Chapter 3

The role of probiotics in maintaining immune homeostasis

Velaphi C. Thipe[1], Shireen Mentor[2], Caroline S.A. Lima[1], Lucas F. Freitas[1], Ana C.M. Fonseca[3], Kamila M. Nogueira[1], Adriana S. Rodrigues[1], Jorge G.S. Batista[1], Aryel H. Ferreira[1] and Ademar B. Lugão[1]

[1]Energy and Nuclear Research Institute (IPEN), University of São Paulo, São Paulo, Brazil, [2]Department of Medical Biosciences, University of the Western Cape, Cape Town, South Africa, [3]Virtual University of the State of Sao Paulo (UNIVESP), São Paulo, Brazil

3.1 Introduction

The immune system is composed of the complex architecture of the collective, coordinated, and interconnected network of cells, tissues, organs, and molecules responsible for surveillance, neutralization, and elimination of pathogens, foreign agents/molecules to maintain dynamic homeostasis of the organism. Homeostasis is referred to as the body's ability to thermodynamically maintain the internal environment in an almost constant balance, regardless of the changes that occur in the external environment (Sattler, 2017). The immune system is divided into two types of immunity characterized by their respective responses: innate or natural immunity as the first line of defense and acquired or adaptive immunity immune responses are carefully regulated pathways facilitated by the release of pro-inflammatory [interleukin (IL)-1β, IL-6, IL-18, and tumor necrosis factor-α (TNF-α)] and antiinflammatory (IL-1, IL-4, IL-10, IL-11, IL-12, and IL-13) cytokines produced by many cell populations but predominantly produced by activated macrophages and helper T cells (Th), respectively (Kany et al., 2019). The innate/adaptive cytokines play pivotal roles in the overall immunity against infected cells in the body.

A significant area of the human body, either internal or external, is colonized by resident microorganisms, and their communities in different regions that exist in symbiosis are called microbiota. The gastrointestinal tract is home to gut microbiota which is one of the most diverse and extremely microbiologically active sites, making up the digestive system, varying among individuals according to factors such as age, ethnicity, diet, stress, and etc. The gut microbiota is composed of 90% bacteria which play a fundamental role in gut-associated lymphoid tissue development, the integrity of the mucosal barrier, and overall immune homeostasis. It is well known that the human gut houses a plethora of microbes that support nutrition, physiology, metabolism, and immunity (Nicholson et al., 2012; Tremaroli & Bäckhed, 2012; van de Wouw et al., 2018; Yadav et al., 2018). An estimated 10^{14} bacteria have been reported to colonize the gut, with $\sim 10^{11}$ bacteria per gram of colon tissue (Dhar & Mohanty, 2020). The gut bacteria within healthy individuals are dominated by four phyla: *Actinobacteria*, *Bacteroidetes*, *Firmicutes*, and *Proteobacteria*. The gut microbiota offers significant stimuli (i.e., gut-brain, gut-lung, and gut-liver axis) for both innate and adaptive immunity, mediating immune and metabolic homeostasis (van Baarlen et al., 2013), apart from its importance in digestion, nutrient absorption, adiposity, satiety, energy expenditure, metabolism, and defense against pathogens (Maldonado Galdeano et al., 2019; Wang et al., 2017; Xiong et al., 2017) as shown in Fig. 3.1.

The intestinal microbiota is often reconstructed overtime by a myriad of factors including the colonization of pathogenic bacteria, constant use of antibiotics, and inflammation in relation to infections and onset of diseases (Calder, 2020). There is an intricate correlation between changes in the gut microbiota composition/activity and common diseases/disorders. The host defenses against pathogens rely on four pivotal functions: (1) creating a physical barrier to prevent the invasion of pathogens; (2) identifying pathogens in case of invasion—facilitating increased immunosurveillance; (3) neutralizing the pathogens; and (4) the generation of immunological memory. The pathological alteration of the gut microbiota is called gut dysbiosis, a condition that is often triggered by a diet rich in industrialized food, sugar, fat, and alcohol, as well as by air pollution and epigenetic factors such as stress. Since the gut microbiota impacts the

Probiotics in The Prevention and Management of Human Diseases. DOI: https://doi.org/10.1016/B978-0-12-823733-5.00024-6

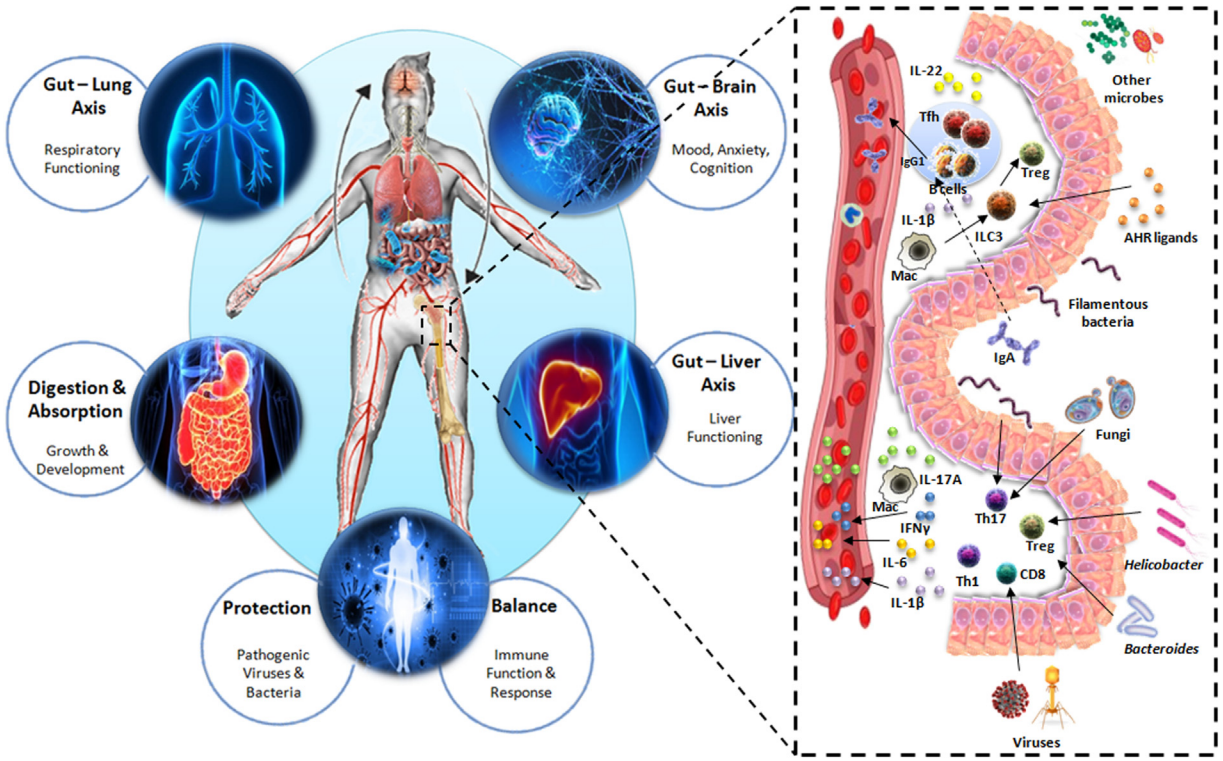

FIGURE 3.1 Gut microbiota regulates potent immunoregulators in a cascade of pathways that facilitate the differentiation of myeloid cell lineages in the bone marrow and splenic macrophages that sense microbe-associated molecular patterns (MAMPs) as well as pathogen-associated molecular patterns (PAMPs) expressed by gut microbes and activated to the release cytokines to regulate innate lymphoid cell (ILC3) and regulatory T cell (Treg) responses that maintain overall immune homeostasis. Filamentous bacteria promote immunoglobulin (IgG1) and IgA production by B cells via T follicular helper (Tfh)-dependent and independent mechanisms, respectively. Indigenous fungi dictate the balance of pro-inflammatory T helper 17 (Th17) and antiinflammatory Treg/Type 1 regulatory T (Tr1) cells in the gut, responsible for pathological implications and serve tissue-protective functions. During chronic intestinal inflammation, loss of intestinal barrier integrity to gut microbes can activate innate and adaptive immune cells to release pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) into the circulatory system, leading to systemic inflammation. *AHR*, Aryl hydrocarbon receptor.

immune responses, situations of dysbiosis may lead to diarrhea, loss of appetite (Videlock & Cremonini, 2012), and to the invasion of these pathogenic bacteria into the system, leading to immunological, neurological, inflammatory, and endocrinological problems (Fioramonti et al., 2003). In addition to the influence on the severity of inflammatory diseases such as asthma, chronic peptic ulcer, tuberculosis, rheumatoid arthritis, periodontitis, ulcerative colitis, type 2 diabetes, Crohn's disease, sinusitis, active hepatitis, neurological disorders (e.g., anxiety and depression), cardiovascular diseases, and of late the coronavirus disease, Covid-19, caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Anderson & Reiter, 2020).

Epidemiological researchers have decoded the inter-connective signaling network between the gut microbiome and diseases for understanding and maintaining immune homeostasis and integrity (Matarazzo et al., 2018). For example, individuals suffering from irritable bowel syndrome are often depressed; this also extends to individuals on the constant intake of antibiotics. In addition, individuals on the autism spectrum tend to have digestive problems. Moreover, individuals with Parkinson's disease are often prone to constipation (Pennisi, 2020), mostly all culminating from immune homeostasis imbalance. Probiotics are important for the balance of the mucosa's immune system, as they reduce its permeability and potentiate local immune responses by augmenting the expression of mediators, such as immunoglobulin G (IgG), IgA, etc. (Hardy et al., 2013; Zheng et al., 2020).

According to the World Health Organization (WHO), probiotics are classified as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" (DuPont & DuPont, 2011; Martin Manuel et al., 2017). Probiotics temporarily colonize the gut; therefore, their supplementation must be continuous in order to be effective. Various microorganisms are beneficial for the human gut and are most commonly present in supplements and probiotic foods. These microorganisms which preferentially colonize the intestines belong to *Lactobacillus* spp., often found in the terminal ileum, and *Bifidobacterium* spp. in the colon (Mikelsaar et al., 2016; Walter, 2008). Among the

lactic acid bacteria belonging to the genus *Lactobacillus* include *Lactobacillus acidophilus*, *Lactobacillus amylovorus*, *Lactobacillus casei*, *Lactobacillus gassei*, *Lactobacillus. helveticus*, *Lactobacillus johnsonii*, *Lactobacillus. pentosus*, *Lactobacillus plantarum*, *Lactobacillus reuteri*, and *Lactobacillus rhamnosus*; and the genus *Bifidobacterium includes Bifidobacterium adolescentis*, *Bifidobacterium animalis*, *Bifidobacterium bifidum*, *Bifidobacterium breve*, *Bifidobacterium infantis*, and *Bifidobacterium longum*. Other probiotic bacteria include *Enterococcus faecium*, *Lactococcus lactis*, *Streptococcus thermophiles*, *Bacillus clausii*, *Escherichia coli Nissle* 1917, and *Saccharomyces cerevisiae* (*boulardii*). However, not all bacteria can be classified as probiotics, as they need to belong to specific strains (Markowiak & Ślizewska, 2017).

Probiotics have been reported to play a major role in influencing the population of the gut microbiota as a means to alleviate a range of disorders such as necrotizing enterocolitis, acute infectious diarrhea, hyperuricemia, hypercholesterolemia, acute respiratory tract infections, antibiotic-associated diarrhea, intestinal disorders, allergies, obesity, epilepsy, sepsis in premature infants, infant colic, neurological conditions (autism, anxiety, AD, depression, Parkinson's disease, and schizophrenia), and influence brain activity related to emotion regulation—psychobiome (Pennisi, 2020; Sarkar et al., 2016; Wallace & Milev, 2017). The regulation of the gut microbiome through the use of probiotics may help treat and prevent several diseases linked to gut dysbiosis, especially by restoring the gut microbial balance in patients under antibiotic treatments, thereby improving their gut microbiota profile. In this context, probiotic supplementation commonly found in fermented foods (i.e., yogurt, kefir, kimchi, kombucha, pickles, miso, tempeh, sauerkraut, sourdough bread, and some cheese varieties), can assist in the rejuvenation of the gut microbiota and produce beneficial effects on the recovery of the host's immune system, thereby restoring and maintaining optimal immune homeostasis (Calder, 2020).

