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Role of gut microbiota in SARS-CoV-2 infection and the beneficial effects of probiotics on the management of the disease

Papel da microbiota intestinal na infecção por SARS-CoV-2 e os benefícios dos probióticos no manejo da doença

Papel de la microbiota intestinal en la infección por SARS-CoV-2 y los beneficios de los probióticos en el manejo de la enfermedad

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Abstract
Objective: The purpose of the present study was to show information about the effects of probiotics on inflammatory and Renin Angiotensin System (RAS) balance, and their potential therapeutic role in the management of COVID-19. Methodology: This is a narrative literature review and the databases used were Google Scholar and Medline/Pubmed. Results: Some components of the intestinal microbiota, including *Coprobacillus*, *Clostridium ramosum*, *Morganella morganii*, and *Streptococcus infantile* were identified as positively correlated with the severity of the disease, while *Faecalibacterium prausnitzii* showed a negative correlation with SARS-CoV-2 infection. Probiotics emerge as a therapeutic alternative for the treatment of inflammatory conditions due to their effects on the maintenance of gastrointestinal integrity and repair properties. More specifically, probiotics from *Bifidobacterium* e *Lactobacillus* genus show benefits in the management of respiratory diseases and might enhance vaccine immunogenicity. Conclusion: The present study demonstrates the complementary therapeutic potential of probiotics in the treatment of respiratory infections, such as COVID-19. Beyond that, considering the diversity of probiotic strains, the evaluations already carried out and the data available in the literature, the present study points to the need for complementary studies to understand the mechanisms related to the effects of probiotics on COVID-19.
Keywords: COVID-19; Renin-angiotensin system; Inflammation; Vaccines.

Resumo
Objetivo: O objetivo do presente estudo foi apresentar informações acerca dos efeitos de probióticos sobre o estado inflamatório e balanço do Sistema Renina Angiotensina (SRA) e potencial terapêutico no manejo da COVID-19. Metodologia: Trata-se de uma revisão narrativa e as bases de dados utilizadas foram Google Scholar e Medline/Pubmed. Resultados: Foram identificados componentes da microbiota intestinal, incluindo *Coprobacillus*, *Clostridium ramosum*, *Morganella morganii* e *Streptococcus infantile*, que estão positivamente correlacionados com a severidade da doença, enquanto *Faecalibacterium prausnitzii* apresentou correlação negativa na infecção por SARS-CoV-2. De acordo com os resultados encontrados, observa-se que os probióticos constituem uma alternativa terapêutica para o tratamento de condições inflamatórias devido aos seus efeitos sobre a manutenção da integridade gastrointestinal e propriedade de reparo. Mais especificamente, os probióticos dos gêneros *Bifidobacterium* e *Lactobacillus* mostram benefícios no manejo de doenças respiratórias, além de proporcionarem aumento da imunogenicidade às vacinas. Conclusão: O presente estudo demonstra o potencial terapêutico complementar dos probióticos no tratamento das infecções respiratórias, incluindo a COVID-19. Além disto, considerando a diversidade de cepas de probióticos, as avaliações já realizadas e os dados disponíveis na literatura, o presente estudo também aponta para a necessidade de estudos complementares buscando compreender os mecanismos relacionados aos efeitos dos probióticos na COVID-19.
Palavras-chave: COVID-19; Sistema renina-angiotensina; Inflamação; Vacinas.

