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Immunity's core reset: Synbiotics and gut microbiota in the COVID-19 era

Dejana Bajić[1], Nemanja Todorović[2], Mladena Lalić Popović[2], Milica Plazačić[3] and Andrea Mihajlović[4]

Abstract

The gut microbiome plays a crucial role in shaping immune responses, and its connection to immunity has never been more relevant than in the COVID-19 era. The interaction between gut microbes and the immune system, known as microbiome-immunity crosstalk, influences both how the body responds to infections and how well it recovers. COVID-19, whether in its acute phase or lingering as long COVID, has been linked to disturbances in the gut microbiome. During infection, many patients experience dysbiosis—an imbalance in gut bacteria—that can contribute to immune dysfunction and excessive inflammation. This imbalance may not only worsen the severity of the disease but also prolong recovery, leading to persistent symptoms like fatigue, brain fog, and digestive issues. Long COVID, in particular, has been associated with ongoing immune dysregulation, where the body's defense system remains in a state of heightened activation, causing chronic inflammation. Given the strong link between gut health and immunity, there is growing interest in strategies to restore microbial balance. Synbiotics—combinations of probiotics (beneficial bacteria) and prebiotics (nutrients that support them)—are being explored as a potential therapeutic approach. By replenishing beneficial gut microbes, synbiotics may help regulate immune responses, reduce inflammation, and support overall recovery from COVID-19. Emerging research suggests that improving gut health could enhance the body's ability to fight infections and recover more efficiently. As we continue to understand the long-term impact of COVID-19, focusing on the gut microbiome offers a promising path forward. Supporting a balanced and diverse microbiome through diet, lifestyle, and targeted interventions like synbiotics may provide a natural way to strengthen immunity and improve health outcomes in both acute and long COVID cases.

Keywords

gut microbiota, dysbiosis, inflammation, COVID-19, long COVID

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Introduction

The COVID-19 pandemic has exerted widespread influence across global health systems, economic structures, and patterns of daily living. While the virus is often recognized for its severe respiratory effects, its impact on the immune system is equally significant. Beyond the immediate symptoms, COVID-19 can deeply affect our body's ability to defend itself, contributing to long-term complications affecting multiple organ systems. In severe cases, the virus disrupts the body's natural defenses, triggering an overactive and poorly regulated immune response. This imbalance can trigger excessive inflammation, often called a "cytokine storm," and strain the immune system, leaving it overactive yet ineffective—a state referred to as immune exhaustion. These effects contribute to the severity of the disease and its long-term complications.[1–3]

The World Health Organization (WHO) defines Long COVID, also known as post-acute sequelae of COVID-19 (PASC), as a chronic condition that develops at least three

[1]Department of Biochemistry, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[2]Department of Pharmacy, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia
[3]Department of Pediatrics, Institute for Child and Youth Health Care of Vojvodina, Novi Sad, Serbia
[4]Department of Physiology, Faculty of Medicine, University of Novi Sad, Novi Sad, Serbia

Corresponding author:
Dejana Bajić, MD, PhD, Department of Biochemistry, Faculty of Medicine, University of Novi Sad, Hajduk Veljkova 3, 21137 Novi Sad, Serbia.
Email: dejana.bajic@mf.uns.ac.rs

months after a SARS-CoV-2 infection. Long COVID, as outlined by the 2024 NASEM (National Academies of Sciences, Engineering, and Medicine) guidelines, is characterized by symptoms lasting at least three months that may be continuous, relapsing and remitting, or progressively worsening, often affecting multiple organ systems and sometimes reemerging after an initial recovery period. Common symptoms include extreme fatigue, heart palpitations, joint and muscle pain, difficulty concentrating or "brain fog," memory issues, and breathing problems. Both active COVID-19 and Long COVID are influenced by immune system dysregulation, including chronic inflammation and impaired recovery. Key immune dysfunctions include excessive production of inflammatory cytokines, which damage tissues, T-cell exhaustion that weakens the body's defense and the potential development of autoimmune-like conditions. These disruptions not only prolong recovery but also contribute to the lingering and complex nature of Long COVID symptoms.[3–8]