3.1.1 Gut microbiota and Covid-19

In light of the looming global Covid-19 pandemic, it is naturally prudent to study its broad range of effects on the overall immune homeostasis. The Covid-19 infection affects immune homeostasis which has been shown to alter gut microbiota by decreasing genera Bacteroidetes, Roseburia, Faecalibacterium, Coprococcus, and Parabacteroides composition, in addition to a higher production of pro-inflammatory cytokines (i.e., IL-18) observed in Covid-19 patients compared with both seasonal flu patients and healthy control group. This suggests that gut microbiota dysbiosis due to Covid-19 infection may contribute to disease severity (Tao et al., 2020). Covid-19 has been reported with compelling evidence that suggests this disease has the ability to affect neurological, cardiovascular, or cerebrovascular functions, primary symptoms being a loss in the sense of smell, taste, and in some cases, delirium (Yavarpour-Bali & Ghasemi-Kasman, 2020). These findings suggest that the virus has the ability to compromise the cerebrovasculature between the blood and the brain paramecium (i.e., the blood-brain barrier, BBB). The BBB functions as a regulatory interface maintaining a stable chemical brain microenvironment. A compromised BBB results in vascular leakage, and inflammation which is one of the major etiological factors associated with disease onset (Bron et al., 2017; Miller et al., 2012). Inflammatory mediators are associated with central nervous system (CNS) damage through neuroinflammation. Covid-19-related cerebrovascular-disorders are a probable link to the disruption of the homeostatic environment of the neuronal milieu, by way of brain endothelial cellular (BEC) inflammation. The BEC, thus, forms the anatomical basis of the BBB which is central to the maintenance of CNS homeostasis. CNS neurons, if compromised, will have a direct impact on the chemical composition of the neuronal milieu, implicating sensory and motor function, subsequently eliciting its negative effects on our psychological persona and hormonal homeostasis (Fisher & Mentor, 2020).

In summary, the link among preexistent conditions, dysbiosis, and the severity of Covid-19 also relies mostly on the decreased butyrate levels which lead to impaired signaling between the gut-brain, gut-lung, and gut-liver axis that results in hypercytokinemia, a hallmark of immune homeostasis imbalance (Anand & Mande, 2018). Additionally, viruses (i.e., SARS-CoV-2) must enter the host cells in order to replicate; therefore, their recognition by the immune system happens when viral antigens are presented to CD8 + cytotoxic T lymphocytes via major histocompatibility complex on the surface of the infected cells, ultimately resulting in the death of the host cell. However, when the infected cells are killed, viral particles are liberated and can infect other cells (Calder, 2020). The composition of the gut microbiota can be shifted towards an increased population of Prevotella and Oscillibacter in mice, both of which produce metabolites responsible for decreasing Th17 polarization of T cells and favoring their differentiation into Th1 regulatory T cells and type-1 T-helper cells, promoting an efficient immunity against infections (Fig. 3.2) (Maldonado Galdeano et al., 2019; Pandiyan et al., 2019).

Regarding SARS-CoV-2, diarrhea related to antibiotic administration was present in 2%−36% of Covid-19 patients in China, and probiotic supplementation was proposed in order to enhance the immunity of those patients against secondary infections (Akbari et al., 2016; Calder, 2020; Din et al., 2021; Morais et al., 2020). In fact, this resulted in a

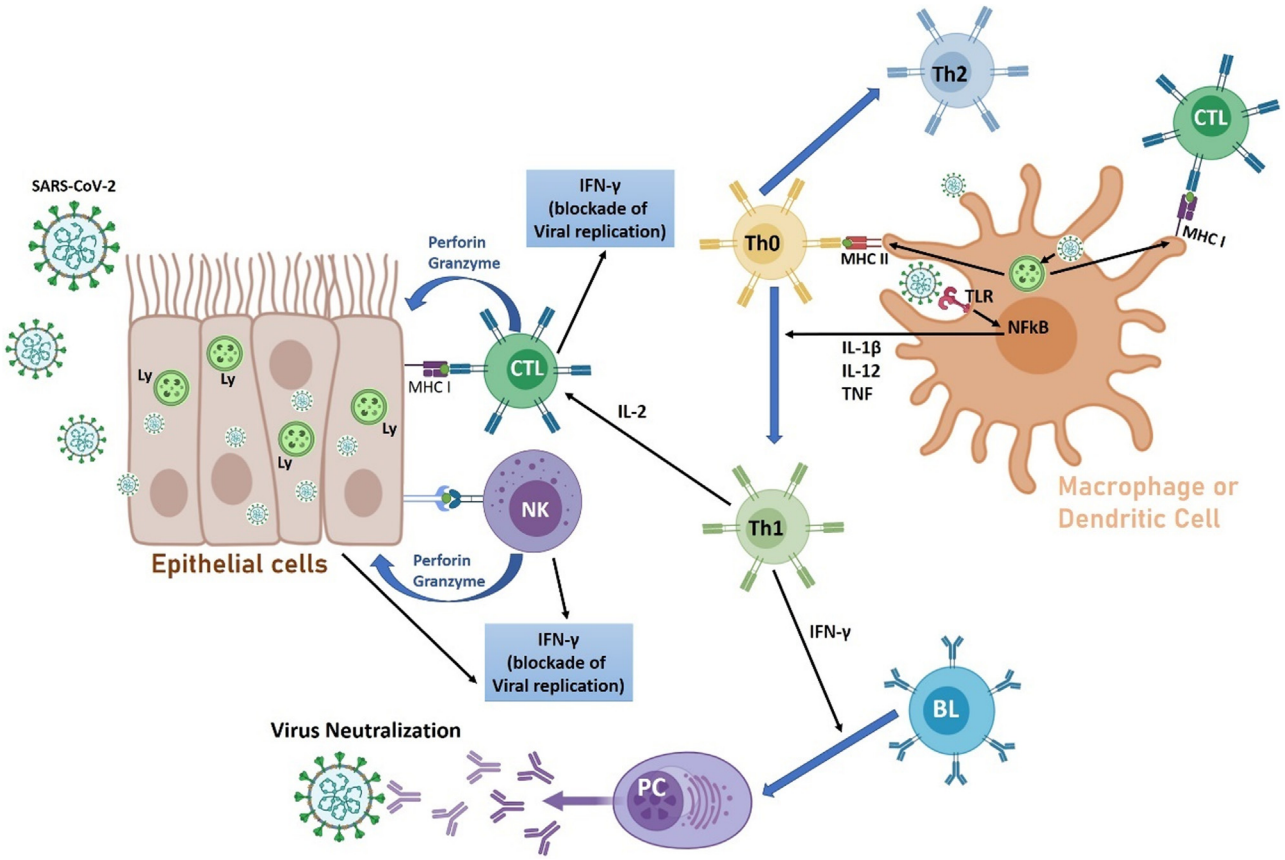

FIGURE 3.2 Innate and adaptive immunity against Covid-19 infection. The virus is digested in the lysosomes (Ly) of epithelial cells and its antigens are presented to cytotoxic T (CTL) and natural killer (NK) cells, both of which kill the host cell by secreting perforins, granzyme, and interferons (interferon-γ) that block the viral replication. This immune response is mediated by T helper type 1 (Th1) cells, which differentiate from Th0 cells after activation of toll-like receptors (TLR) from phagocytes and consequent expression of some interleukins. Th1 immunity is responsible for the differentiation of B lymphocytes (BL) into plasma cells (PC) in order to produce immunoglobulins that neutralize the virus.

reduction in the duration and the severity of Covid-19 complications in Chinese hospitalized adults and children (Akour, 2020; Morais et al., 2020). Patients with severe cases of Covid-19 often present one or more conditions that augment the risk of fatal outcomes, that is, obesity, diabetes, cardiovascular diseases, advanced age, and pulmonary conditions, and some of them are indicative of dysbiosis or can be increased during gut dysbiosis (Fig. 3.3). There is evidence suggesting that the occurrence of dysbiosis, especially when the infiltration of immune cells in the lungs in an effort to neutralize the viruses end up causing immune dysfunction, excessive inflammation, and cytokine dysregulation resulting in "cytokine storm syndrome" with fluid leakage to the alveoli, impairing the blood oxygenation, resulting in sepsis and septic shock which is associated with the higher severity of Covid-19 cases (Anderson & Reiter, 2020; Buszko et al., 2020; Datta & Bhattacharjee, 2020; Hotchkiss et al., 2016). This is attributed to angiotensin-converting enzyme 2 receptors (ACE2 receptors) abundance in the intestinal epithelium (Infusino et al., 2020), it is possible that SARS-CoV-2 can impair the absorption of nutrients (i.e., tryptophan) by the intestine epithelium and this amino acid regulates the expression of peptides with antimicrobial properties, capable of controlling the composition of the gut microbiota (elaborated further in the next section). This results in gastroenteritis symptoms that have been observed in many Covid-19 patients' cases (Infusino et al., 2020). Although the evidence pointing to the success of probiotic supplementation in enhancing the immunity of Covid-19 patients and controlling the inflammation is still mounting, more clinical studies are necessary for the development of an efficient protocol (Akour, 2020).

3.1.2 Importance of probiotic nutrition in modulating immune homeostasis

Nutrition is a cornerstone in modulating immune homeostasis and probiotic nutrition is paramount in maintaining gut microbiota subsequently regulating overall immune homeostasis. Probiotics supplementation is usually administrated

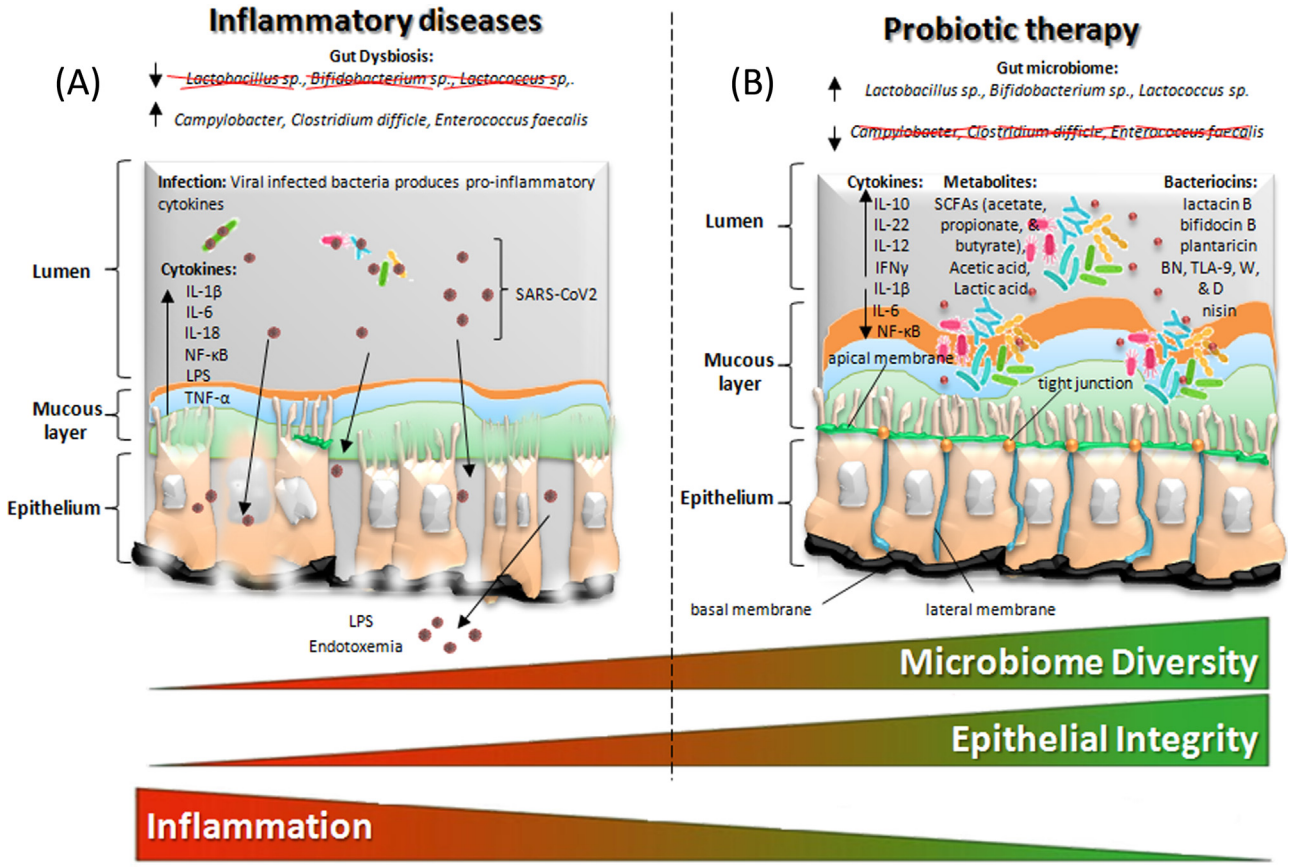

FIGURE 3.3 Influence of the gut microbiota (A) Covid-19 infection causes gut dysbiosis which results in increased proliferation of *Campylobacter, Clostridium difficile, Enterococcus faecalis* and hypercytokinemia "cytokine storm syndrome" of pro-inflammatory cytokines that ultimately impairs immune homeostasis, (B) probiotic therapy (*Lactobacillus* spp., *Bifidobacterium* spp., and *Lactococcus* spp.) that restores the gut microbiota and maintains overall immune homeostasis.

