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The Effectiveness of Probiotics in Alleviating Symptoms in Patients Infected with SARS-CoV-2: An Integrative Review

The Efficacy of Probiotics in Attenuating Symptoms in Those Infected with SARS-CoV-2: An Integrative Review

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Summary

This study presents an integrative review on the influence of the gut microbiota on SARS-CoV-2 infection. The gut microbiota, composed of trillions of microorganisms, plays a fundamental role in human health, especially in modulating the immune response and maintaining intestinal homeostasis. Alterations in this ecosystem, known as dysbiosis, can compromise the body's balance and increase susceptibility to various diseases, including viral infections such as COVID-19. Scientific evidence demonstrates that SARS-CoV-2 infection can cause significant changes in the composition of the gut microbiota, being associated with the onset of gastrointestinal symptoms and potentially worsening the clinical condition of patients. This work reviewed clinical and preclinical studies that investigated the relationship between intestinal dysbiosis and the severity of COVID-19, highlighting possible therapeutic interventions, such as the use of probiotics, prebiotics, and fecal microbiota transplantation. The results indicate that modulating the gut microbiota may represent a promising strategy to improve clinical outcomes and reduce symptom severity in patients with COVID-19. However, further studies are needed to confirm the efficacy and safety of these therapeutic approaches.

Keywords: Dysbiosis; Gut-Lung Axis; Immunology; Gut Microbiota; SARS-CoV-2

Abstract

This study presents an integrative review on the influence of gut microbiota on SARS-CoV-2 infection. The gut microbiota, comprising trillions of microorganisms, plays a crucial role in human health, including modulating immune responses and maintaining intestinal homeostasis. Changes in the microbiota, known as dysbiosis, can negatively impact health by increasing susceptibility to various diseases, including viral infections like COVID-19. Evidence demonstrates that SARS-CoV-2 infection can significantly alter the composition of the gut microbiota, resulting in gastrointestinal symptoms and potentially exacerbating the clinical course of the disease. This work reviewed clinical and pre-clinical studies investigating the relationship between gut dysbiosis and the severity of COVID-19, highlighting therapeutic interventions such as the use of probiotics, prebiotics, and fecal microbiota transplantation. The results indicate that modulating the gut microbiota may be a promising strategy to improve clinical outcomes and reduce symptom severity in COVID-19 patients.

However, further studies are necessary to validate the efficacy and safety of these therapeutic approaches.

Keywords: Dysbiosis, Gut-Lung Axis, Immunology, Gut Microbiota, SARSCoV-2

List of Abbreviations: SARS-CoV-2: Novel Coronavirus; IgA: Immunoglobulin A; ASD: Autism Spectrum Disorder Autism Spectrum Disorder; TNF-ÿ: Tumor Necrosis Factor Alpha; ACE2/ACE2: Enzyme Receptor Angiotensin II Converting Hormone; RNA: Ribonucleic Acid; ARDS: Acute Respiratory Distress Syndrome Acute Respiratory System; NK Cells: Natural Killer Cells; SCFAs: Short-Chain Fatty Acids; FMT: Fecal Microbiota Transplant; MCP-1: Monocyte Chemoattractant Protein 1; QICI: Innate Cytokine Index (TNF-ÿ x IL-1ÿ x IL-18 x IL-8/IL-6); MI: Intestinal Microbiota; GIT: Tract Gastrointestinal; IgG: Immunoglobulin G; IFN-ÿ: Interferon Alpha; IFN-ÿ: Interferon Beta; IL-1:

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Interleukin 1; IL-6: Interleukin 6; IFN-ÿ: Interferon Gamma; IL-8: Interleukin 8.

1. Introduction

The gut microbiota (GM) contains trillions of microorganisms, including the phyla *Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria* make up 90% of the intestinal bacteria present. in adults. It is composed of more than 1,000 different species, mostly anaerobic, playing essential roles in vitamin production, nutrient digestion and function immunological. Changes in the immune system can be caused by several factors, such as diet, overuse. of medications, genetic factors, comorbidities, and acquired infections, resulting in dysbiosis of this microbiota (1-2). The large quantity of bacteria in the intestinal lumen includes approximately 1 gram lipopolysaccharide (LPS), a component of the outer membrane of gram-negative bacteria, Upon entering the systemic circulation, it has great potential to activate recognition patterns of antigens, leading to an inflammatory response. This imbalance can negatively influence the The health of the individual, such as in underlying diseases like diabetes. The inflammation generated by the microbiota. It can inhibit insulin signaling and promote weight gain, with diet being the biggest influencing factor (3). Intestinal dysbiosis is present in several diseases, including inflammatory bowel diseases (4), celiac disease (5), irritable bowel syndrome (6), colorectal cancer (7), chronic liver diseases (8-9) and pancreatic disorders (10-11). In the analysis of children at risk of disease celiac disease, an increase in *Dialister invisus, Parabacteroides spp and Lachnospiraceae* was observed before the onset of the disease, with a reduction in anti-inflammatory bacteria such as *Faecalibacterium prausnitzii and Clostridium clostridioforme* (12). MI also contributes to Obesity, related to factors such as reduced peristalsis, bacterial overgrowth, dysbiosis, loss of intestinal barrier integrity, bacterial translocation, gastroesophageal reflux and alterations in the brain-gut axis. Dysbiosis caused by inadequate nutrition can increase The extraction of energy from food, resulting in lipogenesis and endotoxemia. In obese adults, there is an increase in *Streptococcaceae and Lactobacillaceae* and a decrease in *Christensenellaceae. Clostridiaceae and Dehalobacteriaceae,* correlating positively with the mass index.