Resumen
Meta: El objetivo de este estudio fue presentar información sobre los efectos de los probióticos en el estado inflamatorio y el equilíbrio Sistema Renina-Angiotensina (RAS), el potencial terapéutico en el manejo de COVID-19. Metodología: Se trata de una revisión narrativa y las bases de datos utilizadas fueron Google Scholar y Medline/Pubmed. Resultados: *Coprobacillus*, *Clostridium ramosum*, *Morganella morganii* y *Streptococcus infantil* de la microbiota intestinal mostraron una correlación positiva con la gravedad de la enfermedad, mientras que una correlación negativa se asoció con *Faecalibacterium prausnitzii* en la infección por SARS-CoV-2. Debido a la capacidad de mantener la integridad y reparar el daño intestinal, los probióticos emergen como una alternativa terapéutica para el tratamiento de enfermedades relacionadas con el metabolismo y condiciones inflamatorias inducidas por infecciones intestinales. Los probióticos de los géneros *Bifidobacterium* y *Lactobacillus* muestran beneficios en enfermedades respiratorias además de aumentar la inmunogenicidad de las vacunas. Conclusión: El presente estudio demuestra el potencial terapéutico complementario de los probióticos en el tratamiento de infecciones respiratorias, incluida la COVID-19. Además, considerando la diversidad de cepas probióticas, las evaluaciones ya realizadas y los datos disponibles en la literatura, el presente estudio también apunta a la necesidad de estudios complementarios que busquen comprender los mecanismos relacionados con los efectos de los probióticos en la COVID-19.
Palabras clave: COVID-19; Sistema renina-angiotensina; Inflamación; Vacunas.

1. Introduction

Coronavirus disease (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and is characterized by affecting multi-system and multi-organ (Antunes et al., 2020), including the respiratory system and gastrointestinal tract (Sonkar et al., 2020). The pathogenesis of COVID-19 is divided into the first phase (asymptomatic), characterized by a rapid viral spread, suppression of the innate immune response, and the presence of oxidative stress. In the second phase, there is an imbalance between ACE/Ang II/AT1 and ACE2/Ang (1-7)/Mas axis of the renin-angiotensin system (RAS), and the installation of inflammation, with "cytokine storm" (Mrityunjaya et al., 2020; Trougakos et al., 2021).

Studies show that changes in the intestinal microbiota are related to inflammation and gastrointestinal symptoms (He et al., 2020), and also suggest that the gut microbiome profile could be associated with the severity of SARS-CoV-2 infection and clinical outcome (Chattopadhyay and Shankar, 2021; Zuo *et al.*, 2020). Thus, to prevent secondary bacterial infections and promote intestinal balance, it is recommended the use of probiotics for severe COVID-19 patients (Kurian et al., 2021; Villapol, 2020). Also, it is believed that probiotics can act as modulators of the vaccine response, either directly (changes in the microbiota) or indirectly (microbial products, such as short-chain fatty acid - SCFA) (Praharaj et al., 2015).

Considering that the severity of COVID-19 is associated with an imbalance of RAS, and exacerbated inflammation in the gastrointestinal (GI) tract, this mini-review aims to highlight the interaction of these changes with the gut microbiota. In addition, it presents some aspects related to the effectiveness of probiotics in the clinical management of COVID-19 patients, as well as the duration of the vaccine response associated with probiotics modulation.

2. Methodology

It is a narrative literature review (Pautasso, 2019) characterized by describing the role of gut microbiota in the pathogenesis of COVID-19, the use of probiotics in respiratory diseases, and vaccine response. The databases used were Google Scholar and Medline/Pubmed. The work was carried out between October 2021 and April 2022. The main descriptors used in the search were: "COVID-19", "Gastrointestinal Microbiome", "Inflammation", "Probiotics", "Renin-Angiotensin System", "Respiratory Tract Diseases", "SARS-CoV-2" and "Vaccines".

3. Results and Discussion

Gastrointestinal (GI) tract and microbiota

COVID-19 is mainly considered a respiratory disease. Nonetheless, the GI tract contributes to pathogenesis. The gut and lung communicate through the immune system and the microbiota residents, known as the gut-lung axis. In this sense, studies have been conducted to understand the communication of these organs in viral respiratory infections (Scaldaferri et al., 2020). The GI tract is considered the largest immune organ (Yeoh et al., 2021) and is recognized as the "mucosal firewall" due to its structural and immunological components (Belkaid, 2015). Intestinal epithelial cells protect against infections and inflammation; Goblet and Paneth epithelial cells produce mucins and antimicrobial protein, while enteroendocrine cells produce hormones that regulate digestion (Peterson and Artis, 2014). Glucagon-like peptide 1 (GLP-1), also produced by enteroendocrine cells, acts as an incretin hormone and is associated with inflammatory modulation by factor nuclear kappa B (NF-kB). Additionally, it has already been described that an imbalance of gut microbiota decrease GLP-1 production (Sazgarnejad et al., 2021) and that GLP-1 receptor activation increases angiotensin-converting enzyme 2 (ACE2) expression (Pang et al., 2021).