orally, whether in capsules, oil drops, water-soluble powders, or in children formulations and foods (Fenster et al., 2019; Govender et al., 2014). Orally administered probiotics may interact with approximately 200 m^2 of gut mucosa and lymphoid tissue associated with the intestines where most of the immune cells from the gut are located (Lebeer et al., 2010). This is the reason why several benefits conferred by probiotics are due to the immune system modulation affecting the host's immunity and inflammatory responses (Oelschlaeger, 2010). Furthermore, complex carbohydrates present in dietary fibers (mostly found in whole grains, fruits, vegetables, and cereals) are fermented by some bacteria species from gut microbiota, generating short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which are characterized to be antiinflammatory (Dhar & Mohanty, 2020). They act as signaling molecules to promote antiinflammatory cytokines production (IL-10, IL-12, IL-22, and IFN-γ), reduction of chemotaxis in the respiratory tract, immune cell adherence, increase the function of CD8 + T lymphocytes, and interferon signaling in macrophages in patients with infection and activation of Th2 effector cells in the lungs, which causes a more efficient control of external pathogens propagation (Conte & Toraldo, 2020; He et al., 2020). SCFAs also promote B-cell differentiation and antibody synthesis, thereby improving the antibody-antigen response and increases the levels of endogenous antioxidant enzyme (i.e., glutathione) which reduces oxidative stress (Park et al., 2015; Sharma & Kaur, 2020).

Besides SCFAs, bacteria from the gut microbiota produce some essential amino acids as metabolites, that is, tryptophan, which can inhibit NF-κB activation, thus reducing the expression of pro-inflammatory mediators, and can strengthen the tight junctions of the gut epithelium responsible for the impermeability of the intestinal mucosa. Finally, gut microbiota can synthesize some vitamins from complex B that can act as immune regulators (Morais et al., 2020). As mention above, butyrate is one of the main products derived from gut microbiota metabolism and is responsible for several local and systemic effects. For instance, it contributes to the barrier of the gut epithelium against external pathogens, decreases glial activity in the CNS, inhibition of histone deacetylase (action as an epigenetic regulator), and

optimization of mitochondrial activity via induction of the melatonergic pathway. Furthermore, butyrate can also increase the activity of NK cells, enhancing antiviral immunity which could be useful for inflammatory diseases (Anderson & Reiter, 2020) as shown in Fig. 3.4. Moreover, with the melatonin hormone, either from the mitochondria of immune cells or from the pineal gland, melatonergic downregulation can occur in cases of stress and dysbiosis by the action of induced indoleamine 2,3-dioxygenase, which relocates tryptophan from serotonin and melatonin synthesis for the production of kynurenine products. This inhibits the activation of alpha 7 nicotinic acetylcholine receptor (α7nAChR), an important part of the cholinergic nervous system in the brain. The α7nAChR expression can be beneficial due to the regulation of autophagy in lung epithelial cells and the dampening of pulmonary immune cells; therefore, factors that inhibit α7nAChR expression, such as dysbiosis, might be detrimental to patients suffering from inflammatory diseases such as Covid-19 (Anderson & Reiter, 2020).

Gut dysbiosis itself can cause or intensify some preexistent conditions in a two-way interaction: (1) decreased melatonin levels, consequently increase circulating levels of lipopolysaccharides (LPS), a key pathogenic stimulant for inflammation in the gut; and (2) decreased butyrate levels. Butyrate suppresses platelet activation and pro-inflammatory

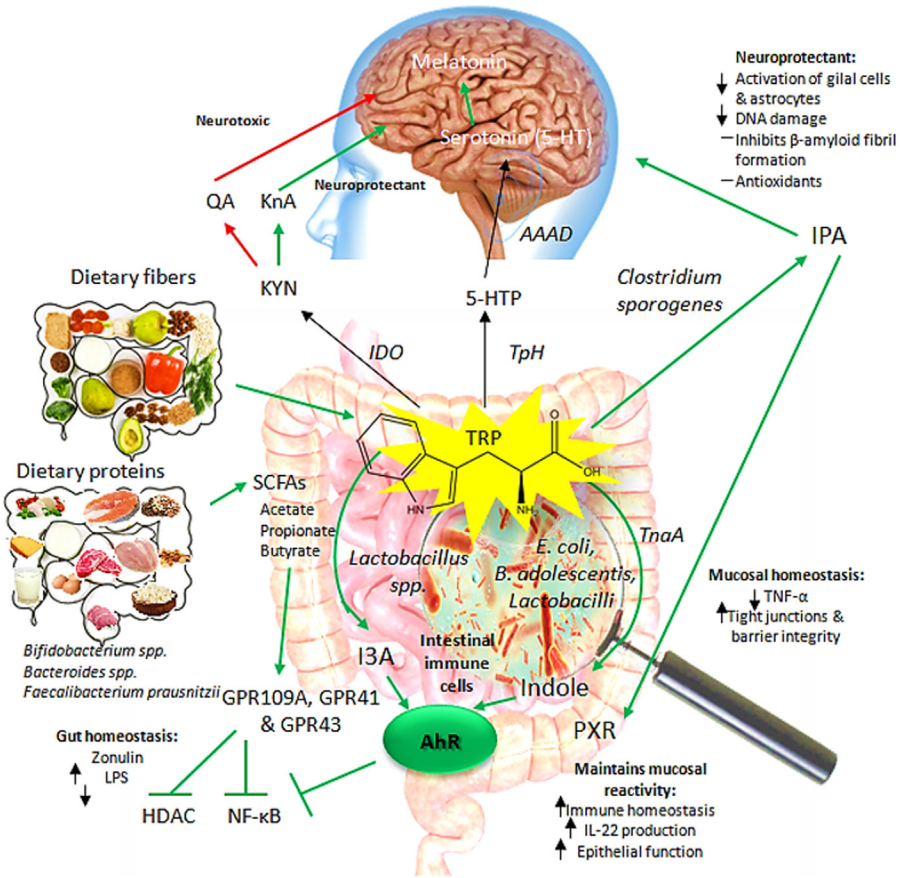

FIGURE 3.4 Probiotic nutritional interconnections from dietary fibers and proteins through a cascade of pathways to main immune homeostasis. Tryptophan (TRP) is metabolized by Clostridium sporogenes into 3-indolepropionic acid (IPA) which confers neuroprotectant activity against neurological disorders. Moreover, IPA binds to pregnane X receptor (PXR) in the intestinal cells to maintain mucosal homeostasis. Indole is produced by *E. coli, B. adolescentis*, and *Lactobacilli* (*L. acidophilus* and *L. reuteri*) from TRP catalyzed by tryptophanase (TnaA). TRP is further metabolized into indole-3-aldehyde (I3A) by Lactobacillus spp., and Bifidobacterium spp., in the intestinal cells to aryl hydrocarbon receptor (AhR) which maintains overall mucosal reactivity increasing the production of IL-22, immune homeostasis, and the suppression of nuclear factor-κB (NF-κB) and pro-inflammatory mediators. TRP is metabolized to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase (TpH), then decarboxylated to 5-hydroxytryptamine (5-HT) by aromatic amino acid decarboxylase (AAAD), and to melatonin involved in sleep regulation, other cyclical bodily activities, and circadian rhythm. TRP is metabolized through the kynurenine (KYN) pathway by indoleamine-2,3-dioxygenase (IDO), KYN is further metabolized to either neuroprotective kynurenic acid (KnA) or neurotoxic quinolinic acid (QA). Dietary fibers are metabolized by some bacteria species from the gut microbiota to generate short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, where acetate and propionate bind to G protein-coupled receptors (GPR41) and GPR43, which can modulate inflammation, and butyrate binds to GPR109A, suppressing NF-κB and inhibition of histone deacetylase (HDAC), lipopolysaccharide (LPS), and increasing the synthesis of zonulin for preventing gut permeability.

cytokines; therefore there is an increased risk of cardiovascular complications (DeGruttola et al., 2016). The BBB permeability and neuron myelination are also impaired in this case, which causes part of the neurological symptoms which is seen in some Covid-19 patients (Anderson & Reiter, 2020). The interactions of the human gut microbial flora with probiotics are far more intimate, as they facilitate an orchestrated symphony that determines the physiological, immunological, metabolic, and behavioral development that can influence future disease susceptibility (Daliri & Lee, 2015). Probiotics have also been considered in past decades as an alternative therapy for inflammatory bowel disease as they exhibited good efficacy when used as adjuvants for treating ulcerative colitis (Furrie et al., 2005; Shen et al., 2018). The use of probiotic cultures excludes potentially pathogenic microorganisms and reinforces the body's natural defense mechanisms. The modulation of the intestinal microbiota by probiotic microorganisms occurs through a mechanism called competitive exclusion. Pathogen exclusion through the production of antagonistic antimicrobial substrates against pathogenic microorganisms can facilitate gut stability. This can neither be pathogenic nor trigger allergic responses even in immunocompromised hosts, thereby serving as adjuvants to stimulate and maintain immune homeostasis.

3.1.3 Probiotic mechanism of action

One of the first evidences of the interaction between the gut microbiota and the immune system was observed in germ-free mice, which tend to present reduced Peyer's patches and decreased amount of regulatory T cells and T helper 17 (Th17) cells in mesenteric lymph nodes (Shi et al., 2017). This situation was fixed rapidly after the colonization of the gut with intestinal bacteria from normal mice (Infusino et al., 2020), corroborated by further investigations which found that the modulation of T cell differentiation in Th1, Th2, Th17 helper, or T-regulatory cells by the gut microbiota, probably as a means to immunize from or to tolerate some luminal bacteria (Infusino et al., 2020; Morais et al., 2020). It is paramount for probiotics to reach the target site (the gut) for their biodistribution and optimal efficacy. This entails probiotics to endure the gastric acidity of the stomach attributed by the presence of HCl at 37°C, resistance to pancreatic enzymatic degradation, as well as navigate the bile in the upper digestive tract before reaching the small intestines (Maldonado Galdeano et al., 2019). Thereafter, allow for efficient intestinal epithelial adhesion—for immune modulation by enhanced damaged mucosa healing, followed by prolonged transient colonization—dictated by their adhesion capacity to the host gut, to other bacterial cells (coaggregation), and to some extent to the same species (auto-aggregation) in order to colonize and promote immunomodulatory effects (Piwat et al., 2015; van Tassell & Miller, 2011).