(13). The brain-gut axis can influence various body pathologies and weight gain. neurological conditions, such as autism spectrum disorder (ASD), characterized by dysfunction of Neurodevelopment is influenced by MI. Gastrointestinal symptoms occur in 40-60% of cases. Patients with ASD, characterized by abdominal pain, diarrhea, and constipation. Changes in Regulation and communication of the axis occur through the vagus nerve, microbiota metabolites, and cytokines. pro-inflammatory and neurotransmitters, such as serotonin. Excess of long-chain fatty acids. Short-term effects, such as propionate, can affect the physiology of the central nervous system, leading to symptoms.

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neurological. Dysbiosis in ASD is associated with the production of fatty acids by bacteria such as Clostridia, Desulfivibrio and Bacteroides (14). In the context of the SARS-CoV-2 pandemic, a virus with primary pulmonary tropism, which had a major impact on global health (24-25), the detection of viral RNA in fecal samples from patients with COVID-19 suggests a possible fecal-oral transmission (26). In addition, infection with the virus has shown several gastrointestinal manifestations, such as Anorexia, diarrhea, vomiting, and abdominal pain, reinforcing the connection between the gut-lung axis and the prognosis of the disease (27). A consequence of this, dysbiosis, with a decrease in bacterial flora. commensal of *Faecalibacterium prausnitzii; Eubacterium rectale and Bifidobacteria* in patients infected (28), caused by the additional expression of ACE2 in the enterocytes of the small intestine and ileum (124-125), with the inflammatory cascade and its cellular invasion, causing the influx of LPS through increased intestinal permeability into the bloodstream (126), in which, in cases Severe cases are intensified by pyroptosis, with the release of pro-inflammatory cytokines, which include: TNF-ÿ, IL-1, IL-6, IL-12, IFN-ÿ, IFN-ÿ, IFN-ÿ, MCP-1, and IL-8, resulting in the storm of cytokines and worse prognosis (127), with emphasis on increasing C-Reactive Protein; Lactate Dehydrogenase; Aspartate aminotransferase and Alpha glutamyltransferase, markers that correlate with a decline in the clinical picture (28). This topic was chosen due to the fact that the high lethality in the COVID-19 pandemic, especially among people weakened by comorbidities, and the curiosity to understand the pathophysiology, along with the possibility of treatment, may saving many lives, with the search for articles on the subject.

2. Materials and Methods

This work constitutes an integrative literature review, with an emphasis on identifying the Efficacy of probiotics in adjuvant treatment in patients infected with SARS-CoV-2. A An integrative review is a methodology that allows for the description and discussion of articles without... requiring strict drafting protocols, making it important for situations requiring speed where Conduct is important, especially for evaluating treatments against a circulating pathogen and of imminent risk of increased lethality with the use of randomized clinical trial articles, the most Strong scientific evidence supports the analysis of treatments.

Databases and Descriptors

For the classification of articles, the PubMed and Library databases were consulted. Virtual Health Library (VHL) from 2020 to 2023. The descriptors used were: (SARS-CoV-2

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OR COVID-19) **AND** Gut Microbiota **AND** Immune Response, validated on the platform DeCS/MeSH (Descriptors in Health Sciences). The search was refined using available filters. in the databases, specifically to retrieve studies using clinical trial methodology, including randomized clinical trials.

Inclusion Criteria

The inclusion criteria were rigorously defined to ensure relevance and quality of the selected studies:

I. Free Access and Full Text: Only scientific articles with free access and full text. Complete data has been included, ensuring transparency and data availability.

II. Randomized Clinical Trials: Only randomized clinical trials were considered, due to their high level of scientific evidence.

III. Specific Themes: Studies related to prognosis and the gut-brain axis were included. Lung function, gastrointestinal symptoms, dysbiosis, and severity regarding the gut microbiota. Furthermore, studies on the use of prebiotics, probiotics and fecal microbiota transplantation for the attenuation of The clinical picture, as well as the nutritional impact on immunity, were considered.