The immune system is a fundamental component of health, serving as the body's protector by identifying and neutralizing harmful invaders while preserving its own tissues. Comparable to immune effector cells, it operates with precision to maintain balance and ensure survival. Around 70% of the body's immune system resides in the gut, making it a major contributor in maintaining overall health and resilience. The gut microbiome is increasingly recognized as a key modulator of immune activity, playing a fundamental role in the development, regulation, and maintenance of both local and systemic immune responses. It coordinates immune functions by maintaining intestinal homeostasis and influencing immune signaling pathways throughout the body. By producing immune-modulating compounds, guiding the activity of immune cells, and strengthening the gut barrier, the microbiome has a significant impact on the body's ability to defend itself. During and after COVID-19, the gut microbiome often becomes imbalanced, contributing to immune dysfunction and chronic inflammation. Synbiotics—combinations of probiotics and prebiotics—offer a way to restore this delicate microbial balance. By replenishing beneficial bacteria and supporting their growth, synbiotics can help restore microbial balance in the gut, thereby reducing inflammation and strengthening immune defenses.

The aim of this article is to examine the role of synbiotics in modulating the gut microbiome, focusing on their capacity to regulate inflammation, enhance immune function, and increase antioxidant activity. By analyzing the effects of synbiotics in these areas, the article highlights their therapeutic potential, particularly regarding both the acute and persistent consequences of COVID-19. The continued global impact of COVID-19, with effects extending beyond the initial infection phase, emphasizes the need to support the immune system. As new viral variants emerge and the long-term effects become better characterized, interventions targeting inflammation, immune regulation, and antioxidant mechanisms may provide effective strategies to improve recovery and reduce the incidence of long-term complications.[1,4,6–11]

Methods of literature search and study selection

A systematic literature search was performed using the electronic databases PubMed, Scopus and Web of Science to identify relevant articles published between January 2020 to March 2025. Keywords included combinations of terms such as "gut microbiota", "synbiotics", "COVID-19", "immune response", "oxidative stress", "immune modulation" and "long COVID". Both original research studies and review articles were considered.

After removing duplicates, titles and abstracts were screened for relevance. The inclusion criteria comprised peer-reviewed English-language articles that reported on human clinical trials, observational studies, and relevant in vivo or in vitro experimental models related to the research topic. Articles were excluded if they did not meet inclusion criteria—for example, non-English publications, studies unrelated to the topic, or those lacking a clear and reproducible methodology. Irrelevant animal studies, such as those not addressing gut microbiota, immune response, or aging-related mechanisms, were also excluded. Full texts of potentially relevant studies were reviewed to confirm eligibility.The final selection includied studies that provided relevant data on the effects of synbiotics on gut microbiota and immune function in the context of COVID-19. The study selection process adhered to the PRISMA guidelines to ensure methodological transparency and reproducibility.

Microbiome-Immune crosstalk

The gut is home to a diverse community of microorganisms (bacteria, fungi, viruses, archaea protozoa, helminths), including important groups of bacteria like *Firmicutes, Bacteroidetes*, and *Actinobacteria*. These microbes are indispensable for our metabolism, helping with digestion, producing vitamins, and protecting us from harmful pathogens. Commensal bacteria assist with digestion by breaking down complex carbohydrates, fibers, and other substances that our body can't process on its own. Gut bacteria produce essential vitamins like vitamin K, B vitamins (B12, B9, B2, B6, B5, and B7), and vitamin D (*Lactobacillus* and *Bifidobacterium* genera are thought to enhance the conversion of vitamin D into its active form), which are crucial for metabolism and immune function. These vitamins support processes like blood clotting, energy metabolism, nerve function, DNA synthesis, and immune defense,

highlighting the vital role of the gut microbiota in maintaining overall health.[11–13]

The diversity and balance of gut bacteria are required to support metabolic processes and immune function. Commensal bacteria are responsible for protecting us from harmful pathogens by competing for nutrients and space in the gut, a process known as competitive exclusion. This helps prevent the growth of harmful microbes and reduces the risk of infections. However, the composition of the microbiome can differ greatly from person to person, influenced by factors like diet, environment, genetics, and lifestyle. This variability can affect how individuals respond to infections, including viruses, and influence their susceptibility to certain diseases, as well as the effectiveness of their innate immunity.[11–14]