Several lines of evidence show that the antiviral adjuvant property of probiotics happens by three main mechanisms: (1) reducing the epithelium permeability by a spatial barrier, (2) reinforcement of the innate immunity in the gut mucosa, and (3) regulating the systemic immune response with an antiinflammatory effect stimulated by increased macrophages activity (Calder, 2020; Infusino et al., 2020). The regulation of inflammatory cytokines plays an important role in the modulation of the immune system due to their biological effects, that is, regulation of immunity, decrease or increase of inflammation, modulation of cell growth, and cell healing (Liu et al., 2013). Those effects are due mostly to the decreased levels of pro-inflammatory cytokines (TNF-α, IL-6, and IL-1β) and inactivation of NF-κB (Hasan et al., 2018; Jang et al., 2019; Liu et al., 2013; Xia et al., 2018).

The complexity of the interconnectivity between probiotics and gut microbiota varies in individuals. However, one major consensus revolves around the improvement of the barrier functions of the gut mucosa able to stimulate epithelial cell signaling pathways—facilitated by Paneth cells responsible for the secretion of diverse antimicrobial peptides [e.g. lysozyme, secretory phospholipase A2, defensins, defensin-like peptides (elafin and SLPI), and cathelicidins] and production of antiinflammatory cytokines (IL-10, IL-12, IL-22, and IFN-γ). Probiotics play a pivotal role in the interaction of intestinal epithelial cells and splenic macrophages in innate immune responses as a result of an increased expression of the receptors toll-like receptor 2 (TLR2) and mannose (CD206) on the surface of macrophages and dendritic cells and later stimulation of an adaptive immune response (Maldonado Galdeano et al., 2019). These results reinforce intestinal and BBBs integrity by increasing gene expression of tight junction proteins, TLR, and the proteoglycan recognition proteins, leading to activation of dendric cells and monocyte chemoattractant protein 1 which consigns signals to other immune cells, resulting in the activation of the mucosal immune system, characterized by an increase in IgA + in the lamina propria of the intestine, bronchus and mammary glands, and the activation of T cells that release IL-10 and produce SCFAs for the growth of desirable microbes (Maldonado Galdeano et al., 2019).

Another mechanism of probiotics in maintaining immune homeostasis is through the production of organic acids (acetic and lactic acids) and bacteriocins (lactacin B, bifidocin B, plantaricin, and nisin) thus inhibiting the proliferation of pathogenic bacteria and enhancing the response of the gut-associated immune repertoire (Gaspar et al., 2018). Skolnick and Greig (2019) and Yuan et al. (2019) have shown that some gut microbes convert guanine to queuine, which is described as a longevity vitamin that has been reported to improve mental well-being. The induction of a

viral/LPS-induced inflammation and subsequent compromising of BBB integrity opens up an avenue of investigation into the role of probiotics as a treatment strategy to reverse the harmful effects of microbiotic-induced inflammation. Most recently, work by Cui et al. (2020) revealed that some gut microbes especially lactic acid bacteria (*Lactobacillus buchneri*, *Levilactobacillus brevis*, *Lactobacillus paracasei*, *L. plantarum*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, and *L. lactis*) and *Bactereroides* (*Bacteroides fragilis*) can produce gamma-aminobutyric acid (GABA), a neurotransmitter that inhibits neural activity in the brain, also plays an important physiological function, such as antihypertensive, antidepressant activities, role in behavior, cognition, and the body's response to stress. GABA is also implicated in enhancing immunity, relieving anxiety and menopausal syndrome, regulating blood pressure, fighting obesity, and improving visual cortical function. However, the unregulation of GABA has been linked to depression and other mental health problems. Individuals with fewer *Bacteroides* bacteria exhibited a robust pattern of hyperactivity in the prefrontal cortex which is associated with severe depression (Bienenstock et al., 2015; Galland, 2014).

Complex, biochemical communication exists between the gut microbiome (weighing 2 kg) and the human brain (weighing 1.4 kg) and is denoted as the gut-brain axis, involving: the CNS, hypothalamic-pituitary-adrenal axis; autonomic nervous system, and gut microbiota linked to the brain, recently known as psychobiome which influences overall immune and brain homeostasis (Sharma & Kaur, 2020). The bacteria within the gut are tantalizing sources of untapped therapeutic potential that produce a plethora of ligands, namely glutamate (neurotransmitter), involved in cognition, learning, and memory (Baj et al., 2019). Note that glutamate levels are suppressed in individuals suffering from anxiety disorders and depression. The main action mechanism proposed for probiotics relies on the immune modulation towards the restoration of health by the influence on systemic immunological and inflammatory parameters, thus enhancing immune response and maintaining well-orchestrated immunity (Bermudez-Brito et al., 2012; Plaza-Diaz et al., 2019).

Immune gut homeostasis serves as a prerequisite for intestinal and BBB integrity which is orchestrated by the regulatory balance of pro- and antiinflammatory responses. During inflammation, enteroendocrine cells release IL-6 which acts as both a pro-inflammatory cytokine and an antiinflammatory myokine; IL-7 primarily acts on T cells (i.e., lymphocytes, produced in the thymus, central function in an immune response) that abundantly express the IL-7 receptor and are increased at the inflammatory sites, predominantly induces Th1 and Th17-associated cytokine secretion (Th2 cells secrete IL-4, IL-5, IL-6, IL-10, and IL-13 cytokines, which mediates the antiinflammatory humoral response and immune suppression via the inhibition of Th1 cytokine) (Dhar & Mohanty, 2020; Pennisi, 2020). An adjunct alternative to maintaining immune homeostasis can be through nutritional therapy which can aid in increasing immune system responsiveness. Likewise, it is also imperative to be aware of the type of food we consume over time, as in the lamina propria, probiotic functions involve the action of T helper (Th) and regulatory T (Treg) cells (Kim et al., 2018). IL-1β and IL-1α interleukins are prototypical pro-inflamed cytokines that perform pleiotropic functions on different cells and play a major role in acute, chronic, and autoimmune disorders. A probiotic formulation (*L. rhamnosus*, *B. lactis*, and *B. longum*) have demonstrated a significant increase in IL-10 and a decrease in inflammatory mediators (IL-1β and IL-6) (Sichetti et al., 2018).

Lactobacillus gasseri strains (SBT2055, TMC0356, and OLL280) have been reported to activate the human dendritic cells through an increase in the secretion of IFN-γ and IL-12 towards Type 1 T-helper polarization (Th1) responses, thereby promoting immunity against infections and other diseases attenuated by the expression of pro-inflammatory cytokines (Kumar et al., 2019; Nishihira et al., 2016) Probiotics can enhance the host defense system by increased expression of myxovirus resistance protein (Mx1) and 2′-5′ oligoadenylate synthetase 1 A, for antiviral immunity and IgA secretion, collaborating in maintaining immune homeostasis and surveillance by providing protective humoral and cellular immunity (Lemme-Dumit et al., 2018; Maldonado Galdeano et al., 2019). Additionally, probiotics have the ability to reduce purine in foods and beverages, which is essential to viral RNA synthesis during viral infections.

Moreover, in vitro investigations demonstrated that some probiotic strains (i.e., *L. paracasei*, *L. plantarum*, and *L. rhamnosus*) are able to inhibit the release of pro-inflammatory cytokines IL-6, IL-8, and prostaglandin E2 by human monocytes, and in macrophages, which modulate the production of TNF via activation of signal transducer and activator of transcription 3 and, consequently, inhibition of JunN-terminal kinases activation (Azad et al., 2018). IL-22, MAPK, and NF-κB are downregulated by various probiotics in dendritic cells, while antiinflammatory cytokines such as IL-10 are upregulated in Wistar rats with edema in the paws, with a significant improvement in the paw inflammation (de Moreno de Leblanc et al., 2011; Ding et al., 2017; Llewellyn & Foey, 2017). These findings were further supported by results reported by Dargahi et al. (2019) and Sichetti et al. (2018). They revealed that the administration of a probiotic formulation (*L. rhamnosus*, *B. lactis*, and *B. longum*) led to increased production of IL-10 and decreased production of IL-1 and IL-6 in cultured macrophages.

Various inflammatory markers (i.e., iNOS, COX-2, TNF, NF-κB, IL-6, and phosphorylated Akt) were found to decrease after the administration of probiotics in some colitis models, while there was upregulation of IL-10 and nitric

oxide (Nanau & Neuman, 2012). Pro- and antiinflammatory markers were also modulated by probiotics in multiple sclerosis in vivo models, with a decreased autoreactive response from T cells contributing to the improvement in the condition (Akour, 2020). The inhibition of H1N1, HIV, rotavirus, and gastric corona by bacteria from *Lactobacillus* family has already been observed experimentally. As mentioned above, these bacteria typically secrete metabolites such as butyrate, acetic acid, lactic acid, and plantaricin, which demonstrated to enhance antiviral immunity (Anwar et al., 2020). *Lactobacillus lactis* has shown antiviral activity against influenza viruses by stimulating plasmacytoid dendritic cells via activation of TLR 9 (TLR9), which leads to an increased interferon expression and consequent antiviral immunity enhancement. Similarly, the production of interferons was augmented after the administration of *L. gasseri* in mice bearing respiratory syncytial virus, with a consequent decrease in the viral titer.

3.1.4 Probiotic interlink with immunization efficacy

The therapeutic effects of probiotics have been mostly studied in the gastrointestinal tract. Modulation of the gut-brain by probiotics has been suggested as a novel therapeutic solution for anxiety and depression. Studies have described the potential therapeutic effects of probiotics and the possible mechanisms of action to prevent and/or treat chronic airway diseases (Martens et al., 2018). Most recently compelling evidence has demonstrated that gut microbiota may influence blood pressure, and, therefore, may be important for people with hypertension. As the composition of the gut microbiota is imperative to maintain intestinal immunity and whole-body homeostasis, it is not surprising that several diseases, such as hypertension, are associated with dysbiosis. The most probable mechanism evolved in the influence of the microbiota on blood pressure is related to its influence on host-cell physiology through bacterial metabolic products or wall components. Consequently, these bacteria are able to control adiposity and inflammatory response, interacting with epithelial and dendritic cells of the gut, which are paramount for innate and adaptive immunities (Robles-Vera et al., 2017). Probiotics may be very useful for lowering cholesterol, improving atherosclerosis, or attenuate myocardial hypertrophy. Probiotics release bioactive peptides (like angiotensin-converting enzyme inhibitory peptides) when food products are being fermented that help with blood pressure regulation. A study evaluated nine controlled clinical trials about the influence of probiotics in blood pressure and concluded that it helps to lower systolic and diastolic blood pressure, especially with the ingestion of multiple species of probiotics for more than 8 weeks (Dong et al., 2019; Sabico et al., 2019).

3.1.5 Clinical translation of probiotic investigation

Albeit there are a number of probiotics in the market that are not effectively regulated by global regulatory authorities such as the FDA, WHO, etc. Probiotics research is still in its infancy with more clinical studies and investigations conducted to determine the health benefits, validity, and safety of probiotics as a function of improving "biomarker deficiency" data. Their effectiveness varies due to limited regulatory frameworks in place to monitor their efficacies. For example, probiotics *L. reuteri* NCIMB 30242 LRC, superstrain *L. acidophilus* DDS-1, *B. lactis* UABla-12, *L. gasseri* BNR17, and *L. plantarum* PPLP-217 (UAS Labs, USA; Micropharma, Canada) has been on the market as the first recognized biomarker of hypercholesterolemia and obesity by lowering cholesterol and sterol absorption, in human trials, however, there is mixed inconsistency in the outcomes.