Exclusion Criteria

The exclusion criteria were established to eliminate studies that did not contribute. directly related to the objectives of the review: I. In vitro studies: These studies were excluded due to its limited practical application in humans. II. Specific Themes: Articles that address Vaccination studies, or studies that do not describe intestinal dysbiosis and its clinical consequences, were excluded. because they do not fall within the main focus of the review. III. Publication Period: Articles outside the The period from 2020 to 2023 was excluded to ensure the accuracy of the information. IV. Type of Publication: Review articles, letters, case reports, book chapters, conference abstracts, Editorial notes, in vitro studies, and animal studies were excluded to maintain methodological quality.

Selection Procedure

The articles were initially screened based on their abstracts to verify compliance with the Inclusion and exclusion criteria. When necessary, the full text was reviewed for evaluation. more detailed. The selected studies were then analyzed in depth, and the data Relevant information was extracted and organized.

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Data Analysis

The data extracted from the articles were analyzed both quantitatively and qualitatively to Identify patterns and trends. The integrative review provided a comprehensive overview of the interactions. between the gut microbiota and SARS-CoV-2, highlighting the importance of maintaining the Intestinal homeostasis for symptom mitigation and improved prognosis in patients infected. The selected studies indicate that interventions such as the use of probiotics and Fecal microbiota transplants have significant therapeutic potential, although they are More studies are needed to validate these approaches in a continuous and safe manner.

3. Results and Discussion

The selection process for the articles in this review followed a rigorous methodology. beginning with the initial identification of relevant studies and culminating in the final inclusion of articles that met the established criteria. This process ensured that only the most suitable studies were included. Relevant and high-quality data were considered for analysis. The initial search in the databases This resulted in a total of 12 articles found on the PubMed platform and 39 articles in the Library. Virtual Health Library (VHL) **(Figure 1).** Next, a screening was performed to exclude duplicates and to ensure that each study was evaluated only once. This initial step was crucial to avoid Redundancies and focusing only on single works. The abstracts of the identified articles were revised to verify their relevance to the previously defined inclusion criteria.

This preliminary verification helped to eliminate studies that, at first glance, did not address directly related to the objectives of the review. Those who passed this initial screening were considered for a more detailed analysis. During the application of the inclusion criteria and Exclusion criteria were followed by a detailed screening of the articles. Studies that did not meet the criteria were excluded. Items that were either included or outside the scope of the review were excluded. This step involved an analysis. thorough review, both of the abstracts and, when necessary, of the full text of the articles. After the applying the inclusion and exclusion criteria to the 12 articles initially identified in PubMed, Two articles met all the criteria and were selected. In the BVS, out of the 39 articles initially... Of the identified articles, 4 underwent detailed screening, resulting in the final inclusion of 1 article that It met all the established criteria. In total, 3 articles were selected to comprise the review.

Finally, these articles highlight therapies that have demonstrated effectiveness in controlling symptoms and... reduction in hospitalizations of patients with COVID-19. The use of probiotics, in particular, was emphasized due to its ability to improve gut flora and reduce the pro- Inflammatory through the proliferation of commensal bacteria and molecules important for

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immunomodulation, as presented below. The results of the selected articles were organized into detailed tables, presenting information about the authors, title, year, design, objectives and main findings of each **study.(Figure 2)**