Innate immunity is the body's initial defender, responding quickly to threats, while adaptive immunity acts like a skilled strategist, remembering past encounters to better tackle future challenges. The body's immediate response system promptly attacks any unfamiliar invaders with a broad, general approach, using cells like macrophages and neutrophils. In contrast, adaptive immunity takes longer to activate but offers a more precise, targeted defense through T and B cells, which recognize specific threats and remember them for future protection.[11,15]

In the gut, innate immunity relies on components like physical barriers (epithelial lining and mucus), chemical defenses (stomach acid and antimicrobial peptides), phagocytic cells (macrophages, neutrophils, and dendritic cells), inflammatory mediators (cytokines and chemokines), and natural killer (NK) cells, all working together to rapidly and effectively defend against potential threats. Its complexed activity is based on cells like macrophages, dendritic cells, and natural killer cells, which work together to spot and eliminate possible dangers. At the heart of this system are pattern recognition receptors (PRRs) located on and within immune cells, such as Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which detect specific markers on pathogens and trigger the immune response to fight off infections. Through several mechanisms, the gut microbiota helps fine-tune the body's innate immune responses, defending against harmful pathogens while maintaining balance. It activates PRRs, trains immune cells, and promotes tolerogenic responses. Furthermore, the production of short-chain fatty acids (SCFAs), as well as the stimulation of mucin and antimicrobial peptide production by commensal bacteria, strengthens the gut's protective mucus layer. A healthy gut barrier prevents pathogens from entering and triggers unnecessary immune activation.[8,11,14]

Microbe-associated molecular patterns (MAMPs) such as lipopolysaccharides (LPS), peptidoglycan, and flagellin are produced by the gut microbiota, and are recognized by PRRs on immune cells. This controlled activation by commensal bacteria ensures proper immune vigilance while preventing excessive immune reactions. Beneficial microbes are important in engaging innate immune cells such as macrophages and neutrophils to respond quickly and effectively, while also regulating dendritic cells to ensure they properly present antigens to adaptive immune cells without triggering unnecessary responses to harmless stimuli. Certain gut bacteria (such as *Akkermansia muciniphila, Bacteroides fragilis, Lactobacillus species, Bifidobacterium species*) encourage tolerogenic responses, helping the immune system learn to tolerate harmless substances and preventing excessive activation that could lead to autoimmune reactions.[1,12,16,17]

The gut microbiota plays an essential role in shaping the body's immune responses and one important way it does this is by producing SCFAs (like butyrate, acetate and proprionate) from the fermentation of dietary fibers by microbes. Butyrate plays a vital role in immune regulation by activating regulatory T cells to control inflammation, enhancing dendritic cell function to initiate immune responses, and strengthening the gut barrier to prevent harmful pathogens from entering the bloodstream. It particularly reduces pro-inflammatory cytokines like TNF-α, IL-1β, and IL-6 by inhibiting NF-κB (Nuclear Factor kappa-light-chain-enhancer of activated B cells; under normal conditions it is kept inactive, but inder stress and infection signals it is activated) . Furthermore, the metabolites produced by microbes (such as proprionate, acetate, indole-3 acetic acid,vitamin B12, kynurenine) can influence how immune cells are activated, communicate, and develop, helping to keep the immune system in balance.[8,14,17]

Propionate helps reduce inflammation by promoting anti-inflammatory cytokines like IL-10, IL-4, and IL-13, and by influencing immune cells such as macrophages and dendritic cells. On the other hand, acetate supports the growth of regulatory T cells, which help control inflammation and autoimmune responses, while also strengthening the gut barrier to prevent harmful pathogens from entering. Indole-3-acetic acid (IAA) and kynurenine, both metabolites of tryptophan produced by gut bacteria, play key roles in immune modulation, with IAA promoting T cell activation and anti-inflammatory cytokine production, while kynurenine influences T cell differentiation and immune tolerance to balance immune responses and prevent excessive inflammation.[18,19]