Among the most common diseases that affect children, urinary tract infection (UTI) is detrimental because it can lead to severe conditions such as kidney ulcers or renal failure (Leung et al., 2019; Rostami et al., 2018). UTI is usually treated with antibiotics and researchers have found that probiotics may play an important role as a complementary therapy, thus increasing the effectiveness of the medication and preventing the incidence of UTIs (Rostami et al., 2018). Probiotic supplementation has also been demonstrated to play a positive impact on the treatment of depression symptoms, improving mood and cognition conditions. Major depressive disorder (MDD) is associated with high levels of pro-inflammatory cytokines (IL-6 and TNF-α) which causes several comorbidities and inflammatory conditions like rheumatoid arthritis, multiple sclerosis, and coronary heart disease, among others (Köhler et al., 2017). Furthermore, studies have shown that conventional antiinflammatories have antidepressant effects in patients, and those conventional pharmacotherapies such as selective serotonin reuptake inhibitors also have antiinflammatory properties. Inflammation may be associated with resistance to depression treatment (Bron et al., 2017; Miller et al., 2012). Accordingly, probiotics can act as an adjuvant in antidepressant treatment by reducing inflammation (Vlainić et al., 2016). Probiotics also help with metabolic complications such as obesity and diabetes which are associated with high levels of peripheral inflammatory markers and, consequently, related to mood and cognitive illnesses (Akbari et al., 2016).

TABLE 3.1 Clinical trials focusing on the role of probiotics in various diseases.

S. no	Clinical trial title	Trial no.	Probiotic formulation	Outcome	References
1	Effect of probiotic administration on gut flora composition	NCT03330678	VSL#3 capsule (a mixture of eight species—*S. thermophilus*, *B. breve*, *B. longum*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, and *L. delbrueckii*)	Reduction in circulating Th17 cells, and monocyte-derived cytokines in response to LPS stimulation.	Singh et al. (2018)
2	The effect of probiotic capsule supplementation on severity depression among patients with major depressive disorder (MDD) under treatment with citalopram	IRCT2014060717993N1	Probiotic capsules containing strains of *L. acidophilus, L. casei, and B. bifidum*	Significantly lower Beck Depression Inventory scores in comparison to those who received the placebo. Reductions in inflammatory markers like serum insulin and serum hs-CRP were also observed in these patients	Akkasheh et al. (2016)
3	Effect of probiotic supplementation on endothelial function	NCT01952834	GoodBelly probiotic (a mixture of *L. Plantarum* 299 v (Lp299v)., *B. lactis* Bi-07, and *L. acidophilus*)	Men with stable coronary artery disease improved vascular endothelium dilation and reduced systemic inflammation attributed to reduction in cytokine (IL-8 and IL-12) expression and leptin, a biomarker of cardiovascular risk, the peptide circulates the bloodstream, and is responsible for regulating energy balance and signals to the hypothalamus in the brain.	Malik et al. (2018)
4	Effect of probiotics on gut-liver axis of alcoholic liver disease	NCT01501162	Lactowell whey permeate (*L. subtilis*/*S. Faecium*)	Intestinal flora restoration and microbial LPS improvement in patients with alcoholic hepatitis, thus revealing the therapeutic effect of probiotics on the gut-liver axis of ALD disease.	Han et al. (2015)
5	Safety of BB-12 supplemented strawberry yogurt for healthy children	NCT01652287	*B. lactis* strain BB-12 (BB-12)-supplemented yogurt	No significant differences between the treatment and control group, suggesting that BB-12 is safe and well-tolerated when consumed by healthy children.	Merenstein et al. (2011)

(*Continued*)

TABLE 3.1 (Continued)

S. no	Clinical trial title	Trial no.	Probiotic formulation	Outcome	References
6	Impact of emergency department probiotic (LGG) treatment of pediatric gastroenteritis	NCT01773967	*L. rhamnosus* GG (ATCC 53103/LGG)	No significant outcomes between the ATCC 53103/GG group and those who received placebo.	Schnadower et al. (2018)
7	Efficacy of *Lactobacillus* GG with diosmectite in treatment children with acute gastroenteritis	NCT01657032			Schnadower et al. (2017)
8	Efficacy and safety study in the prevention of antibiotic-associated diarrhea (AAD) and *Clostridium difficile*-associated diarrhea (CDAD) in hospitalized adult patients exposed to nosocomial Infection	NCT00958308	BIO-K + CL-1285 (mixture of *L. acidophilus* CL1285 and *L. casei* LBC80R)	BIO-K + CL-1285 was well tolerated and effective for reducing risk of AAD and, in particular, CDAD in hospitalized patients on antibiotics	Gao et al. (2010)
9	Role of probiotics in recovery of children with severe acute malnutrition (SAM)	ISRCTN16454889	*B. animalis* subsp. *lactis* BB-12 and *L. rhamnosus* LGG	No effect on diarrhea in children with SAM	Grenov et al. (2017) and Lanyero et al. (2019)
10	Effect of probiotics (Bio-Three) in children's enterocolitis	NCT00463190	Bio-Three (*Bacillus mesentericus*, *S. faecalis* and *Clostridium butyricium*)	Bio-Three reduced the severity of diarrhea and hospital stay in children with acute diarrhea. In addition, cytokines IL-10, IFN-γ, and IL-12 were upregulated and TNF-α was downregulated in the probiotic group compared to the placebo group.	Chen et al. (2010)
11	The probiotic *Bifidobacterium breve* strain BBG-01 administrated early to preterm infants to prevent infection, necrotizing enterocolitis, and death	ISRCTN05511098	*B. breve* BBG-01	No evidence of benefit for routine use of *B. breve* BBG-001 for prevention of necrotizing enterocolitis and late-onset sepsis in very preterm infants	Costeloe et al. (2016)

Albeit microbiota composition varies from person to person, there is evidence that alteration in the enterotype of individuals with MDD, contributing to the biosignature of this condition. For example, it was found that patients with MDD present increased levels of Bacteroidetes, Proteobacteria, and Actinobacteria beyond a bigger bacterial diversity and decreased level of Firmicutes (Akkasheh et al., 2016; Jiang et al., 2015). Several studies point that the restoration of the microbiota may be related to the reduction of peripheral inflammation. This is due to the action of probiotics in the composition of the intestinal microbiota which are responsible for their antiinflammatory effects. Reducing stress-induced inflammation, obesity-and-diet-induced-inflammation and intestinal permeability are other benefits of probiotics (Lobionda et al., 2019; Miller & Raison, 2016; Vlainić et al., 2016). In the US, probiotics are rarely prescribed by physicians; however, probiotics are marketed as dietary supplements, and manufacturers suggest use while their relevance has not yet been established. The US and European government agencies remain concerned about the effectiveness and safety of probiotics. Tables 3.1 and 3.2 shows some of the probiotic clinical trials conducted for various diseases and Covid-19 listed on the WHO's International Clinical Trials Registry Platform.

TABLE 3.2 Role of probiotic in Covid-19.

S. no.	Clinical trial title	Trial no.	Probiotic formulation	Aim of the study
1	Evaluation of the complementary effect of symbiotic adjuvant on inflammatory markers and clinical manifestations in patients with Covid-19	IRCT20200923048815N1	Two lactocar brand synbiotic adjuvant capsules	Evaluation of the treatment inflammatory markers (CRP, ESR, IL-6, CBC) and clinical prognosis before and 8 weeks after treatment in patients with Covid-19
2	Effects of Lactocare synbiotic against Covid-19 infection in the staff of emergency department	IRCT20101020004976N6	Lactocare synbiotic capsule	Evaluate the effects of Lactocare synbiotic against Covid-19 infection
3	Study for the application of novel coronavirus pneumonia (Covid-19) intestinal tract toxicity in diagnosis and its prognostic effect	ChiCTR2000032686	Rifximine intervention versus probiotic intervention	Monitor the influence of treatment on changes of microbiota, virology and metabolomics
4	Stress-reduction using probiotics to promote ongoing resilience throughout Covid-19 for healthcare workers: A randomized placebo-controlled trial	ACTRN12620000480987	*L. rhamnosus* N001	To monitor mental health of nurses using the Perceived Stress Scale to evaluate their psychological stress level, cognitive function and behavior during the Covid-19 pandemic
5	Oxygen-ozone as adjuvant treatment in early control of Covid-19 progression and modulation of the gut microbial flora (PROBIOZOVID)	NCT04366089	SivoMixx composition (*S. thermophiles*) DSM322245, *B. lactis* DSM 32246, *B. lactis* DSM 32247, *L. acidophilus* DSM 32241, *L. helveticus* DSM 32242, *L. paracasei* DSM 32243, *L. plantarum* DSM 32244, *L. brevis* DSM 27961	To evaluate effectiveness of oxygen-ozone therapy accompanied by probiotics supplementation for preventing the progression of Covid-19
6	Efficacy of *L. plantarum* and *P. acidilactici* in adults with Covid-19	NCT04517422	*L. plantarum* CECT7481, *L. plantarum* CECT 7484, *L. plantarum* CECT 7485, and *P. acidilactici* CECT 7483	To evaluate safety and efficacy of the probiotics to reduce gastrointestinal Covid-19 severity and modulate the levels of IgG/IgM

A study by Nishihira et al. (2016) evaluated the efficacy of drinkable yogurt containing 1×10^9 CFU/100 g of *L. gasseri* strain SBT2055 (LG2055) in stimulating immunoglobulin production and innate immunity for influenza vaccine-specific antibody responses after trivalent influenza [A/California/7/2009(X-179A)(H1N1)pdm09, A/New York/39/2012(X-233A)(H3N2), B/Massachusetts/2/2012(BX-51B)] vaccination in healthy adult volunteers against influenza viruses A/H1N1 and B; the control group receiving the placebo (drinkable yogurt without LG2055). LG2055 (Megmilk Snow Brand Co., Ltd., Tokyo, Japan) has been reported to lower the fecal *Staphylococcus* population and p-cresol concentration (cholesterol-lowering effect in humans with mild hypercholesterolemia), and prevent abdominal adiposity in rats and humans. LG2055 was also found to confer a protective effect against influenza A virus infection through the induction of antiviral genes by type I IFN signaling and IgA production in the mouse small intestine.

This compelling evidence raises the possibility that administration of LG2055 may enhance both innate and adaptive immunity. Results from the study demonstrated that the administration of LG2055 increased hemagglutination inhibition titers and the rate of seroprotection against influenza viruses A/H1N1 and B after vaccination, in addition to elevated levels of total IgG and IgA in plasma and sIgA production in saliva as compared with the control group that received the placebo. Furthermore, LG2055 was found to enhance natural killer cell activity and myxovirus resistance A gene expression, which is one of the antiviral genes stimulated by type I or type III interferons in peripheral blood mononuclear cells. Recently, some clinical trials have shown that the administration of probiotics can prevent

ventilator-associated pneumonia in patients with Covid-19, but the effectiveness in reducing deaths in these patients has yet to be proven. Table 3.2 reviewed some of the registered clinical trials focused on the role of probiotics in Covid-19. A targeted approach to the modulation of the intestinal microbiota of patients with Covid-19 in order to define the treatment with the appropriate probiotic is necessary (Kalantar-Zadeh et al., 2020; Sundararaman et al., 2020).

3.2 Conlusion

The gut microbiota functions as a motherboard for overall immune homeostasis and gut dysbiosis is linked to a variety of inflammatory diseases and disorders. Probiotics have been shown to restore gut dysbiosis to main immune homeostasis; however, biomarker deficiency data is limited to determine the health benefits, validity, and safety of probiotics as a function of improving immunity against infections. Probiotics might be useful in regulating and enhancing immune response through antiinflammatory cytokines, improve gut barrier function by antagonistic effects against pathogens bacterial strains as a result of gut dysbiosis including patients with Covid-19. The race for an effective and safe Covid-19 vaccine has been on everyone's radar worldwide. Expert virologists believe that a single dose alone would not be as effective for prolonged immunity against the virus. This is true for patients with immunosenescence; thus, the older the person becomes, the more susceptible to infections they are. In addition, immunization by vaccines is also impaired. Vaccination is an adaptive immunity through the expression of antigen-specific antibodies and cytotoxic T cells in the most effective mechanism to prevent viral infections. As demonstrated by previous influenza vaccination, immune responses are different in individuals, weakened by specific lifestyle attributes, such as obesity, stress, and smoking cigarettes which ultimately influences overall immune homeostasis. Probiotics that activate both the innate and adaptive human immune responses are imperative, especially amid the Covid-19 vaccination paradigm; it is paramount to explore any other effective intervention strategies such as probiotics as an adjuvant synergistic approach for a more effective and beneficial prolonged antibody defense against the coronavirus and future pandemics. Therefore, probiotic supplementation can serve as armament against infectious pathogens, such as viruses, and can be included in a patient's dietary nutrition, especially since it has been demonstrated that long-term probiotics consumption does not affect the intestinal homeostasis.