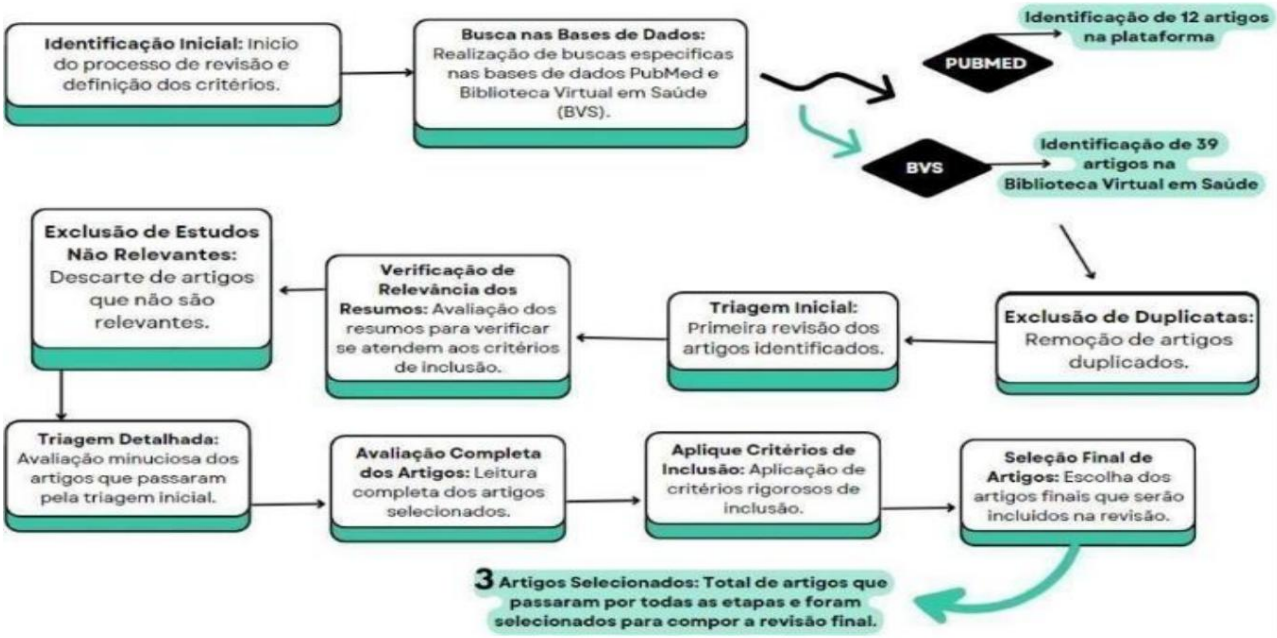

Figure 2 - Articles from PubMed and BVS showing clinical improvement with adjuvant use of probiotics.

Authors	Title	Outline	Main Finding
Gutiérrez-Castrellón P, Gandara-Martí T, Abreu Y Abreu AT, Nieto-Rufino CD, López-Orduña E, Jiménez-Escobar I et.al. (2021)	Probiotic improves symptomatic and viral clearance in Covid19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial.	Quadruple-blind clinical trial with placebo arm	*The Probiotic Arm with 4 strains and variants of Lactiplantibacillus plantarum + Pediococcus acidilactici* caused an improvement in symptoms and Viral clearance up to day 30 in infected patients and increased immunoglobulins compared to placebo
Forsgård RA, Rode J, Lobenius-Palmer K, Kamm A, Patil S, Tacken MGJ, Lentjes MAH, Axelsson J, Grompone G, Montgomery S, Brummer RJ (2023)	*Limosilactobacil lus reuteri DSM 17938* supplementation and SARS-CoV-2 specific antibody response in healthy adults: a randomized, triple-blinded, placebo-controlled trial	Randomized, triple-blind, placebo-controlled clinical trial	Supplementation with *Limosylactobacillus reuteri DSM 17938* showed a trend of increasing levels of specific IgG and IgA for SARS-CoV-2, especially in infected individuals during the study.

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Kageyama Y, Nishizaki Y, Aida K, Yayama K, Ebisui T, Akiyama T, et al. (2022) -BVS Article	Lactobacillus plantarum induces innate cytokine responses that potentially provide a protective benefit against COVID-19: A single-arm, double-blind, prospective trial combined with an in vitro cytokine response assay	Single-arm, double-blind, prospective clinical trial	L. plantarum obtained greater QICI in relation to B. longum, with increased cell activity. *Natural Killer.*

COVID-19 and gastrointestinal tract infection

The most common gastrointestinal symptom reported in patients with COVID-19 was diarrhea, which manifested predominantly in the late stage of the disease. This phenomenon is resulting from a complex set of pathophysiological changes that occur in the organism. Among Among these changes, dysfunction of the renin-angiotensin-aldosterone system stands out, which is essential in Regulation of blood pressure and fluid and electrolyte balance. SARS-CoV-2, through its protein spike interacts with Angiotensin-Converting Enzyme 2 (ACE2), a crucial enzyme in this process. The system. The virus's binding to ACE2 leads to its internalization and subsequent decrease in ACE2 in the system. cell surface, which disrupts the system's homeostasis and contributes to systemic and local inflammation (95-97). In addition, direct viral invasion of intestinal cells, particularly enterocytes, exacerbates the inflammatory response. Studies show that SARS-CoV-2 can directly infect human enterocytes, leading to intestinal cell dysfunction and significant local inflammation (95).

Viral proteins, such as Orf3a and protein E, play a crucial role in this process. Orf3a, for example, is involved in the induction of apoptosis and the modulation of inflammatory responses (96), while protein E participates in the assembly and release of new virions, as well as in the activation of inflammatory responses (97). This invasion and subsequent viral replication in Intestinal cells not only cause direct damage, but also disrupt the intestinal barrier. increasing its permeability. This increase in permeability allows for the translocation of pathogens and endotoxins are released from the intestinal lumen into the systemic circulation, exacerbating inflammation and potentially leading to sepsis in severe cases. Activation of the innate immune system, along with the production of pro-inflammatory cytokines, it contributes to the "cytokine storm". frequently observed in severely ill COVID-19 patients, increasing morbidity and