Gut-associated lymphoid tissue (GALT) plays a critical role in regulating the immune system by interacting with the gut microbiota to defend against harmful invaders while tolerating harmless substances. Found in structures like Peyer's patches and lymphoid follicles, GALT helps immune cells, including dendritic cells and T cells, recognize and respond to pathogens while maintaining balance. By training these immune cells to differentiate between threats and non-threats, GALT ensures an appropriate immune response. This interaction highlights the vital connection between gut

health and overall immune function, emphasizing the importance of maintaining a healthy gut microbiome.[20]

Dysbiosis and immune dysregulation in COVID-19

Dysbiosis occurs when the normal balance of microbes in the gut is disturbed, leading to an overgrowth of harmful bacteria and a reduction in beneficial ones. This disruption can be triggered by factors such as the use of antibiotics, poor dietary habits, and infections, which can all alter the delicate balance of the gut microbiota. Key mechanisms behind this connection include increased intestinal permeability ("leaky gut"), disrupted immune regulation that overactivates inflammatory pathways, and altered production of SCFAs.[11–14]

When harmful bacteria (such as *Clostridium* or *Enterococcus* species) outgrow the beneficial ones, they can contribute to increased inflammation and immune dysfunction by triggering an exaggerated immune response, which leads to the release of pro-inflammatory cytokines. They can also disrupt the gut barrier, allowing pathogens and toxins to enter the bloodstream, further activating the immune system and causing chronic inflammation that impairs normal immune function. Dominance of pathogenic bacteria can interfere with the development and function of regulatory T cells, leading to immune dysregulation and excessive inflammation. It can also damage the gut lining, making it more permeable and allowing harmful substances and pathogens to enter the circulatory system.[11–15,17,21]

An imbalance in gut microbes, has been closely linked to autoimmune diseases such as rheumatoid arthritis (RA), type 1 diabetes (T1D), and multiple sclerosis (MS). In RA, overgrowth of bacteria like *Prevotella copri* can activate Th17 cells, triggering systemic inflammation and joint damage, especially when a "leaky gut" allows microbial antigens to enter the bloodstream. For T1D, studies show reduced microbial diversity and fewer SCFA-producing bacteria like *Faecalibacterium prausnitzii*, which weakens immune regulation and increases the activity of T cells that attack pancreatic beta cells. Similarly, MS patients exhibit low levels of beneficial bacteria (*Bacteroides fragilis*) and a rise in pro-inflammatory species, disrupting the gut-brain axis and fueling neuroinflammation. These findings highlight the gut microbiome's critical role in regulating immune responses and suggest that restoring microbial balance could offer new approaches for managing autoimmune conditions.[15,17,21]

Research has shown that COVID-19 can cause notable changes in the gut microbiome, often leading to a decrease in microbial diversity and an increase in harmful bacteria. These disruptions in the gut microbiota are associated with systemic inflammation, cytokine storms, and immune exhaustion, all of which can worsen the severity of the infection and impair the body's ability to regulate immune responses effectively. In Long COVID, ongoing dysbiosis can contribute to persistent inflammation and immune dysfunction. The imbalance in the gut microbiota may keep the immune system in a constant state of activation, leading to continuous inflammation and weakened immune responses, which can worsen long-term symptoms and health problems.[1–8]

Inflammation and the gut microbiome

Inflammation is the body's natural defense mechanism to fight infections and heal injuries, but when it becomes excessive or prolonged, it can cause harm. Acute inflammation is the body's rapid, short-term response to injury or infection, aimed at repair and protection . Chronic inflammation is a prolonged immune response that persistently damages tissues and contributes to the development of long-term pathological conditions. Long-term inflammation poses serious risks because it keeps the immune system constantly active, which can contribute to conditions such as heart disease, cancer, and autoimmune disorders. The gut microbiome is key in controlling inflammation, and when it's out of balance (dysbiosis), it can contribute to ongoing inflammation and interfere with the body's ability to heal properly. In cases like COVID-19, elevated levels of markers such as IL-6 (Interleukin-6) and CRP (C-reactive protein) point to ongoing immune activation and widespread inflammation, which can make the disease more severe. These markers reflect the transition from acute to chronic inflammation, contributing to prolonged symptoms and complications.[1–8,14–17]