Acknowledgment

The authors would like to thank the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) Grant No. 2019/15154-0 for support to Velaphi Clement Thipe.

References

Akbari, E., Asemi, Z., Daneshvar Kakhaki, R., Bahmani, F., Kouchaki, E., Tamtaji, O. R., Hamidi, G. A., & Salami, M. (2016). Effect of probiotic supplementation on cognitive function and metabolic status in Alzheimer's disease: A randomized, double-blind and controlled trial. *Frontiers in Aging Neuroscience*, *8*, 256. Available from https://doi.org/10.3389/fnagi.2016.00256.

Akkasheh, G., Kashani-Poor, Z., Tajabadi-Ebrahimi, M., Jafari, P., Akbari, H., Taghizadeh, M., Memarzadeh, M. R., Asemi, Z., & Esmaillzadeh, A. (2016). Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. *Nutrition (Burbank, Los Angeles County, Calif.)*, *32*(3), 315–320. Available from https://doi.org/10.1016/j.nut.2015.09.003.

Akour, A. (2020). Probiotics and COVID-19: Is there any link? *Letters in Applied Microbiology*, *71*(3), 229–234. Available from https://doi.org/10.1111/lam.13334.

Anand, S., & Mande, S. S. (2018). Diet, microbiota and gut-lung connection. *Frontiers in Microbiology*, *9*, 2147. Available from https://www.frontiersin.org/article/10.3389/fmicb.2018.02147.

Anderson, G., & Reiter, R. J. (2020). COVID-19 pathophysiology: Interactions of gut microbiome, melatonin, vitamin D, stress, kynurenine and the alpha 7 nicotinic receptor: Treatment implications. *Melatonin Research*, *3*(3), 322–345. Available from https://doi.org/10.32794/mr11250066.

Anwar, F., Altayb, H. N., Al-Abbasi, F. A., Al-Malki, A. L., Kamal, M. A., & Kumar, V. (2020). Antiviral effects of probiotic metabolites on COVID-19. *Journal of Biomolecular Structure and Dynamics*, 1–10. Available from https://doi.org/10.1080/07391102.2020.1775123.

Azad, M. A. K., Sarker, M., & Wan, D. (2018). Immunomodulatory effects of probiotics on cytokine profiles. *BioMed Research International*, *2018*, 8063647. Available from https://doi.org/10.1155/2018/8063647.

Baj, A., Moro, E., Bistoletti, M., Orlandi, V., Crema, F., & Giaroni, C. (2019). Glutamatergic signaling along the microbiota-gut-brain axis. *International Journal of Molecular Sciences*, *20*(6). Available from https://doi.org/10.3390/ijms20061482.

Bermudez-Brito, M., Plaza-Díaz, J., Muñoz-Quezada, S., Gómez-Llorente, C., & Gil, A. (2012). Probiotic mechanisms of action. *Annals of Nutrition and Metabolism*, *61*(2), 160–174. Available from https://doi.org/10.1159/000342079.

Bienenstock, J., Kunze, W., & Forsythe, P. (2015). Microbiota and the gut−brain axis. *Nutrition Reviews*, *73*(Suppl. 1), 28−31. Available from https://doi.org/10.1093/nutrit/nuv019.

Bron, P. A., Kleerebezem, M., Brummer, R.-J., Cani, P. D., Mercenier, A., MacDonald, T. T., Garcia-Ródenas, C. L., & Wells, J. M. (2017). Can probiotics modulate human disease by impacting intestinal barrier function? *British Journal of Nutrition*, *117*(1), 93−107. Available from https://doi.org/10.1017/S0007114516004037.

Buszko, M., Park, J.-H., Verthelyi, D., Sen, R., Young, H. A., & Rosenberg, A. S. (2020). The dynamic changes in cytokine responses in COVID-19: A snapshot of the current state of knowledge. *Nature Immunology*, *21*(10), 1146−1151. Available from https://doi.org/10.1038/s41590-020-0779-1.

Calder, P. C. (2020). Nutrition, immunity and COVID-19. *BMJ Nutrition, Prevention and Health*, *3*(1). Available from https://doi.org/10.1136/bmjnph-2020-000085, 74 LP—92.

Chen, C.-C., Kong, M.-S., Lai, M.-W., Chao, H.-C., Chang, K.-W., Chen, S.-Y., Huang, Y.-C., Chiu, C.-H., Li, W.-C., Lin, P.-Y., Chen, C.-J., & Li, T.-Y. (2010). Probiotics have clinical, microbiologic, and immunologic efficacy in acute infectious diarrhea. *The Pediatric Infectious Disease Journal*, *29*(2), 135−138. Available from https://doi.org/10.1097/inf.0b013e3181b530bf.

Conte, L., & Toraldo, D. M. (2020). Targeting the gut-lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. *Therapeutic Advances in Respiratory Disease*, *14*. Available from https://doi.org/10.1177/1753466620937170, 1753466620937170−1753466620937170.

Costeloe, K., Hardy, P., Juszczak, E., Wilks, M., & Millar, M. R. (2016). Bifidobacterium breve BBG-001 in very preterm infants: A randomised controlled phase 3 trial. *Lancet*, *387*(10019), 649−660. Available from https://doi.org/10.1016/S0140-6736(15)01027-2.

Cui, Y., Miao, K., Niyaphorn, S., & Qu, X. (2020). Production of gamma-aminobutyric acid from lactic acid bacteria: A systematic review. *International Journal of Molecular Sciences*, *21*(3), 1−21. Available from https://doi.org/10.3390/ijms21030995.

Daliri, E. B.-M., & Lee, B. H. (2015). New perspectives on probiotics in health and disease. *Food Science and Human Wellness*, *4*(2), 56−65. Available from https://doi.org/10.1016/j.fshw.2015.06.002.

Dargahi, N., Johnson, J., Donkor, O., Vasiljevic, T., & Apostolopoulos, V. (2019). Immunomodulatory effects of probiotics: Can they be used to treat allergies and autoimmune diseases? *Maturitas*, *119*, 25−38. Available from https://doi.org/10.1016/j.maturitas.2018.11.002.

Datta, C., & Bhattacharjee, A. (2020). Cytokine storm and its implication in Coronavirus disease 2019 (COVID-19). *Journal of Immunological Sciences*, *4*(3), 4−21. Available from https://doi.org/10.29245/2578-3009/2020/3.1190.

de Moreno de Leblanc, A., Del Carmen, S., Zurita-Turk, M., Santos Rocha, C., van de Guchte, M., Azevedo, V., Miyoshi, A., & Leblanc, J. G. (2011). Importance of IL-10 modulation by probiotic microorganisms in gastrointestinal inflammatory diseases. *ISRN Gastroenterology*, *2011*, 892971. Available from https://doi.org/10.5402/2011/892971.

DeGruttola, A. K., Low, D., Mizoguchi, A., & Mizoguchi, E. (2016). Current understanding of dysbiosis in disease in human and animal models. *Inflammatory Bowel Diseases*, *22*(5), 1137−1150. Available from https://doi.org/10.1097/MIB.0000000000000750.

Dhar, D., & Mohanty, A. (2020). Gut microbiota and Covid-19-possible link and implications. *Virus Research*, *285*, 198018. Available from https://doi.org/10.1016/j.virusres.2020.198018.

Din, A. U., Mazhar, M., Wasim, M., Ahmad, W., Bibi, A., Hassan, A., Ali, N., Gang, W., Qian, G., Ullah, R., Shah, T., Ullah, M., Khan, I., Nisar, M. F., & Wu, J. (2021). SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotics role. *Biomedicine & Pharmacotherapy*, *133*, 110947. Available from https://doi.org/10.1016/j.biopha.2020.110947.

Ding, Y. H., Qian, L. Y., Pang, J., Lin, J. Y., Xu, Q., Wang, L. H., Huang, D. S., & Zou, H. (2017).). The regulation of immune cells by Lactobacilli: A potential therapeutic target for anti-atherosclerosis therapy. *Oncotarget*, *8*(35), 59915−59928. Available from https://doi.org/10.18632/oncotarget.18346.

Dong, Y., Xu, M., Chen, L., & Bhochhibhoya, A. (2019). Probiotic foods and supplements interventions for metabolic syndromes: A systematic review and meta-analysis of recent clinical trials. *Annals of Nutrition and Metabolism*, *74*(3), 224−241. Available from https://doi.org/10.1159/000499028.

DuPont, A. W., & DuPont, H. L. (2011). The intestinal microbiota and chronic disorders of the gut. *Nature Reviews Gastroenterology & Hepatology*, *8*(9), 523−531. Available from https://doi.org/10.1038/nrgastro.2011.133.

Fenster, K., Freeburg, B., Hollard, C., Wong, C., Rønhave Laursen, R., & Ouwehand, A. C. (2019). The production and delivery of probiotics: A review of a practical approach. *Microorganisms*, *7*(3), 83. Available from https://doi.org/10.3390/microorganisms7030083.

Fioramonti, J., Theodorou, V., & Bueno, L. (2003). Probiotics: What are they? What are their effects on gut physiology? *Best Practice & Research. Clinical Gastroenterology*, *17*(5), 711−724. Available from https://doi.org/10.1016/S1521-6918(03)00075-1.

Fisher, D., & Mentor, S. (2020). Are claudin-5 tight-junction proteins in the blood-brain barrier porous? *Neural Regeneration Research*, *15*(10), 1838−1839. Available from https://doi.org/10.4103/1673-5374.280308.

Furrie, E., Macfarlane, S., Kennedy, A., Cummings, J. H., Walsh, S. V., O'neil, D. A., & Macfarlane, G. T. (2005). Synbiotic therapy (Bifidobacterium longum/Synergy 1) initiates resolution of inflammation in patients with active ulcerative colitis: A randomised controlled pilot trial. *Gut*, *54*(2), 242−249. Available from https://doi.org/10.1136/gut.2004.044834.

Galland, L. (2014). The gut microbiome and the brain. *Journal of Medicinal Food*, *17*(12), 1261−1272. Available from https://doi.org/10.1089/jmf.2014.7000.

Gao, X. W., Mubasher, M., Fang, C. Y., Reifer, C., & Miller, L. E. (2010). Dose-response efficacy of a proprietary probiotic formula of *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R for antibiotic-associated diarrhea and *Clostridium difficile*-associated diarrhea prophylaxis in adult patients. *The American Journal of Gastroenterology*, *105*(7), 1636−1641. Available from https://doi.org/10.1038/ajg.2010.11.

Gaspar, C., Donders, G. G., Palmeira-de-Oliveira, R., Queiroz, J. A., Tomaz, C., Martinez-de-Oliveira, J., & Palmeira-de-Oliveira, A. (2018). Bacteriocin production of the probiotic *Lactobacillus acidophilus* KS400. *AMB Express*, *8*(1), 153. Available from https://doi.org/10.1186/s13568-018-0679-z.

Govender, M., Choonara, Y. E., Kumar, P., du Toit, L. C., van Vuuren, S., & Pillay, V. (2014). A review of the advancements in probiotic delivery: Conventional vs. non-conventional formulations for intestinal flora supplementation. *AAPS PharmSciTech*, *15*(1), 29−43. Available from https://doi.org/10.1208/s12249-013-0027-1.

Grenov, B., Namusoke, H., Lanyero, B., Nabukeera-Barungi, N., Ritz, C., Molgaard, C., Fris, H., & Michaelsen, K. F. (2017). Effect of probiotics on diarrhea in children with severe acute malnutrition: A randomized controlled study in Uganda. *Journal of Pediatric Gastroenterology and Nutrition*, *64*(3), 396−403. Available from https://doi.org/10.1097/MPG.0000000000001515.

