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LETTER TO EDITOR

Therapeutic and preventive potential of probiotics against COVID-19

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Dear Editor:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), was first detected in Wuhan, China and has since spread across continents. Although the globe grapples with the COVID-19 pandemic, neither a vaccine nor a drug has been proven to be effective for prevention and treatment of the disease. With millions of individuals are at high risk of contracting the disease, there is undoubtedly a need for finding a solution to control the spread of SARS-CoV-2 (1).

Probiotics are living microorganisms, which exert health-beneficial attributes when consumed in sufficient amounts (2). Based on mechanism of immune regulation, probiotics can be categorized into two distinct groups, namely immunostimulatory and immunoregulatory probiotics. The former induces production of Interleukin-12 (IL-12), which stimulates interferon gamma (IFN-γ) in natural killer cells and promotes the development of T helper 1 (Th1) responses, whereas the latter is able to suppress pro-inflammatory responses through induction of IL-10 production and activation of regulatory T cells (Tregs) (3). Some probiotics can also enhance production of secretory Immunoglobulin A (sIgA) in lung tissues (4). Furthermore, probiotics are capable of interacting with intruding pathogens in several ways. For instance, they can bind to viral particles or saturate their host receptors, resulting in blockade of viral attachment (4).

The genera *Lactobacillus* and *Bifidobacterium* are among the most frequently used probiotics in the management of various gastrointestinal disorders. For example, supernatants of *Lactobacillus plantarum* Probio-38 and *Lactobacillus salivarius* Probio-37 have been observed to impede *in vitro* infectivity of transmissible gastroenteritis virus (5), a coronavirus infecting enteric and respiratory tissues of newborn piglets with a mortality rate of almost 100%. This finding suggests that probiotics can ameliorate the severity of gastrointestinal symptoms caused by coronaviruses.

Accumulating evidence also abounds on the prophylaxis and therapeutic effects of probiotics against respiratory tract viral infections (RTVIs). In this respect, pre-treatment of human laryngeal epithelial cell line HEp-2 and mouse lung epithelial cell line MLE12 with *Lactobacillus gasseri* SBT2055 (LG2055) suspension significantly protected the cells from respiratory syncytial virus (RSV) infection (6). In BALB/cCrSlc mice, daily oral administration of LG2055 for 21 days resulted in a perceptible decrement of RSV titers and pro-inflammatory cytokine

production as well as up-regulating gene expression of type I and type II interferon in lung tissues (6).

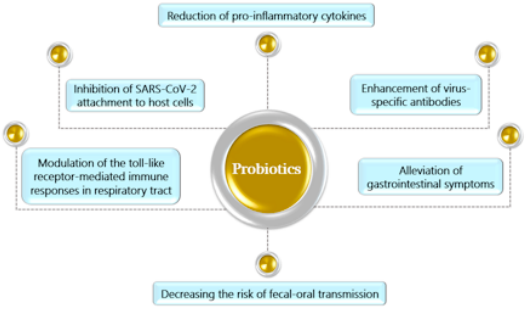

Figure 1: Possible anti-viral properties of probiotics against SARS-CoV-2 infection

In a randomized, double-blind, placebo-controlled trial, preterm infants receiving oral probiotics (*Lactobacillus rhamnosus* GG, ATCC 53103) exhibited a substantially lower incidence of RTVIs compared to those receiving placebo (7). One study showed that oral administration of *L. rhamnosus* GG is useful for achieving a reduction of antibiotics prescribed for hospitalized patients with ventilator-associated pneumonia (VAP) (2). In consistent with these findings, another randomized controlled multicenter trial demonstrated that consumption of *Bacillus subtilis* and *Enterococcus faecalis* prevents VAP as well as gastric colonization of potentially pathogenic microorganisms in critically ill patients (8).

A pilot study demonstrated that nasal spray administration of *Streptococcus salivarius* 24SMBc for 3 days was well tolerated by all 20 healthy adult volunteers, of whom 95% were colonized by the probiotic in rhinopharynx tissues at least in the first 4 h after administration (9). According to these results, colonization of upper respiratory tract with probiotics may confer protection from viruses causing pulmonary infections, in particular rhinovirus, coronavirus, influenza virus, and RSV.

Based on above-mentioned studies, we hypothesize that oral administration or even inhalation of aerosolized probiotics employing various formulations (in the form of live or heat-inactivated microorganisms) not only acts as prophylaxis, but also has the potential for adjunct therapy against SARS-CoV-2 infection. Possible beneficial roles of probiotics in COVID-19 therapy are depicted in Fig. 1. Nevertheless, clinical trials are needed to evaluate anti-viral effects of specific probiotic strains for treatment of SARS-CoV-2 infection.

Acknowledgments
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Conflict of interest
The authors have no conflict of interest to declare.

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