The shift from acute to chronic inflammation represents a complex change in the immune system, moving from a short-term, protective response to a prolonged, often harmful state. When acute inflammation fails to resolve or the body's healing processes become disrupted, this transition can occur. The persistence of inflammatory signals, even after the initial trigger has been resolved, sustains immune activation and facilitates the transition from an acute to a chronic inflammatory state. Chronic inflammation involves the ongoing activity of immune cells like macrophages and T-cells, which can mistakenly target healthy tissues, leading to tissue damage and fueling the progression of chronic diseases. Factors like the gut microbiome significantly influence the shift from acute to chronic inflammation, as an imbalance in gut bacteria (dysbiosis) can amplify inflammation and disrupt immune regulation. This persistent immune activation creates a pathway to chronic inflammation, which is linked to the development of various long-term health conditions.[14–17,22]

Gut microbiome and immune modulation

Gut microbes significantly influence inflammation; some species exert protective effects, whereas others promote

inflammation or contribute to tissue damage. Beneficial microbes, such as those producing SCFAs like butyrate, modulate inflammatory responses by suppressing pro-inflammatory pathways and enhancing regulatory T cell function, thereby supporting gut barrier integrity. Butyrate-producing bacteria like *Faecalibacterium prausnitzii*, *Roseburia* species, and *Eubacterium rectale* are key members of the Firmicutes phylum, known for their anti-inflammatory properties, ability to strengthen the gut barrier, and role in maintaining a healthy gut lining. Conversely, pathogenic microbes, or pathobionts, can disrupt the gut's balance and drive inflammation by promoting the release of pro-inflammatory cytokines, potentially worsening conditions like COVID-19.[23–25]

Several pathobionts, such as *Escherichia coli*, *Enterococcus faecalis*, *Bacteroides fragilis*, *Klebsiella pneumoniae*, and *Clostridioides difficile*, are naturally present in the gut microbiome in small numbers, coexisting with beneficial bacteria under normal conditions. However, when the balance of the microbiome is disrupted, these microbes can overgrow, triggering inflammation and contributing to disease.[13,14]

The gut microbiome plays a key role in keeping the gut barrier strong by producing substances that support the gut lining and prevent harmful pathogens from reaching the bloodstream. When this barrier is weakened, often referred to as "leaky gut," toxins and bacteria may translocate into the systemic circulation, triggering widespread inflammation and contributing to chronic diseases and conditions, including worsening the effects of COVID-19. The gut microbiome creates several substances that are vital for maintaining a healthy gut barrier. SCFAs help strengthen the gut lining, while mucins form a protective layer to shield the gut from harmful pathogens. Antimicrobial peptides (such as defensins, cathelicidins, and resistin-like molecules) exert antimicrobial activity against pathogenic bacteria, while secondary bile acids and polyphenol metabolites support gut health by reducing inflammation, regulating gut barrier function, and maintaining microbiome balance.[13–18]

Recent studies highlight the gut's vital role in regulating immune cells and inflammatory pathways, functioning as a regulatory axis that mediates interactions between the immune system and external antigens. A healthy, balanced microbiome is essential for maintaining immune tolerance and ensuring that the immune system responds appropriately without overreacting. In contrast, when the gut microbiome is disrupted, or dysbiosis occurs, it can trigger chronic inflammation by impairing immune regulation. This imbalance has been associated with a range of health issues, including autoimmune diseases, inflammatory bowel diseases, cardiovascular problems, and even neurological disorders. Dysbiosis promotes long-lasting inflammation, which not only weakens immune function but also plays a key role in the development and progression of these chronic conditions.[21,23,24]

Synbiotics as therapeutic approach

Synbiotics, a combination of prebiotics and probiotics, were first defined in 1995 by Dr Gerhard L. R. Gibson and Dr Marcel B. R. F. as a strategy to improve the composition and function of the gut microbiome, particularly in conditions associated with dysbiosis. Initially, their application focused on gastrointestinal disorders such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), and infections caused by microbiome imbalance (e.g., *Clostridium difficile*, *Candida albicans*).[26–28]