Han, S. H., Suk, K. T., Kim, D. J., Kim, M. Y., Baik, S. K., Kim, Y. D., Cheon, G. J., Choi, D. H., Ham, Y. L., Shin, D. H., & Kim, E. J. (2015). Effects of probiotics (cultured *Lactobacillus subtilis*/*Streptococcus faecium*) in the treatment of alcoholic hepatitis: Randomized-controlled multicenter study. *European Journal of Gastroenterology & Hepatology*, *27*(11), 1300−1306. Available from https://doi.org/10.1097/MEG.0000000000000458.

Hardy, H., Harris, J., Lyon, E., Beal, J., & Foey, A. D. (2013). Probiotics, prebiotics and immunomodulation of gut mucosal defences: Homeostasis and immunopathology. *Nutrients*, *5*(6), 1869−1912. Available from https://doi.org/10.3390/nu5061869.

Hasan, M. T., Jang, W. J., Kim, H., Lee, B.-J., Kim, K. W., Hur, S. W., Lim, S. G., Bai, S. C., & Kong, I.-S. (2018). Synergistic effects of dietary *Bacillus* sp. SJ-10 plus β-glucooligosaccharides as a synbiotic on growth performance, innate immunity and streptococcosis resistance in olive flounder (*Paralichthys olivaceus*). *Fish & Shellfish Immunology*, *82*, 544−553. Available from https://doi.org/10.1016/j.fsi.2018.09.002.

He, Y., Wang, J., Li, F., & Shi, Y. (2020). Main clinical features of COVID-19 and potential prognostic and therapeutic value of the microbiota in SARS-CoV-2 infections. *Frontiers in Microbiology*, *11*, 1302. Available from https://doi.org/10.3389/fmicb.2020.01302.

Hotchkiss, R. S., Moldawer, L. L., Opal, S. M., Reinhart, K., Turnbull, I. R., & Vincent, J.-L. (2016). Sepsis and septic shock. *Nature Reviews Disease Primers*, *2*(1), 16045. Available from https://doi.org/10.1038/nrdp.2016.45.

Infusino, F., Marazzato, M., Mancone, M., Fedele, F., Mastroianni, C. M., Severino, P., Ceccarelli, G., Santinelli, L., Cavarretta, E., Marullo, A. G. M., Miraldi, F., Carnevale, R., Nocella, C., Biondi-zoccai, G., Pagnini, C., Schiavon, S., Pugliese, F., Frati, G., & Ettorre, G. (2020). In SARS-CoV-2 infection: A scoping review. *Nutrients*, *12*(6), 1−21.

Jang, W. J., Lee, J. M., Hasan, M. T., Lee, B.-J., Lim, S. G., & Kong, I.-S. (2019). Effects of probiotic supplementation of a plant-based protein diet on intestinal microbial diversity, digestive enzyme activity, intestinal structure, and immunity in olive flounder (*Paralichthys olivaceus*). *Fish & Shellfish Immunology*, *92*, 719−727. Available from https://doi.org/10.1016/j.fsi.2019.06.056.

Jiang, H., Ling, Z., Zhang, Y., Mao, H., Ma, Z., Yin, Y., Wang, W., Tang, W., Tan, Z., Shi, J., Li, L., & Ruan, B. (2015). Altered fecal microbiota composition in patients with major depressive disorder. *Brain, Behavior, and Immunity*, *48*, 186−194. Available from https://doi.org/10.1016/j.bbi.2015.03.016.

Kalantar-Zadeh, K., Ward, S. A., Kalantar-Zadeh, K., & El-Omar, E. M. (2020). Considering the effects of microbiome and diet on SARS-CoV-2 infection: Nanotechnology roles. *ACS Nano*, *14*(5), 5179−5182. Available from https://doi.org/10.1021/acsnano.0c03402.

Kany, S., Vollrath, J. T., & Relja, B. (2019). Cytokines in inflammatory disease. *International Journal of Molecular Sciences*, *20*(23), 1−31.

Kim, H. W., Hong, R., Choi, E. Y., Yu, K., Kim, N., Hyeon, J. Y., Cho, K. K., Choi, I. S., & Yun, C.-H. (2018). A probiotic mixture regulates T Cell balance and reduces atopic dermatitis symptoms in mice. *Frontiers in Microbiology*, *9*, 2414. Available from https://www.frontiersin.org/article/10.3389/fmicb.2018.02414.

Köhler, C. A., Freitas, T. H., Maes, M., de Andrade, N. Q., Liu, C. S., Fernandes, B. S., Stubbs, B., Solmi, M., Veronese, N., Herrmann, N., Raison, C. L., Miller, B. J., Lanctôt, K. L., & Carvalho, A. F. (2017). Peripheral cytokine and chemokine alterations in depression: A meta-analysis of 82 studies. *Acta Psychiatrica Scandinavica*, *135*(5), 373−387. Available from https://doi.org/10.1111/acps.12698.

Kumar, S., Jeong, Y., Ashraf, M. U., & Bae, Y. S. (2019). Dendritic cell-mediated Th2 immunity and immune disorders. *International Journal of Molecular Sciences*, *20*(9). Available from https://doi.org/10.3390/ijms20092159.

Lanyero, B., Grenov, B., Barungi, N. N., Namusoke, H., Michaelsen, K. F., Mupere, E., Molgaard, C., Jiang, P., Frokiaer, H., Wiese, M., Muhammed, M. K., Pesu, H., Nielsen, D. S., Friis, H., Rytter, M. J., & Christensen, V. B. (2019). Correlates of gut function in children hospitalized for severe acute malnutrition, a cross-sectional study in Uganda. *Journal of Pediatric Gastroenterology and Nutrition*, *69*(30), 292−298. Available from https://doi.org/10.1097/MPG.0000000000002381.

Lebeer, S., Vanderleyden, J., & De Keersmaecker, S. C. J. (2010). Host interactions of probiotic bacterial surface molecules: Comparison with commensals and pathogens. *Nature Reviews. Microbiology*, *8*(3), 171−184. Available from https://doi.org/10.1038/nrmicro2297.

Lemme-Dumit, J. M., Polti, M. A., Perdigón, G., & Galdeano, M. M. (2018). Probiotic bacteria cell walls stimulate the activity of the intestinal epithelial cells and macrophage functionality. *Beneficial Microbes*, *9*(1), 153−164. Available from https://doi.org/10.3920/BM2016.0220.

Leung, A. K. C., Wong, A. H. C., Leung, A. A. M., & Hon, K. L. (2019). Urinary tract infection in children. *Recent Patents on Inflammation & Allergy Drug Discovery*, *13*(1), 2−18. Available from https://doi.org/10.2174/1872213X13666181228154940.

Liu, W., Ren, P., He, S., Xu, L., Yang, Y., Gu, Z., & Zhou, Z. (2013). Comparison of adhesive gut bacteria composition, immunity, and disease resistance in juvenile hybrid tilapia fed two different Lactobacillus strains. *Fish & Shellfish Immunology*, *35*(1), 54−62. Available from https://doi.org/10.1016/j.fsi.2013.04.010.

Llewellyn, A., & Foey, A. (2017). Probiotic modulation of innate cell pathogen sensing and signaling events. *Nutrients*, *9*(10). Available from https://doi.org/10.3390/nu9101156.

Lobionda, S., Sittipo, P., Kwon, H. Y., & Lee, Y. K. (2019). The role of gut microbiota in intestinal inflammation with respect to diet and extrinsic stressors. *Microorganisms*, *7*(8), 271. Available from https://doi.org/10.3390/microorganisms7080271.

Maldonado Galdeano, C., Cazorla, S. I., Lemme Dumit, J. M., Vélez, E., & Perdigón, G. (2019). Beneficial effects of probiotic consumption on the immune system. *Annals of Nutrition and Metabolism*, *74*(2), 115−124. Available from https://doi.org/10.1159/000496426.

Malik, M., Suboc, T. M., Tyagi, S., Salzman, N., Wang, J., Ying, R., Tanner, M. J., Kakarla, M., Baker, J. E., & Widlanksy, M. E. (2018). *Lactobacillus plantarum* 299v supplementation improves vascular endothelial function and reduces inflammatory biomarkers in men with stable coronary artery disease. *Circulation Research*, *123*(9), 1091−1102. Available from https://doi.org/10.1161/CIRCRESAHA.118.313565.

Markowiak, P., & Ślizewska, K. (2017). Effects of probiotics, prebiotics, and synbiotics on human health. *Nutrients*, *9*(9). Available from https://doi.org/10.3390/nu9091021.

Martens, K., Pugin, B., De Boeck, I., Spacova, I., Steelant, B., Seys, S. F., Lebeer, S., & Hellings, P. W. (2018). Probiotics for the airways: Potential to improve epithelial and immune homeostasis. *Allergy*, *73*(10), 1954−1963. Available from https://doi.org/10.1111/all.13495.

Martin Manuel, P., Elena, B., Carolina, M. G., & Gabriela, P. (2017). Oral probiotics supplementation can stimulate the immune system in a stress process. *Journal of Nutrition & Intermediary Metabolism*, *8*, 29−40. Available from https://doi.org/10.1016/j.jnim.2017.06.001.

Matarazzo, I., Toniato, E., & Robuffo, I. (2018). Psychobiome feeding mind: Polyphenolics in depression and anxiety. *Current Topics in Medicinal Chemistry*, *18*(24), 2108−2115. Available from https://doi.org/10.2174/1568026619666181210151348.

Merenstein, D., Gonzalez, J., Young, A. G., Roberts, R. F., Sanders, M. E., & Petterson, S. (2011). Study to investigate the potential of probiotics in children attending school. *European Journal of Clinical Nutrition*, *65*, 447−453. Available from https://doi.org/10.1038/ejcn.2010.290.

Mikelsaar, M., Sepp, E., Štšepetova, J., Songisepp, E., & Mändar, R. (2016). Biodiversity of intestinal lactic acid bacteria in the healthy population. *Advances in Experimental Medicine and Biology*, *932*, 1−64. Available from https://doi.org/10.1007/5584_2016_3.

Miller, A. H., & Raison, C. L. (2016). The role of inflammation in depression: From evolutionary imperative to modern treatment target. *Nature Reviews. Immunology*, *16*(1), 22−34. Available from https://doi.org/10.1038/nri.2015.5.

Miller, F., Afonso, P. V., Gessain, A., & Ceccaldi, P.-E. (2012). Blood-brain barrier and retroviral infections. *Virulence*, *3*(2), 222−229. Available from https://doi.org/10.4161/viru.19697.

Morais, A. H. A., Passos, T. S., Maciel, B. L. L., & da Silva-Maia, J. K. (2020). Can probiotics and diet promote beneficial immune modulation and purine control in coronavirus infection? *Nutrients*, *12*(6), 1737. Available from https://doi.org/10.3390/nu12061737.

Nanau, R. M., & Neuman, M. G. (2012). Nutritional and probiotic supplementation in colitis models. *Digestive Diseases and Sciences*, *57*(11), 2786−2810. Available from https://doi.org/10.1007/s10620-012-2284-3.

Nicholson, J. K., Holmes, E., Kinross, J., Burcelin, R., Gibson, G., Jia, W., & Pettersson, S. (2012). Host-gut microbiota metabolic interactions. *Science (New York, N.Y.)*, *336*(6086). Available from https://doi.org/10.1126/science.1223813, 1262 LP—1267.

Nishihira, J., Moriya, T., Sakai, F., Kabuki, T., Kawasaki, Y., & Nishimura, M. (2016). Lactobacillus gasseri SBT2055 stimulates immunoglobulin production and innate immunity after influenza vaccination in healthy adult volunteers: A randomized, double-blind, placebo-controlled, parallel-group study. *Functional Foods in Health and Disease*, *6*(9), 544. Available from https://doi.org/10.31989/ffhd.v6i9.284.