The gut immunological component is organized into three compartments: epithelial layer, lamina propria, and mucosa-associated lymphoid tissue (MALT). Innate immunity conferred by phagocytic cells (neutrophils, monocytes, macrophages, natural killer) is associated with pathogens destruction and is the first defense and protection against infection. These phagocytic cells and proteins activate an adaptive immune response through antigen-presenting cells (APC). The adaptive response associated with the presence of specific antigen receptors on B and T cells (subdivided into CD_4^+ T and CD_8^+ T lymphocytes) acts in a more specific and effective way. In the GI tract, the epithelial layer and lamina propria induce early responses, while MALT is related to adaptive immune responses (Azad et al., 2018).

The cell population in the different intestinal anatomical regions is very similar. The intestinal epithelium is characterized by the high density of stem cells in the intestinal crypts, in addition to the presence of secretory and absorptive cells (Harrison and Powrie, 2013). However, there is, for example, a high concentration of regulatory T cells (T reg) in the colon compared to the duodenum (James *et al*., 2020). In addition, it is known that the signaling promoted by Pattern Recognition Receptors (PRRs) regulates the composition and location of the microbiota (Harrison and Powrie, 2013).

The colon retains the largest microbial community (microbiota) (Litvak et al., 2018) such as bacteria, fungi, viruses, and protozoa (Kurian et al., 2021). The microbiota regulates cellular homeostasis by producing secondary metabolites and antimicrobial peptides and regulating innate and adaptive immunity (Chattopadhyay and Shankar, 2021). In healthy individuals, major bacterial phyla are *Actinobacteria, Firmicutes, Proteobacteria,* and *Bacteroidetes* (Adak and Khan, 2019; Dhar and Mohanty, 2020). However, the composition of the gut microbiota is personal, associated with genetics and environment, such as birth mode, food, medications, presence of stress, and infection (Cenit et al., 2017). Disturbances in healthy microbiota, through decreased diversity and composition of the microbiota, known as dysbiosis, are related to various diseases or disorders, including asthma, diabetes, and obesity (Aktas and Aslim, 2020).

Diseases occur when the immune system and intestinal microbiota are imbalanced. The microbiota is involved in the development and maturation of the immune system. In contrast, the immune system affects the composition and functions of the microbiota. In COVID-19, the increase in circulating pro-inflammatory cytokines changes the microbiota and increases intestinal permeability. Consequently, it promotes the translocation of bacterial antigens into the systemic circulation, a characteristic of the septic stage. Considering the direct relationship between the intestinal microbiota and the immune system, strategies to normalize the microbiota may be essential for the symptoms relief and shorter recovery time in patients with the disease (Aktas & Aslim, 2020).

Role of renin-angiotensin system (RAS) in COVID-19

RAS has been consistently considered an important regulatory component for the maintenance of cardiovascular and renal homeostasis, regulating vasoconstriction and renal sodium excretion. In RAS, initially, the precursor angiotensinogen is cleaved by renin to angiotensin (Ang) I, and the peptide is cleaved to the nonapeptide angiotensin II (Ang II), by angiotensin I-converting enzyme (ACE) (Oliveira et al., 2021). Ang II is the key regulator of RAS and influences immune response, inflammation, cell growth, and proliferation by acting through Ang II type 1 receptors (AT1 and AT2) (Benigni et al., 2009). On the other hand, the conversion of Ang I into Ang (1-9) as well as Ang II into Ang (1-7) is modulated by the ACE2 enzyme. Both peptide products (Ang 1-7 and 1-9) exert their effects via Mas receptors, and it is well documented that Ang (1-7) is associated with cardioprotective effects, vasorelaxation, anti-inflammatory and antioxidant responses (Xiao et al., 2020).

