orally administered into microbially colonized body sites to reach the intestine, or by a direct way to the skin or vaginal tract [6]. Prebiotics include lactosucrose, oligosaccharides, isomaltooligosaccharides, fructans, xylooligosaccharides, resistant starch, lactobionic acid, galactomannan, arabinooligosaccharides, psyllium, polyphenols and polyunsaturated fatty acids [6-8]. The health benefits of prebiotics to the gastrointestinal tract such as stimulation of immune system and inhibition of pathogens are because of their ability to modulate the activity and composition of human microbiota [1]. Prebiotics, which enhance probiotics survivability and growth, may have an excellent potential effect against COVID-19 [1]. Prebiotics could block the ACE enzymes, which may have a direct effect on

gastrointestinal symptoms caused by COVID-19 [1]. There are many ongoing registered trials aiming to investigate the efficiency of probiotics in treating COVID-19 patients [9].

Some COVID-19 patients showed intestinal microbial dysbiosis characterized by decreased probiotics such as Lactobacillus and Bifidobacterium. Prebiotic or probiotic supplementation, and nutritional support has been recommended to re-normalize the balance of intestinal microbiota and decrease the risk of secondary infection due to bacterial translocation [10]. Probiotic supplementation could be a promising strategy given previous studies of the potential application of probiotics in treatment and prevention of various viral infections [1,11,12]. The elderly and disordered microbiota patients are the most susceptible groups to COVID-19. Thus, it is suggested that probiotics supplementation in those groups could increase the ability of the gastrointestinal microbiota in modulation of immunity and help in prevention of viral infections including COVID-19 [1]. Competition with pathogens for nutrients, production of anti-microbial substances, enhancement of the intestinal epithelial barrier, and adhesion to the intestinal epithelium, and modulation of the host immune system might explain clinical success of probiotics [13,14]. Saavedra and colleagues conducted randomized control trial of 55 infants and found that enteral supplementation with a combination of Streptococcus thermophiles and Bifidobacterium bifidum decreased the incidence of diarrhea and rotavirus shedding [15], which may indicate interference with entry of the virus into cells and/or inhibition of viral replication in the intestine. Although probiotics were not administered to the respiratory tract, this mechanism may play a role in lowering dissemination of SARS-CoV-2 through the gut. Therefore, direct inhibition may be impossible at the respiratory tract. Having said that, lungs have their own microbiota and a gut-lung connection has been previously reported whereby microbe-microbe host-microbe, and immune interactions could affect the course of respiratory diseases [14,16].

Growing evidence showed that the gut-lung axis plays a pivotal role in the pathogenicity of viral and bacterial and infections, as the intestinal microbiota could enhance the activity of alveolar macrophage, thus having a prophylactic role in host defense against pneumonia [17]. Respiratory tract infections such as influenza are linked with a dysbiosis in the microbial communities of the both gastrointestinal and respiratory tracts [18,19], which could alter immune function and facilitate secondary bacterial infection [14]. Previous studies reported that COVID-19 could be associated with intestinal dysbiosis leading to inflammatory reactions and poorer response to pathogens [20,21], the case exists for probiotics that could restore gut homeostasis [22]. Arroyo and colleagues evaluated the efficacy of oral administration of Lactobacillus fermentum CECT5716 or Lactobacillus salivarius CECT5713, two lactobacilli strains isolated from breast milk, compared with the efficacy of antibiotic therapy in treatment of lactational mastitis [23]. They found that females took the probiotics improved more and had reduced recurrence of mastitis than those who took the antibiotic therapy.

The gut microbiome plays a pivotal role in systemic immune responses, including those at distant mucosal sites such as the lungs [24,25]. Administration of certain lactobacilli or bifidobacteria helps in clearance of influenza virus from the respiratory tract [24,26]. Probiotic strains increase type I interferon levels, the activity and number of T cells, NK cells, antigen presenting cells, as well as the levels of systemic and mucosal specific antibodies in the lungs [24,27,28]. Growing evidence showed that probiotic strains could regulate the dynamic balance between proinflammatory and immunoregulatory cytokines that facilitate viral clearance with minimum immune response-mediated lung damage [14]. This seems be particularly important as a way to inhibit acute respiratory distress syndrome, which is the most feared complication of COVID-19.

Chong and colleagues reported that Lactobacillus plantarum DR7 suppressed plasma pro-inflammatory cytokines (TNF-α, IFN-γ,) in middle-aged adults, and enhanced anti-inflammatory cytokines (IL-10, IL-4,) in young adults, along with decreased levels of oxidative stress and plasma peroxidation [29]. This type of modulation is considered to be very important, especially for many COVID-19 patients, who have from cytokine storm. Orally administered probiotic strains appear to involve the immune response originating from the intestine, a main site of the body's defenses. Thus, probiotic strains, which could improve the integrity of tight junctions, for example through butyrate augmentation, a fuel for colonocytes, may in theory decrease SARS-CoV-2 invasion [14]. Zuo and colleagues found that faecal samples with signature of low-to-none SARS-CoV-2 infectivity had higher abundances of short-chain fatty acid producing bacteria, Bacteroides stercoris, Parabacteroides merdae, Lachnospiraceae bacterium 1_1_57FAA, and Alistipes onderdonkii [30]. A recent study tested the impact of short-chain fatty acids (acetate, propionate and butyrate) in the infection by SARS-CoV-2 [31]. They found that short-chain fatty acids did not change SARS-CoV-2 entry or replication in intestinal cells. These metabolites had no effect on permeability of intestinal cells and had only little effect on the synthesis of anti-viral and inflammatory mediators. Although this may seem discouraging, we propose that testing real short-chain fatty acid-producing bacteria (not short-chain fatty acids only) may give good results. Testing bacteria is different from testing metabolite, especially that there are many current pieces of research that speak about virus-bacteria interactions [32,33].

Ren and colleagues reported that faecal and oral microbial diversity was remarkably decreased in confirmed COVID-19 patients versus healthy controls [34]. They found that there was a reduction in butyric acid-producing bacteria and an increase in lipopolysaccharide-producing bacteria in COVID-19 patients in oral cavity. Researchers reported that confirmed recovery COVID-19 patients showed depletion in 47 lipid molecules, including sphingomyelin (SM)(d40:4), SM(d38:5) and monoglyceride(33:5), and enrichment of phosphatidylcholine(36:4p), phosphatidylethanolamine (PE)(16:0p/20:5) and diglyceride(20:1/18:2) versus confirmed COVID-19 patients. This is the first study that explores the alterations in the human oral and gut microbiomes and lipidomics in COVID-19 patients, which may be involved in the development and progression of COVID-19 and could be also useful as an auxiliary diagnostic tool. Previous clinical and experimental studies reported that some probiotic strains have antiviral effects against common respiratory viruses, including respiratory syncytial virus, rhinovirus, influenza [12,28,35,36]. Although these mechanisms or effects have yet to be tested on the SARS-CoV-2, this should not refute considering this new line of investigation, especially when effects of probiotics against other coronavirus strains such as transmissible gastroenteritis virus have been reported [37-40]. Research is urgently needed to assess the effect of probiotics and prebiotics against SARS-CoV-2, which may lead to a better understanding of the bacterial dynamics in the gastrointestinal tract.

Conflict of Interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Consent Statement/Ethical Approval

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