Oelschlaeger, T. A. (2010). Mechanisms of probiotic actions—A review. *International Journal of Medical Microbiology*, *300*(1), 57−62. Available from https://doi.org/10.1016/j.ijmm.2009.08.005.

Pandiyan, P., Bhaskaran, N., Zou, M., Schneider, E., Jayaraman, S., & Huehn, J. (2019). Microbiome dependent regulation of T(regs) and Th17 cells in mucosa. *Frontiers in Immunology*, *10*, 426. Available from https://doi.org/10.3389/fimmu.2019.00426.

Park, J., Kim, M., Kang, S. G., Jannasch, A. H., Cooper, B., Patterson, J., & Kim, C. H. (2015). Short-chain fatty acids induce both effector and regulatory T cells by suppression of histone deacetylases and regulation of the mTOR−S6K pathway. *Mucosal Immunology*, *8*(1), 80−93. Available from https://doi.org/10.1038/mi.2014.44.

Pennisi, E. (2020). Meet the psychobiome. *Science (New York, N.Y.)*, *368*(6491). Available from https://doi.org/10.1126/science.368.6491.570, 570 LP—573.

Piwat, S., Sophatha, B., & Teanpaisan, R. (2015). An assessment of adhesion, aggregation and surface charges of Lactobacillus strains derived from the human oral cavity. *Letters in Applied Microbiology*, *61*(1), 98−105. Available from https://doi.org/10.1111/lam.12434.

Plaza-Diaz, J., Ruiz-Ojeda, F. J., Gil-Campos, M., & Gil, A. (2019). Mechanisms of action of probiotics. *Advances in Nutrition*, *10*(Suppl. 1), S49−S66. Available from https://doi.org/10.1093/advances/nmy063.

Robles-Vera, I., Toral, M., Romero, M., Jiménez, R., Sánchez, M., Pérez-Vizcaíno, F., & Duarte, J. (2017). Antihypertensive effects of probiotics. *Current Hypertension Reports*, *19*(4), 26. Available from https://doi.org/10.1007/s11906-017-0723-4.

Rostami, F. M., Mousavi, H., Mousavi, M. R. N., & Shahsafi, M. (2018). Efficacy of probiotics in prevention and treatment of infectious diseases. *Clinical Microbiology Newsletter*, *40*(12), 97−103. Available from https://doi.org/10.1016/j.clinmicnews.2018.06.001.

Sabico, S., Al-Mashharawi, A., Al-Daghri, N. M., Wani, K., Amer, O. E., Hussain, D. S., Ahmed Ansari, M. G., Masoud, M. S., Alokail, M. S., & McTernan, P. G. (2019). Effects of a 6-month multi-strain probiotics supplementation in endotoxemic, inflammatory and cardiometabolic status of T2DM patients: A randomized, double-blind, placebo-controlled trial. *Clinical Nutrition*, *38*(4), 1561−1569. Available from https://doi.org/10.1016/j.clnu.2018.08.009.

Sarkar, A., Lehto, S. M., Harty, S., Dinan, T. G., Cryan, J. F., & Burnet, P. W. J. (2016). Psychobiotics and the manipulation of bacteria–gut–brain signals. *Trends in Neurosciences*, *39*(11), 763−781. Available from https://doi.org/10.1016/j.tins.2016.09.002.

Sattler, S. (2017). The role of the immune system beyond the fight against infection BT. In S. Sattler, & T. Kennedy-Lydon (Eds.), *The Immunology of Cardiovascular Homeostasis and Pathology* (pp. 3−14). Springer International Publishing. Available from https://doi.org/10.1007/978-3-319-57613-8_1.

Schnadower, D., Tarr, P. I., Casper, T. C., Gorelick, M. H., Dean, J. M., O'Connell, K. J., Mahajan, P., Levine, A. C., Bhatt, S. R., Roskind, C. G., Powell, E. C., Rogers, A. J., Vance, C., Sapien, R. E., Olsen, C. S., Metheney, M., DIckey, V. P., Hall-Moore, C., & Freedman, S. B. (2018). *Lactobacillus rhamnosus* GG versus placebo for acute gastroenteritis in children. *The New England Journal of Medicine*, *379*(21), 2002−2014. Available from https://doi.org/10.1056/NEJMoa1802598.

Schnadower, D., Tarr, P. I., Casper, T. C., Gorelick, M. H., Dean, M. J., O'Connell, K. J., Mahajan, P., Chun, T. H., Bhatt, S. R., Roskind, C. G., Powell, E. C., Rogers, A. J., Vance, C., Sapien, R. E., Gao, F., & Freedman, S. B. (2017). Randomised controlled trial of *Lactobacillus rhamnosus* (LGG) versus placebo in children presenting to the emergency department with acute gastroenteritis: The PECARN probiotic study protocol. *BMJ Open*, *7*, e018115. Available from https://doi.org/10.1136/bmjopen-2017-018115.

Sharma, V., & Kaur, S. (2020). The effect of probiotic intervention in ameliorating the altered central nervous system functions in neurological disorders: A review. *The Open Microbiology Journal*, *14*(1), 18−29. Available from https://doi.org/10.2174/1874285802014010018.

Shen, Z.-H., Zhu, C.-X., Quan, Y.-S., Yang, Z.-Y., Wu, S., Luo, W.-W., Tan, B., & Wang, X.-Y. (2018). Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation. *World Journal of Gastroenterology*, *24*(1), 5−14. Available from https://doi.org/10.3748/wjg.v24.i1.5.

Shi, N., Li, N., Duan, X., & Niu, H. (2017). Interaction between the gut microbiome and mucosal immune system. *Military Medical Research*, *4*(1), 14. Available from https://doi.org/10.1186/s40779-017-0122-9.

Sichetti, M., De Marco, S., Pagiotti, R., Traina, G., & Pietrella, D. (2018). Anti-inflammatory effect of multistrain probiotic formulation (*L. rhamnosus, B. lactis*, and *B. longum*). *Nutrition*, *53*, 95−102. Available from https://doi.org/10.1016/j.nut.2018.02.005.

Singh, A., Sarangi, A. N., Goel, A., Sirvastava, R., Gaur, P., Aggarwal, A., & Aggarwal, R. (2018). Effect of administration of a probiotic preparation on gut microbiota and immune response in healthy women in India: An open-label, single-arm pilot study. *BMC Gastroenterology*, *18*, 85. Available from https://doi.org/10.1186/s12876-018-0819-6.

Skolnick, S. D., & Greig, N. H. (2019). Microbes and monoamines: Potential neuropsychiatric consequences of dysbiosis. *Trends in Neurosciences*, *42*(3), 151−163. Available from https://doi.org/10.1016/j.tins.2018.12.005.

Sundararaman, A., Ray, M., Ravindra, P. V., & Halami, P. M. (2020). Role of probiotics to combat viral infections with emphasis on COVID-19. *Applied Microbiology and Biotechnology*, *104*(19), 8089−8104. Available from https://doi.org/10.1007/s00253-020-10832-4.

Tao, W., Zhang, G., Wang, X., Guo, M., Zeng, W., Xu, Z., Cao, D., Pan, A., Wang, Y., Zhang, K., Ma, X., Chen, Z., Jin, T., Liu, L., Weng, J., & Zhu, S. (2020). Analysis of the intestinal microbiota in COVID-19 patients and its correlation with the inflammatory factor IL-18. *Medicine in Microecology*, *5*, 100023. Available from https://doi.org/10.1016/j.medmic.2020.100023.

Tremaroli, V., & Bäckhed, F. (2012). Functional interactions between the gut microbiota and host metabolism. *Nature*, *489*(7415), 242−249. Available from https://doi.org/10.1038/nature11552.

van Baarlen, P., Wells, J. M., & Kleerebezem, M. (2013). Regulation of intestinal homeostasis and immunity with probiotic lactobacilli. *Trends in Immunology*, *34*(5), 208−215. Available from https://doi.org/10.1016/j.it.2013.01.005.

van de Wouw, M., Boehme, M., Lyte, J. M., Wiley, N., Strain, C., O'Sullivan, O., Clarke, G., Stanton, C., Dinan, T. G., & Cryan, J. F. (2018). Short-chain fatty acids: Microbial metabolites that alleviate stress-induced brain−gut axis alterations. *The Journal of Physiology*, *596*(20), 4923−4944. Available from https://doi.org/10.1113/JP276431.

van Tassell, M. L., & Miller, M. J. (2011). Lactobacillus adhesion to mucus. *Nutrients*, *3*(5), 613−636. Available from https://doi.org/10.3390/nu3050613.

Videlock, E. J., & Cremonini, F. (2012). Meta-analysis: Probiotics in antibiotic-associated diarrhoea. *Alimentary Pharmacology & Therapeutics*, *35*(12), 1355−1369. Available from https://doi.org/10.1111/j.1365-2036.2012.05104.x.

Vlainić, J. V., Šuran, J., Vlainić, T., & Vukorep, A. L. (2016). Probiotics as an adjuvant therapy in major depressive disorder. *Current Neuropharmacology*, *14*(8), 952−958. Available from https://doi.org/10.2174/1570159x14666160526120928.

Wallace, C. J. K., & Milev, R. (2017). The effects of probiotics on depressive symptoms in humans: A systematic review. *Annals of General Psychiatry*, *16*, 14. Available from https://doi.org/10.1186/s12991-017-0138-2.

Walter, J. (2008). Ecological role of lactobacilli in the gastrointestinal tract: Implications for fundamental and biomedical research. *Applied and Environmental Microbiology*, *74*(16), 4985−4996. Available from https://doi.org/10.1128/AEM.00753-08.

Wang, X., Sun, Y., Wang, L., Li, X., Qu, K., & Xu, Y. (2017). Synbiotic dietary supplement affects growth, immune responses and intestinal microbiota of *Apostichopus japonicus*. *Fish & Shellfish Immunology*, *68*, 232−242. Available from https://doi.org/10.1016/j.fsi.2017.07.027.

Xia, Y., Lu, M., Chen, G., Cao, J., Gao, F., Wang, M., Liu, Z., Zhang, D., Zhu, H., & Yi, M. (2018). Effects of dietary *Lactobacillus rhamnosus* JCM1136 and *Lactococcus lactis* subsp. lactis JCM5805 on the growth, intestinal microbiota, morphology, immune response and disease resistance of juvenile *Nile tilapia, Oreochromis niloticus*. *Fish & Shellfish Immunology*, *76*, 368−379. Available from https://doi.org/10.1016/j.fsi.2018.03.020.

Xiong, J., Dai, W., Zhu, J., Liu, K., Dong, C., & Qiu, Q. (2017). The underlying ecological processes of gut microbiota among cohabitating retarded, overgrown and normal shrimp. *Microbial Ecology*, *73*(4), 988−999. Available from https://doi.org/10.1007/s00248-016-0910-x.

Yadav, M., Verma, M. K., & Chauhan, N. S. (2018). A review of metabolic potential of human gut microbiome in human nutrition. *Archives of Microbiology*, *200*(2), 203−217. Available from https://doi.org/10.1007/s00203-017-1459-x.

Yavarpour-Bali, H., & Ghasemi-Kasman, M. (2020). Update on neurological manifestations of COVID-19. *Life Sciences*, *257*, 118063. Available from https://doi.org/10.1016/j.lfs.2020.118063.

Yuan, Y., Zallot, R., Grove, T. L., Payan, D. J., Martin-Verstraete, I., Šepić, S., Balamkundu, S., Neelakandan, R., Gadi, V. K., Liu, C.-F., Swairjo, M. A., Dedon, P. C., Almo, S. C., Gerlt, J. A., & de Crécy-Lagard, V. (2019). Discovery of novel bacterial queuine salvage enzymes and pathways in human pathogens. *Proceedings of the National Academy of Sciences*, *116*(38). Available from https://doi.org/10.1073/pnas.1909604116, 19126 LP—19135.

Zheng, D., Liwinski, T., & Elinav, E. (2020). Interaction between microbiota and immunity in health and disease. *Cell Research*, *30*(6), 492−506. Available from https://doi.org/10.1038/s41422-020-0332-7.