Currently, it is believed that SARS-Cov-2 infects host cells, through the spike (S) protein, functionally divided into S1 and S2. Thus, the S1 unit binds to the ACE2 receptor and then exposes the S2 unit, in which the transmembrane serine protease (TMPRSS2) is involved (Campione et al., 2020; Jackson et al., 2021; Wan et al., 2020). Although the physiological activity of TMPRSS2 is still unknown (Jackson et al., 2021) it is believed that SARS-Cov-2 infection is related to the entry of the viral genome, through the fusion of cell membranes and the virus (Yu et al., 2021).

The expression of ACE2 varies among different locations, being present in nasal ciliated cells, testis, kidneys, heart, small and large intestine (Jackson et al., 2021). ACE2 is a negative regulator of RAS (Kopel et al., 2020), but also, the regulator of nutrient absorption (He et al., 2020) and innate immunity (Yu et al., 2021). In the GI tract, the downregulation of ACE2 results in lower secretion of microbial peptides by reduction of intestinal absorption of tryptophan. On the other hand, while ACE2 enzyme levels decrease, the Ang II levels elevate, contributing to intestinal permeability, dysbiosis, and intestinal inflammation (Chattopadhyay and Shankar, 2021; Kim *et al*., 2018; Penninger *et al*., 2021; Robles-Vera *et al*., 2020).

In this context, literature indicates that RAS therapies act by direct mechanisms in the GI tract but also by changes in the intestinal microbiota because intestinal modulation might affect RAS (Jaworska et al., 2021). A study carried out by Zuo and colleagues (2020) showed that the genus *Coprobacillus*, the species *Clostridium ramosum* and *Clostridium hathewayi*, exhibited a direct correlation with the severity of COVID-19. In mice, *Coprobacillus* is associated with increased expression of ACE 2. On the other hand, *Bacteroides dorei*, *Bacteroides thetaiotaomicron*, and *Bacteroides massiliensis* induced down-regulating of ACE 2 and was inversely correlated with the viral load in fecal samples (He et al., 2020).

RAS dysfunction exacerbates inflammation in the GI tract through down-regulation of ACE2 during SARS-CoV-2 infection (Mitsuyama et al., 2020; Trougakos et al., 2021; Villapol, 2020). As shown in Figure 1, suppression of ACE2 and increased Ang II induce leakage in pulmonary blood vessels, contributing to inflammation in lung tissue, and when sustained, inflammation also promotes leakage in the capillaries. Consequently, the virus reaches the circulation (viremia), contributing to activation of the ACE/ Ang II/ AT1 axis, and extensive inflammation known as “cytokine storm”. Due to the high inflammatory signaling, as a counter-regulatory mechanism, there is an increase in the ACE2/ Ang (1-7)/ Mas pathway, contributing to the entry into the circulating virus in the organs. The ACE/ Ang II/ AT1 axis is activated, triggering systemic failure (Trougakos et al., 2021).

Role of gastrointestinal inflammation in the severity of COVID-19

Humans are constantly exposed to pathogens and food antigens, requiring an effective immune system to protect against infection (Azad et al., 2018; Belkaid, 2015). It is well known that tissue homeostasis is essential for the survival, requiring appropriate innate and adaptive responses, through the participation of metabolites, cytokines, or hormones, composing a complex network regulatory pathway (Belkaid, 2015).

Currently, these regulatory pathways have been extensively studied in the gut (Belkaid, 2015). It is known that commensals bacteria, compete with pathogens for nutrition and space by the release of antimicrobial peptides. PRRs are essential in the innate immune response. Among the PRRs, highlight toll-like receptors (TLR), recognize microbe-associated molecular patterns (MAMPs) and pathogen-associated molecular patterns (PAMPs), promoting specific immune responses according to the type of cell, ligand, or receptor (Chattopadhyay and Shankar, 2021; Kurian *et al*., 2021).

However, as mentioned, interruption or imbalance between beneficial and pathogenic bacteria induced by infections contributes to dysbiosis (Olaimat et al., 2020). In SARS-Cov-2 infection, after the virus infection into the small intestine there is an increase in the content of CD_4^+ T lymphocytes, inducing systemic and local inflammation. In the intestine, inflammation is evident in the Th17 profile, characterized by the recruitment of neutrophils. This inflammatory process induces cell damage and destroys the epithelial barrier (Delgado-Gonzalez et al., 2021), increasing intestinal permeability, leakage, and translocation of the gut microbiota to the lungs (Olaimat et al., 2020). However, it should be noted that this communication is bidirectional, and therefore inflammation in the lungs affects the intestinal microbiota as well (Hunt et al., 2021).