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mortality associated with the disease (98). The ACE2 receptor is widely distributed in cells
Epithelial cells of various tissues, including the lungs and gastrointestinal tract. Studies have shown that the
Enterocytes in the small intestine express this receptor, which facilitates viral infection and the
subsequent dysbiosis of the gut microbiota. The presence of viral RNA in the stool of patients
Infected individuals corroborate this route of infection and intestinal disruption, leading to symptoms such as
diarrhea, inflammatory bowel disease, and ulcerative colitis (111-112). The alteration in the integrity of the barrier
Intestinal inflammation due to viral infection exacerbates the inflammatory response, contributing to the severity of
gastrointestinal symptoms (126). The pathophysiology of COVID-19 involves a significant increase in
production of inflammatory cytokines, which play a central role in the immune response to
Viruses. These cytokines can cause symptoms ranging from mild, similar to those of a common cold, to
Severe Acute Respiratory Syndrome (SARS). Although cytokine production is a response
necessary for the viral pathogen, its excessive release can result in tissue damage, especially
in lung tissue. Patients with mild cases of COVID-19 are usually able to regulate this.
inflammatory response, preventing progression to more severe stages of the disease (112-113). A factor
Crucial to the body's response to infection is the state of the gut microbiota. Patients with a
Dysbiotic microbiota tend to present worse prognoses, as the gut microbiota is
A healthy gut microbiota is fundamental in modulating the immune response. It contributes to the production of
of soluble substances that circulate throughout the body, modulating the activation of cells in the system.
immune system. These circulating microbial substances are detected by immune cells in
organs distant from the intestine, and the lack of these signaling molecules can lead to changes in
immune function, increasing vulnerability to systemic infections (114, 118). The process of
Aging also has a significant impact on the gastrointestinal tract (GIT), resulting in
several physiological changes. These include degeneration of the enteric nervous system, alterations in
intestinal motility and mucosal barrier integrity, as well as a reduction in defense function.
immunological. These age-related changes contribute to an altered gut microbiota.
and a weakened immune system, increasing susceptibility to infections and inflammatory diseases (115, 119).
Recent studies have investigated the relationship between the gut microbiota and the
The severity of COVID-19 was investigated using advanced Mendelian randomization techniques. These studies...
They indicate that certain microbial compositions can influence susceptibility and
disease severity. For example, the presence of certain bacterial taxa, such as *Intestinimonas* and
Bifidobacterium has been associated with an increased risk of severe COVID-19 and hospitalization, while (120,
such as *Ruminococcaceae UCG014,* have shown a protective effect. 121). In addition, others,
Supplementation with probiotics has shown potential in modulating the immune response in
patients with Covid-19.

Randomized clinical trials, such as the one conducted by Gutiérrez-Castrellón P, Gandara-Martí

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T, Abreu Y Abreu AT, Nieto-Rufino CD, López-Orduña E, Jiménez-Escobar I, et al, demonstrated that the administration of *Lactiplantibacillus plantarum* and *Pediococcus acidilactici* resulted in a Significant improvement in symptoms and viral clearance in outpatients with COVID-19. 19. These probiotics helped increase immunoglobulin levels, strengthening the patients' immune response (122;123). The impact of nutrition on immunity has also been widely discussed. studied, highlighting the importance of a balanced diet for maintaining intestinal health and immune response. Supplementation with prebiotics and probiotics may play a role. crucial in maintaining intestinal eubiosis, reducing inflammation and improving prognosis in patients with COVID-19 (122). In addition, differences in diet, antibiotic use and conditions Pre-existing conditions in patients can influence the results. For example, patients with diets rich in... Fiber and natural probiotics can present a microbiota that is more resistant and less susceptible to changes induced by SARS-CoV-2 (122). · A critical discussion of the findings in relation to the literature. existing knowledge allows for a deeper understanding of the complex interactions between the microbiota. intestinal and SARS-CoV-2 infection. Although there is promising evidence regarding the role of Microbiota in modulating the immune response and the severity of symptoms; more research is needed. necessary to clarify discrepancies and validate effective therapeutic interventions.

Gut microbiota and immune system

Dysbiosis is a direct consequence of an increased pro-inflammatory environment and a reduction of antimicrobial peptides, mediated by the amino acid receptor B0AT1, which is crucial for the Tryptophan uptake. This process occurs along with a decrease in receptor activity. mTOR (mammalian target of rapamycin), which is affected by the interaction of the virus with the ACE2 receptor. As a result, a reduction in normal gut flora and an overgrowth of bacteria is observed. pathogenic bacterial species. Specifically, there is a decrease in *Faecalibacterium. prausnitzii, Bifidobacterium bifidum and Eubacterium rectale,* while there is an increase in *Enterococcus faecalis, Enterococcus faecium, Streptococcus anginosus, Escherichia coli, Shigella, Coprobacillus, Clostridium ramosum, and Clostridium hathewayi* (94, 99, 100). The intestinal microbiota It plays an essential role in the immunological context, especially in the gut-lung axis. The metabolites produced by the bacteria in the microbiota, known as long-chain fatty acids. Short-chain fatty acids (SCFAs) are products of the fermentation of dietary fiber. These include acetate, butyrate, and propionate, which reduces inflammation and inhibits the spread of highly cytokine-producing cells, such as T helper lymphocytes of profile 17 (Th17) (101). In addition, maintaining the The organic mucosal barrier, which prevents the passage of toxins into the systemic circulation, is another (102). of homeostasis between organs. Studies demonstrate that butyrate, a SCFA, is a crucial form