Synbiotics consist of live beneficial microorganisms (e.g., *Lactobacillus*, *Bifidobacterium*, *Saccharomyces boulardii*) and prebiotics—non-digestible compounds that selectively stimulate their growth and activity. Common prebiotics include inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), resistant starch, and pectin. This combination improves gut microbial composition, enhances digestion, and supports mucosal and systemic immune function.[26–30]

Mechanistically, synbiotics promote colonization by beneficial microbes, increase short-chain fatty acid (SCFA) production, reinforce gut barrier integrity, and reduce inflammation by downregulating pro-inflammatory cytokines. These effects also enhance the activity of key immune cells, such as natural killer (NK) cells, macrophages, and T cells, supporting antiviral defense mechanisms including responses to SARS-CoV-2.[26–28]

Probiotics modulate immune function by interacting with antigen-presenting cells (APCs)—such as dendritic cells and macrophages—via PRRs that detect microbial-associated molecular patterns. This leads to activation of adaptive immune responses, including B cell differentiation into plasma cells and secretion of immunoglobulins (e.g., IgA, IgG). Moreover, probiotics help regulate the balance between Th1 and Th2 responses by promoting cytokines like IFN-γ and IL-12, which suppress Th2-mediated hypersensitivity, thereby mitigating allergic responses.[13–15,17,21,27–29]

Role of synbiotics in mitigating oxidative stress

Preliminary data suggest synbiotics may help attenuate oxidative stress by modulating the gut microbiota and supporting balanced host metabolic activity, although further research is needed. They enhance the production of SCFAs, which contribute to improved mitochondrial function and modulation of inflammatory responses. Furthermore, synbiotics promote the activity of antioxidant enzymes such as superoxide dismutase (SOD) and catalase, thereby reducing the accumulation of reactive oxygen species (ROS).

In addition, synbiotics facilitate the biotransformation of dietary polyphenols into bioactive antioxidant compounds, including flavonoids and phenolic acids. These metabolites exert systemic antioxidative effects and modulate

inflammatory signaling. Synbiotics also downregulate pro-inflammatory cytokines and upregulate anti-inflammatory mediators, indirectly contributing to reduced oxidative damage associated with chronic inflammation.

Glutathione, a key intracellular antioxidant involved in neutralizing ROS and maintaining redox homeostasis, is supported by synbiotic supplementation. Probiotic strains within synbiotic formulations can increase the bioavailability of cysteine, a rate-limiting precursor in glutathione synthesis, thereby contributing to cellular antioxidant defenses and protection against oxidative injury.[26–31]

Prolonged ROS production during acute and post-acute SARS-CoV-2 infection, including Long COVID, can surpass the capacity of endogenous antioxidant systems and lead to immune exhaustion. This sustained oxidative stress has been implicated in the pathophysiology of Long COVID, including persistent inflammation, fatigue, and immune dysregulation.[2–6]

Evaluation of synbiotic therapies: efficacy and limitations

Studies have demonstrated that the gut microbiome is critically involved in regulating the immune system, affecting host responses to infections, vaccines, and cancer therapies. Recent research indicates potential efficacy of advanced microbiome-based interventions, including probiotics, prebiotics, and fecal microbiota transplantation (FMT), which have been associated with improved clinical outcomes and modulation of immune responses, particularly enhancing the efficacy of vaccines and cancer immunotherapies.[13,14,26–29]

Studies have explored the potential of synbiotics to modulate the immune system and reduce inflammation. Clinical trials have demonstrated that synbiotic supplementation can positively influence immune function and gut microbiota composition in healthy individuals. For instance, a randomized controlled trial reported that an 8-week synbiotic regimen resulted in alterations in immune markers such as IL-10 and sIgA, indicative of a shift in gut microbiota associated with reduced inflammation.[26–28]

One pertinent study examining the effects of synbiotics in COVID-19 patients was a randomized controlled trial involving hospitalized individuals with confirmed SARS-CoV-2 infection. A total of 78 participants were randomized into two groups: one receiving synbiotic capsules and the other a placebo, over a two-week period. The synbiotic formulation included probiotics such as Lactobacillus and Bifidobacterium species, combined with the prebiotic fructooligosaccharides. The results demonstrated that participants receiving synbiotics exhibited a significant decrease in the inflammatory marker IL-6 and improvements in white blood cell counts, suggesting that synbiotics may contribute to inflammation reduction and immune recovery in COVID-19 patients.[32]