In a study carried out by Zuo *et al*., (2021) among the identified pathogens related to high infectivity by SARS-CoV-2, there was an abundance of *Collinsella aerofaciens*, *Morganella morganii*, and *Streptococcus infantile* in feces. The last bacteria mentioned is usually found in the upper respiratory tract and oral cavity, suggesting the passage of the extraintestinal. In addition, *Collinsella aerofaciens* and *Morganella morganii* are classified as opportunistic bacteria in humans.

Patients with SARS-CoV-2 infection, in addition to intestinal dysbiosis, present significant increased levels of interleukin (IL) 18 (Tao et al., 2020), a pro-inflammatory cytokine found in the cytoplasm of immune cells, epithelial cells of the GI tract, and endothelial cells, that can induce the production of interferon-gamma (IFN-γ) (Vecchié et al., 2021). Tissues with epithelial cells, including GI and respiratory tract, skin, and lungs, present IFN-γ receptors, whose main function is to inhibit viral multiplication. However, patients with COVID-19 show a reduction in IFN-γ which contributes to the spread of infection, followed by cell death, the release of PAMPs, and damage-associated molecular patterns (DAMPs) promoting "cytokine storm" and fibrosis (Abdel-Hamed et al., 2021; Roy et al., 2021).

The continuous inflammatory process with the release of cytokines, infection of lymphocytes, or aggression of lymphatic organs may contribute to the lymphopenia associated with COVID-19. The decrease of circulating lymphocytes is associated with disease severity, gastrointestinal symptoms and is inversely correlated with viral load. In the microbiota, lymphopenia contributes to alterations and predisposition to opportunistic germs (Battaglini et al., 2021). Patients with COVID-19 also show neutrophilia, notable through the increase in calprotectin, which corresponds to about 60% of the cytoplasmic proteins of these cells (Gasmi et al., 2020; Shokri-Afra et al., 2021). Inflammatory stimuli in the gut promote neutrophil recruitment and calprotectin release, indicating intestinal inflammation (Gasmi et al., 2020). Shokri-Afraet and colleagues (2021) showed that calprotectin in serum and feces was not associated with gastrointestinal symptoms in patients with COVID-19; on the other hand calprotectin was increased in patients with diarrhea and dependent of oxygen support (Udeh et al., 2021).

Although additional studies are needed to understand the consequences induced by SARS-CoV-2 infection, some evidence points to the protective functions of cytokines IL-2, tumor necrosis factor alpha (TNF-α), and IL-10 against damage to the GI and respiratory tract. IL-2, after mechanical injuries and infections, binds to lymphocytes and macrophages for the preservation of the intestinal epithelium (Kopel et al., 2020). Additionally, TNF-α can exert beneficial functions on the intestine (protection against inflammation and intestinal barrier rupture) or be harmful (damage to the barrier), depending on the local inflammatory state (Ruder et al., 2019).

The anti-inflammatory cytokine IL-10 is protective by inhibiting excessive inflammatory responses generated by T cells against microbial antigens. It is a cytokine produced by several immune cells, mainly by macrophages from the intestinal

lamina propria, and acts in the induction of T reg (Rutz and Ouyang, 2016). A study carried out by Britton *et al*., (2021) observed a low content of IL-10 in fecal samples from patients with COVID-19. Furthermore, in SARS-CoV-2 infection there was a negative correlation between the beneficial bacteria such as *Faecalibacterium prausnitzii* and anti-inflammatory properties (Zuo et al., 2020b).

Although little known in humans, in a rhesus macaque model, GI tract infections contribute to systemic cytokine levels (Roy et al., 2021), emphasizing the influence of maintenance of intestinal on inflammatory and metabolic processes (Barssotti et al., 2021).