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synthesized by the gut microbiome (including bacteroides, lactobacillus, and bifidobacteria), It promotes the differentiation of peripherally induced regulatory T cells, inhibiting inflammation. Systemic. Other SCFAs, such as pentanoate, have the ability to inhibit Th17 cells and induce Regulatory B cells. These modulations allow the microbiome to suppress excessive inflammatory responses, preventing tissue destruction (111). Furthermore, signaling molecules Released by the microbiota, these substances enter the bloodstream and modulate cell development. immunological responses occur during hematopoiesis. Signals derived from the microbiota also modulate defenses. innate immune responses, stimulating lymph nodes in the spleen, modulating migration and function of neutrophils, inducing and activating macrophages and stimulating the maturation of natural killer cell functions (114). In this way, the microbiota can influence the progression of COVID-19. The phylum *Lachnospira* has the potential to produce SCFAs, contributing to patient recovery, while the phylum *Faecalibacterium* has anti-inflammatory properties (116). Dysbiosis of The gut microbiota impacts the defense against infectious agents, especially those that colonize the airways, through the gut-lung axis, which connects these organs via the bloodstream. Therefore, the gut microbiota acts directly on the pulmonary immune response (111). Furthermore, It has been shown that intestinal dysbiosis can induce allergic airway diseases, increasing Susceptibility to asthma and modulating the innate and adaptive immune response against viral and bacterial infections (117). COVID-19 infection causes a dynamic change in the respiratory and gut microbiomes, with a synchronous restoration of both as the disease progresses (116).

Changes in the intestinal barrier contributed to increased systemic inflammation and Consequently, a negative prognosis, with emphasis on comorbidities such as obesity, which It promotes endotoxemia and alteration of tight junctions. And also diarrhea, with which it is associated. with ionic imbalance, important findings were found during SARS-CoV infection-2, with the production of Interferon I and III, which may limit the gastrointestinal infectious picture (94, 99, 100). Individual factors, such as diet, antibiotic use, and pre-existing health conditions, also play a role. They play a crucial role in the results. Patients with diets rich in fiber and probiotics Natural foods may present a more resilient gut microbiota, less susceptible to changes. induced by SARS-CoV-2. This demonstrates that dietary interventions can be an effective strategy to maintain microbiota health and reduce the severity of COVID-19 symptoms (101, 102, 111). The interaction between the gut microbiota and the immune system is complex and multifaceted. The metabolites produced by the microbiota, such as short-chain fatty acids (SCFAs), They play a crucial role in modulating inflammation and maintaining the integrity of the intestinal barrier. For example, butyrate promotes the differentiation of regulatory T cells, which They help suppress excessive inflammatory responses. Dysbiosis, therefore, not only compromises the It provides protection against SARS-CoV-2, but it can also exacerbate the systemic inflammatory response.

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contributing to the severity of symptoms (111, 114). In addition, intestinal dysbiosis can induce allergic diseases of the airways and increase susceptibility to respiratory infections, modulating the innate and adaptive immune response. COVID-19 infection causes dynamic changes in Respiratory and gut microbiomes, with synchronous restoration of both as the disease progresses. of the disease. Therefore, it is understood that interventions targeting the gut microbiota could have beneficial effects not only on the gastrointestinal tract, but also on respiratory health (116, 117) .

Supplementation with probiotics has shown potential in modulating the immune response in patients with COVID-19. Randomized clinical trials have demonstrated that the administration of *Lactiplantibacillus plantarum and Pediococcus acidilactici* resulted in significant improvement of These probiotics helped to increase symptoms and viral clearance in outpatients. Immunoglobulin levels, strengthening the immune response of patients (122). Nutrition also It plays a vital role in maintaining gut health and the immune response. Diets Balanced diets, rich in prebiotics and probiotics, help maintain intestinal eubiosis and reduce... inflammation and improve prognosis in patients with COVID-19. Furthermore, studies suggest that Supplementation with specific micronutrients, such as B vitamins, vitamin D, and zinc, supports immune health and improves clinical outcomes (122). In conclusion, a A critical analysis of the findings, in relation to existing literature, allows for a deeper understanding. of the complex interactions between the gut microbiota and SARS-CoV-2 infection. Although there are Promising evidence regarding the role of microbiota in modulating the immune response and in Given the severity of the symptoms, further research is needed to resolve the discrepancies. observed and to confirm the effectiveness of the proposed therapeutic interventions.