A cohort study titled "Assessment of the Prophylactic Effects of Probiotics, Prebiotics, and Synbiotics" explored the effectiveness of these supplements in preventing COVID-19. The study followed high-risk individuals, such as nursing home residents and healthcare workers, as well as healthy adults and household contacts of infected patients. The findings revealed no significant difference in COVID-19 incidence or antibody levels between the groups that received synbiotics and those who took a placebo, suggesting that these supplements did not offer a preventive benefit.[33]

In the open-label study titled "Gut microbiota-derived synbiotic formula (SIM01) as a novel adjuvant therapy for COVID-19," 25 hospitalized COVID-19 patients received a SIM01 for 28 days, while a control group of 30 patients did not. The study revealed that a greater proportion of patients in the SIM01 group developed SARS-CoV-2 IgG antibodies by Day 16 compared to the control group. Furthermore, the SIM01 group showed significantly reduced levels of pro-inflammatory markers like IL-6 and TNF-α, and metagenomic analysis indicated that the synbiotics promoted beneficial bacteria while suppressing harmful pathogens in these patients.[30]

While these key trials provide promising preliminary data on the effects of synbiotics in COVID-19, it is important to consider certain methodological limitations. The sample sizes in these studies are relatively small, which may limit the statistical power and generalizability of the findings. The open-label design of the SIM01 study introduces potential bias due to the lack of blinding and placebo controls. Additionally, detailed information on randomization methods, blinding procedures, and control measures is often lacking or insufficiently described. These limitations highlight the necessity for further large-scale, randomized, double-blind, placebo-controlled trials to robustly evaluate the efficacy and safety of synbiotic therapies in COVID-19 and related immune disorders.

Research on the immune response in COVID-19 highlights how inflammation plays a pivotal role in disease severity and symptom persistence. Studies show that factors such as age, gender, and immune regulation impact outcomes, with some patients experiencing prolonged symptoms linked to immune dysregulation. Men may face a higher risk of severe COVID-19 outcomes due to the immune-suppressive effects of testosterone, which weakens T-cell activity and antibody production, while women benefit from estrogen's immune-enhancing properties and the redundancy of immune-related genes on their two X chromosomes. Additionally, males are more susceptible to cytokine storms—an excessive inflammatory response—that can cause significant tissue damage and worsen disease severity. As people age, their immune system weakens due to reduced production of naïve T-cells and B-cells, limiting the ability to respond effectively to new infections like

SARS-CoV-2. Coupled with chronic low-grade inflammation ("inflammaging") and common comorbidities such as diabetes and heart disease, older individuals face delayed viral clearance and heightened immune activation, increasing the risk of severe outcomes.[1–4,34,35]

Notably, research on long COVID reveals a significant increase in mast cell activation, which contributes to persistent inflammation and symptom recurrence, emphasizing the potential for targeted interventions like synbiotics to help modulate these immune pathways. Mast cells release inflammatory mediators like histamine, cytokines, and prostaglandins to combat infection or injury. In long COVID, these cells can become hyperactive, leading to chronic inflammation and ongoing symptoms such as fatigue, brain fog, joint pain, and digestive issues. Gut dysbiosis—emerges as a significant trigger for this overactivation, disrupting the gut-immune axis and amplifying inflammation through mechanisms involving gut-associated lymphoid tissue (GALT).[2–4,20,36,37]

Current research is investigating the use of synbiotics for managing post-viral syndromes, including long COVID. A clinical trial conducted in Hong Kong evaluated the synbiotic treatment SIM01 for its efficacy in alleviating symptoms of post-acute COVID-19 syndrome (PACS), reporting significant reductions in several symptoms associated with long COVID, thus indicating its potential as a therapeutic option.[30–32]