Probiotics during COVID-19

Probiotics are species of live bacteria that confer beneficial effects for the host when ingested in adequate amounts (10^8 to 10^{10} CFU, daily doses) (Buts, 1999; Olaimat et al., 2020). It contributes not only to the GI tract but also systemically, due to it is role in immune modulation, through the release of ILs, TNFs, IFNs (Azad et al., 2018; Kurian et al., 2021). In this way, probiotics can be considered immunostimulatory or immunoregulatory. The immunostimulatory class acts against viral infections, and allergies, through the induction of IL-12, natural killer cells, and Th1 cells. In contrast, immunoregulatory probiotics act by repressing autoimmune diseases, allergies, and inflammatory bowel diseases through the increase of IL-10 and T reg (Azad et al., 2018; Mirzaei et al., 2021).

Probiotics have been indicated in the initial phases of the COVID-19 infection (Mrityunjaya et al., 2020). These bacteria act on the integrity of the intestinal barrier and repair damage, through increased expression of tight junction and mucus production (Almada et al., 2015). In face of its ability to maintain the integrity and repair intestinal damage, probiotics emerge as a therapeutic alternative for the treatment of metabolic-related diseases and inflammatory conditions promoted by intestinal infections (Almada et al., 2015; Barssotti et al., 2021).

In RAS, probiotics directly or indirectly exert effects on ACE enzymes. It is known that bioactive peptides produced by probiotics during food fermentation, as well as dead probiotic cells, act as blockers of ACE receptors, the SARS-CoV-2 access pathway in cells (Olaimat et al., 2020). In addition, *Lacticaseibacillus paracasei* supplementation showed gut health benefits, by increasing Ang (1-7) and concomitantly decreasing Ang II (Carter et al., 2020).

Other probiotics, including *Bifidobacterium* and *Lactobacillus* genus, showed benefits during influenza infection (Bottari et al., 2021; Sundararaman et al., 2020). The Lab4P supplementation, which consists of the association of some strains of *Lactobacillus* and *Bifidobacterium*, mitigated the symptoms of upper respiratory tract infection in obese individuals. Although there were no significant differences in the gut microbiome profile after supplementation, the respiratory benefits suggested an improvement in the intestinal barrier, which is disrupted in cases of infection and obesity (Mullish et al., 2021). Symptoms of upper respiratory tract infection were also reduced after administration of *Lactiplantibacillus plantarum* DR7. In this study, both groups (middle-aged adults and young adults) had improvement in symptoms, nonetheless, the action mechanisms were different. The authors also argued that *Lactiplantibacillus plantarum* DR7 activated natural killer cells, consequently protecting the infiltration of antigens and the integrity of the mucosa (Chong et al., 2019).

Commercial formulation composed of strains of *Lactobacillus*, *Bifidobacterium*, and *Streptococcus thermophiles* showed antiviral activity, against influenza, for example. The formulation increased nuclear factor erythroid 2p45 related to factor 2 (Nrf2) and Heme oxygenase-1 (HO-1), both acts inhibit the virus by limitation of oxidative stress (Ceccarelli et al., 2021). It is well known, that *Lactobacillus* in combination with *Bifidobacterium, Bacteroides*, and gut commensals produce SCFA, including butyrate, acetate, and propionate (Chattopadhyay and Shankar, 2021). Butyrate has been suggested as a potential molecule for the prevention and management of COVID-19. This molecule binds mainly to the G protein-coupled receptor (GPR) 41 and reduces the inflammatory process through the induction of the T regs and inhibition of histone

deacetylases (HDACs), suppressing the expression of mononuclear and neutrophil cells and reducing TNF and NF-kB (Kim, 2021; Ratajczak *et al*., 2019; Rooks and Garrett, 2016). In addition to these mechanisms, sodium butyrate is associated with ACE2 suppression in gut cells and reduction of gastrointestinal symptoms promoted by COVID-19 (Shetty et al., 2021). In the handling of COVID-19, the symbiotic *(Pediococcus pentosaceus* 5-33:3, *Leuconostoc mesenteroides* 32-77:1, *Lacticaseibacillus paracasei ssp. Paracasei* 19, *Lactiplantibacillus plantarum* 2,362, inulin, pectin and resistant starch) resulted in important clinical outcomes, such as reduced in the number of days in intensive care units, mechanical ventilation, systemic inflammation, sepsis, and mortality (Baud et al., 2020).