Use of probiotics and improvement of the immune response

Complementary therapies to reduce the severity of the infection, such as specific diets, Probiotics, prebiotics, and fecal microbiota transplantation have been extensively studied. Dietary changes with micronutrient supplementation have the potential to help balance... intestinal microbiota and, consequently, improve the immune response. B vitamins B vitamins, such as thiamine, riboflavin, and niacin, as well as fat-soluble vitamins like A, D, and K, and minerals. Elements such as magnesium, potassium, phosphorus, and iron promote the growth of commensal bacteria and create a an antimicrobial environment less favorable to pathogens. Diets rich in fiber and antioxidant foods also play a crucial role in this process(103). Vitamin D, for For example, it reduces the risk of respiratory infections, while zinc is essential for maturation and Activation of immune cells. Antioxidant vitamins, such as C and E, help protect the cells. against oxidative stress, thus reducing the pro-inflammatory environment. Diets rich in vegetables.

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Green vegetables, grains such as wheat, lentils and chickpeas, yogurt and cheese promote the growth of Symbiotic bacteria, such as *Bacteroides, Bifidobacterium, and Lactobacilli.* These foods increase the production of short-chain fatty acids (SCFAs), such as lactic acid, acetic acid and propionic acid, which have anti-inflammatory properties and aid in the health of the intestinal epithelium(104).

Clinical trials have shown that individuals who use probiotics have a lower incidence and better prognosis for respiratory infections, due to the reduction of the inflammatory response of

Probiotics are live microorganisms or viral pathogenesis and improvement in respiratory symptoms. Probiotics are live microorganisms or components of bacteria used to maintain the integrity of the gut microbiota. They can conferring various benefits by inducing resistance against antibiotics, xenobiotics, and factors of pathogenicity or toxicity, in addition to strengthening immunity. Bifidobacterium strains , *Enterococcus, Lactobacillus, Saccharomyces boulardii, Lactococcus, Leuconostoc, Pediococcus and Streptococcus bacteria* are widely used as probiotics and can be effective as adjuncts. in the treatment of various diseases and disorders of the gastrointestinal tract (GIT) and allergies. Furthermore, The use of probiotics is being studied as a therapy for diseases affecting the respiratory system. due to its correlation with the gut-lung axis. It has been shown that administration of *Lactobacillus casei, L. rhamnosus, and Bifidobacterium bifidum* decrease viral titers and alleviate symptoms of influenza virus infection (105, 106). The use of probiotics is associated with improved pathogenicity due to its ability to modulate monocyte chemoattractant protein-1 (MCP-1), a mediator linked to the SARS-CoV-2 virus, improving inflammation. In addition, probiotics They have the property of modulating dysbiosis, alleviating intestinal symptoms caused by COVID-19 and reducing the severity of the disease. A clinical trial concluded that the use of probiotics containing *Lactobacillus rhamnosus GG, live Bacillus subtilis and Enterococcus faecalis* in patients COVID-19 resulted in a lower incidence of ventilator-associated pneumonia in comparison with those without probiotic supplementation(121). Some specific species of Probiotics have been studied, such as *Lactobacillus acidophilus, Bifidobacterium bifidum and Lactobacillus plantarum,* and were associated with reduced hospitalization rates and lower severity. of the infection, in addition to increasing interferon production, preventing the cytokine storm. The Prebiotics are substrates used by the gut microbiota for the production of SCFAs. The subtypes studied include fructooligosaccharides, galactooligosaccharides, and inulin, which are... fermented locally to produce SCFAs, such as butyrate. However, there are no conclusive studies on their efficacy and safety in humans(119).

The only pharmacological agent approved for specific use against SARS-CoV-2 is... Remdesivir, an RNA-dependent RNA polymerase inhibitor. However, failures in the effectiveness of this Drug overdoses have been reported in about 30 countries due to mutations in the virus, which highlights the The need for other therapeutic means for viral control. Fecal microbiota transplantation.

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involves the transfer of gut microbiota from a healthy donor to a patient with dysbiosis. This procedure, successfully used in cases of pseudomembranous colitis, is reported. It is considered safe and without serious adverse effects, but its continuous use is not yet recommended. Microbiota is administered via nasogastric or nasojejunal tube.