These findings suggest that synbiotics may represent a promising approach to modulate the immune system and reduce inflammation, potentially serving as a strategy for managing post-viral conditions such as Long COVID, though further robust clinical evidence is needed to substantiate their therapeutic use. Additional components may enhance the effects of synbiotics and support recovery, particularly in Long COVID. Notable examples include vitamin D, zinc, and magnesium, which contribute to immune function, maintain gut barrier integrity, and alleviate fatigue. Anti-inflammatory compounds such as polyphenols (derived from green tea or curcumin) and omega-3 fatty acids provide supplementary benefits by reducing inflammation and supporting neurological and cardiovascular health.[38–40]

Synbiotics could potentially contribute to mitigating severe COVID-19 complications by decreasing the risk of cytokine storm—an excessive immune response associated with critical illness; however, definitive conclusions cannot yet be drawn due to limited and heterogeneous clinical data. They help regulate immune activity and promote a balanced inflammatory response, potentially reducing disease severity and supporting recovery from Long COVID by addressing chronic inflammation. Furthermore, synbiotics may enhance the production of glutathione, a key antioxidant involved in combating oxidative stress, thereby protecting cells and facilitating recovery. This dual mechanism additionally supports pulmonary function, reduces muscle fatigue, and strengthens overall immune defense, underscoring the therapeutic potential of synbiotics in COVID-19 recovery.[23,27,29,30,41,42]

The gut microbiome is essential for immune regulation and inflammation control, serving as a critical interface between host defenses and environmental factors. When the gut microbiome is balanced, it modulates immune cell activity and promotes the production of anti-inflammatory mediators, ensuring proper immune system function without eliciting detrimental inflammation.[13–17]

Translational challenges and research gaps in synbiotics for COVID-19 outcomes

Strengths

Research highlights the potential of synbiotics to modulate inflammation, enhance immune responses, and reduce oxidative stress, suggesting their possible role as adjunctive agents in COVID-19 treatment strategies. A variety of study designs, including clinical trials and observational studies, have been employed, providing diverse insights into the effects of synbiotics across different populations.

Limitations:

Results from synbiotics research have been inconsistent, with some studies demonstrating significant improvements in inflammatory markers and clinical outcomes, while others report limited or no benefit. These discrepancies may result from differences in study design, patient demographics, and sample size. The complexity and interindividual variability of the gut microbiome complicate standardization of research methodologies and interpretation of findings across heterogeneous populations. Furthermore, while preclinical studies indicate promising effects, the translation of these findings into clinical practice requires addressing challenges such as optimal dosing, patient selection, and long-term safety evaluation.

Although synbiotics exhibit biologically plausible mechanisms and some preliminary clinical benefits, the current evidence base is limited by small study sizes, methodological constraints, and inconsistent results. There remains a critical need for well-designed, large-scale randomized controlled trials (RCTs) to validate their efficacy and safety, particularly in the context of COVID-19 and post-viral syndromes. Future research should also address optimal dosing, formulation, and patient stratification to tailor therapies effectively.

In summary, these strengths and limitations underscore the necessity for more extensive, rigorous clinical trials to establish the efficacy and safety of synbiotics in managing COVID-19 and related immune conditions. Additional research is warranted to investigate the long-term effects of gut microbiome modulation and to elucidate the influence of factors such as age, comorbidities, and individualized patient

profiles on synbiotic effectiveness, ultimately facilitating the development of personalized therapeutic approaches.

Conclusion

Current evidence indicates that a balanced gut microbiome, potentially supported by synbiotic interventions, may play a role in modulating immune responses, attenuating inflammation, and reducing oxidative stress. Preliminary findings suggest that synbiotics could enhance microbial diversity and promote the production of endogenous antioxidants such as glutathione. These mechanisms are biologically plausible and may be relevant in the context of conditions characterized by immune dysregulation and gut dysbiosis, including COVID-19 and long COVID.

However, the clinical implications of these findings remain uncertain. Robust evidence from large-scale, well-designed RCTs is needed to confirm the therapeutic potential of synbiotics in viral infections. Furthermore, future research should explore the integration of synbiotics into personalized medicine approaches, including microbiome-based stratification, to optimize efficacy and safety across diverse populations.

ORCID iD

Dejana Bajić https://orcid.org/0000-0002-7958-068X

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The data that support the findings of this study are available from the corresponding author upon reasonable request.

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