In work carried out in the State of Mexico, the probiotic yeast *Saccharomyces boulardii* was explored along with other nutrients (B-complex vitamins, inulin, spirulina, glutamine, magnesium, omega-3, among others components). In the study, the treatment in COVID-19 patients had a 97.5% increase in survival rate and a 2.5% reduction in mortality, compared to patients with the disease but with no intervention (Leal-Martínez et al., 2022). A recent study by Gutiérrez-Castrellón and colleagues (2022) found that *Lactiplantibacillus plantarum* KABP022, KABP023, and KAPB033, in association with *Pediococcus acidilactici* KABP021, reduced viral load and duration of symptoms of COVID-19, increased IgG and IgM antibodies but did not change the fecal microbiota. These data suggest that these probiotics could alter the immune system before promoting changes in the microbiota.

In addition to decreasing inflammation, other functions such as appetite regulation and glycemic homeostasis are attributed to the probiotic-induced increase in acetate, which increases the release of GLP-1 (Pegah et al., 2021).

Although some authors consider probiotics safe even in vulnerable individuals and under intensive care (Baud et al., 2020), it is important to emphasize that the prescription of conventional probiotics should not be recommended indiscriminately (Akour, 2020) because not every strain generates the same responses among individuals (Villapol, 2020). Kim (2021) highlights that, in addition to supplementation with probiotics, fecal transplantation and fiber consumption can prevent and reduce the severity of inflammation in individuals affected by COVID-19. Thus, these findings suggest the necessity for modulation of the intestinal microbiota as a therapeutic route in COVID-19 and associated comorbidities (Zuo et al., 2020b).

Perspectives – probiotics and vaccines

Trillions of vaccine doses against COVID-19 have been delivered worldwide, according to the World Health Organization (2021). Vaccines act by producing Ag-specific antibodies from B cells. After initial exposure, Ag-specific antibodies are produced, although some vaccines require additional doses for a stronger and longer-lasting immune response. In addition to B cells, T cells are essential in inducing immunological memory antibodies (Lynn &7Pulendran, 2017). In children, the abundance of CD_4^+ T cells was attributed to the high presence of *Bifidobacterium*, suggesting that the gut microbiota may also be involved in the durability of the immune response (Jong *et al*., 2020), and activation and differentiation of B cells (Kim & Kim, 2017).

Although, the mechanisms of the microbiota involved in the response to vaccines remain elusive, probably, the gut microbiota interferes with the immunogenicity of vaccines through the production of SCFA. The mechanism of action is related to the increased metabolism of B cells (increased oxidative phosphorylation, glycolysis, and fatty acid synthesis) providing more energy for these cells. Furthermore, SCFA appears to be associated with increased plasma cell differentiation and class switching (Lynn et al., 2021).

Therefore, as mentioned, due to the ability of probiotics in the production of SCFA (Chattopadhyay and Shankar, 2021), modulation of the immune system, and balance of the microbiota, these supplements may be promising in responses to vaccines against respiratory infections (Vignesh et al., 2021), according to Figure 1. New generations of probiotics, such as *Faecalibacterium prausnitzii*, as well as symbiotic formulations (probiotics and prebiotics) due to their ability to produce