It is concluded that intestinal dysbiosis caused by SARS-CoV-2 is an important factor for The increased morbidity and mortality of patients is due to the intense systemic immune response. This This scenario can persist even after viral recovery in the lower respiratory tract, highlighting the... More studies are needed to standardize and analyze the safety and efficacy of therapeutic measures. promising. Microbiota modulation through probiotics, prebiotics, and transplantation of The fecal microbiota has great potential to alleviate the clinical symptoms of infection and prevent further complications. to alleviate the strain on healthcare systems in mild cases and improve patients' quality of life. increasing the production of SCFAs in the gastrointestinal tract and reducing the pro-inflammatory environment. Systemically. Supplementation with probiotics and prebiotics not only maintains integrity It not only breaks down the intestinal barrier, but also modulates the immune response, increasing antibody production. specific and anti-inflammatory cytokines. Studies have shown that the administration of probiotics It can reduce the viral load and the duration of symptoms in respiratory infections. Furthermore, the The ability of probiotics to modulate the gut-lung axis indicates therapeutic potential. significant in the prevention and treatment of respiratory complications associated with COVID-19. SCFAs produced by probiotic fermentation play a crucial role in regulating immune response, promoting the production of regulatory T cells and inhibiting the differentiation of Th17 cells, which are responsible for exacerbated inflammatory responses. The inclusion of Probiotics in the diet can therefore provide additional support in maintaining homeostasis. immunological. In addition to probiotics and prebiotics, fecal microbiota transplantation has shown Promising results in restoring intestinal eubiosis and improving the immune response in patients. with severe dysbiosis. This procedure has the potential to be a valuable therapeutic tool in Management of severe viral infections, including COVID-19, especially in patients with a high response rate. compromised immune system. Given the significant impact of dysbiosis on the pathogenesis and progression of With COVID-19, it is essential to continue exploring and validating these therapeutic approaches. Implementing strategies based on modulating the gut microbiota may not only to improve clinical outcomes in patients with COVID-19, but also to provide a basis for The development of innovative therapies for future viral pandemics.

Final Considerations

The SARS-CoV-2 infection has had a significant impact on global public health.

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standing out for its multifaceted manifestations, including gastrointestinal symptoms. Among
Among these symptoms, diarrhea is the most prevalent intestinal disorder, frequently associated with infection.
Late transmission of the gastrointestinal tract is due to the bidirectional connection between the intestines and lungs. This
This phenomenon, known as the gut-lung axis, indicates that dysbiosis of the gut microbiota can...
to directly influence the course of COVID-19 infection. Reviewed studies demonstrate that
Patients with intestinal dysbiosis have worse prognoses compared to those with
A healthy microbiome. The gut microbiota plays a crucial role in regulating
immune system, especially through the production of short-chain fatty acids (SCFAs),
which are responsible for attenuating systemic inflammation. These metabolites are products of
fermentation of dietary fiber by commensal bacteria, such as *Bacteroides, Lactobacillus and*
Bifidobacterium, and include butyrate, propionate, and acetate. The presence of these SCFAs promotes
Greater control of the inflammatory response, preventing tissue destruction caused by inflammation.
exacerbated. In the therapeutic context, the review highlighted the potential of dietary interventions and
probiotics in modulating the gut microbiota to improve clinical conditions of
Patients infected with SARS-CoV-2. Diets enriched with micronutrients, such as vitamins.
B complex vitamins (thiamine, riboflavin, niacin), fat-soluble vitamins (A, D, and K), and minerals.
(magnesium, potassium, phosphorus and iron) have shown potential to promote the growth of
commensal bacteria and create an antimicrobial environment less favorable to pathogens. Vitamin
D, for example, has the added benefit of reducing the risk of respiratory infections, while...
Zinc plays a crucial role in the maturation and activation of immune cells. Assays
Clinicians have indicated that administering probiotics containing specific strains, such as
Lactobacillus casei, Lactobacillus rhamnosus, Bifidobacterium bifidum and Enterococcus faecalis,
These probiotics can reduce viral load and improve respiratory and gastrointestinal symptoms.
They help strengthen the integrity of the intestinal barrier and modulate the immune response, decreasing
the inflammatory response associated with viral pathogenesis. For example, the administration of *Lactobacillus*
Plantarum has proven effective in inducing innate immune responses that potentially
They offer protective benefits against COVID-19. Fecal microbiota transplantation (FMT) is another
This intervention has been explored and has shown promise in restoring intestinal eubiosis and
to improve the immune response in patients with severe dysbiosis. This procedure involves
transfer of gut microbiota from a healthy donor to a patient with dysbiosis,
promoting a recovery of microbial diversity and improving intestinal homeostasis.
Despite the promising results, it is important to note that the efficacy and safety of some of these...
Interventions, such as the continued use of prebiotics and FMT in patients with COVID-19, are still...
They require further studies for validation. The only pharmacological intervention approved for use.
Remdesivir, a drug specifically designed to combat SARS-CoV-2, has already shown efficacy failures in several countries.

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highlighting the need for complementary therapeutic approaches. It is concluded that dysbiosis
The gut is a significant factor in the progression and severity of COVID-19, affecting the response.
immunological and increasing morbidity and mortality in patients. Microbiota modulation
Intestinal therapy through probiotics, prebiotics, and FMT presents great therapeutic potential, not
not only for COVID-19, but also for other infectious and autoimmune diseases.
Continued research and validation of these therapeutic strategies are essential for improvement.
Clinical management and improving the quality of life of patients affected by this and future pandemics.
viral.

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