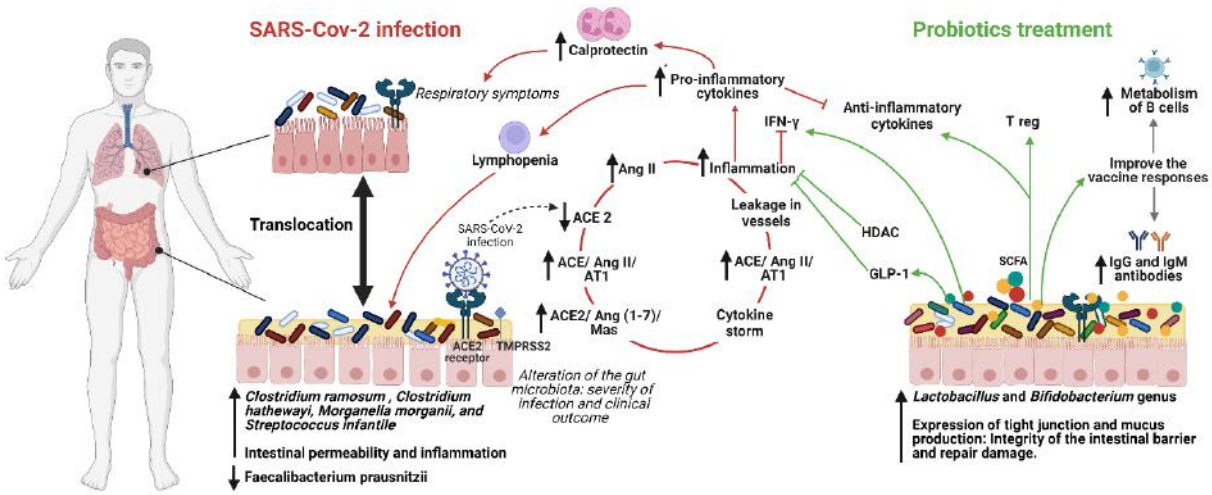
butyrate are associated with increased intestinal immune response, showing promise in the efficacy and safety of vaccines against COVID-19 (Chen et al., 2021).

Furthermore, probiotic genus such as *Bifidobacterium* and *Lactobacillus* are associated to enhance vaccine immunogenicity through structural components (bacteriocins, exopolysaccharides, lipoteichoic acids) and secreted factors (reactive oxygen species) (Vitetta et al., 2017). *Lacticaseibacillus paracasei*, *Lacticaseibacillus rhamnosus*, *Bifidobacterium* improved vaccine responses by preventing infections such as H1N1, H3N2, and H5N1 (He et al., 2020), in the same way, *Lactobacillus casei Shirota*, in the elderly, showed efficiency in vaccination by increasing the response to antibodies (Bottari et al., 2021). However, a systematic review and meta-analysis conducted by Lei and colleagues (2017) concluded that the duration of probiotic supplementation affects vaccine response more than age.

In the experimental model, the administration of *Lactiplantibacillus plantarum* GUANKE (LPG) immediately after SARS-CoV-2 vaccination, promoted neutralization antibodies for this disease for 6 months. Regarding the mechanisms, this strain down-regulates inflammatory and apoptotic pathway, and increase IFN levels (Xu et al., 2021). Wang and colleagues (2020) developed the recombinant *Lactiplantibacillus plantarum CGMCC 1557* (known as Lp 18), whose differential is the expression of S protein of the SARS-CoV-2 on the bacterial surface, being considered a possible candidate for a mucosal vaccine. In another study, recombinant *Lactiplantibacillus plantarum* showed greater immunogenicity than the *Lactococcus lactis* strain (Villena et al., 2021).

Although the use of probiotics is promising in the vaccine response, there are several challenges in studies involving this topic, such as diversity of strains, period of administration, vaccines investigated, population, and a small sample of studies (Jong *et al*., 2020; Lynn & Pulendran, 2017).

Figure 1: Schematic depiction of mechanisms in SARS-COV-2 infection (red arrows) and the role of probiotics on the management of the disease (green arrows).



Source: Created in Biorender.com.

4. Conclusion

The present review revealed that pathogenesis of COVID-19 promotes changes in RAS and inflammation. Decreased ACE2 resulting from SARS-CoV-2 infection contributes to increased Ang II and inflammation. An inflammatory state is

associated with the permeability of vessels and the gut, for example. The gut permeability affects the microbiota and immune system in the lungs, through the communication established by the gut-lung axis.

In this way, probiotics can be used in the management of respiratory infections, like COVID-19, due to their capacity to repair intestinal damage, protect the host from secondary bacterial infections and act as immunomodulators. Probiotics, as vaccine adjuvants, are shown to be effective by increasing immunogenicity. However, due to the diversity of strains and protocols conducted, many studies will be needed to deeply understand the role of probiotics in diseases such as COVID-19. Therefore, new studies to understand long term interactions among gut microbiota, probiotics and vaccine will minimize some gaps in the literature.

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