The effect of microbiome therapy on COVID-19-induced gut dysbiosis: A narrative and systematic review

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ABSTRACT

Aims: Emerging evidence highlights the role of COVID-19 in instigating gut dysbiosis, with repercussions on disease severity and bidirectional gut-organ communication involving the lung, heart, brain, and liver. This study aims to evaluate the efficacy of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT) in addressing gut dysbiosis associated with COVID-19, as well as their impact on related disease severity and clinical outcomes.

Materials and methods: We systematically review 27 studies exploring the efficacy of different microbiome-modulating therapies: probiotics, prebiotics, synbiotics, and fecal microbiota transplantation as potential interventions for COVID-19.

Key findings: The probiotics and synbiotics investigated encompassed a spectrum of eight bacterial and fungal genera, namely *Lactobacillus, Bifidobacterium, Streptococcus, Enterococcus, Pediococcus, Bacillus, Saccharomyces,* and *Kluyveromyces*. Noteworthy prebiotics employed in these studies included chestnut tannin, galactooligosaccharides, fructooligosaccharides, xylooligosaccharide, and resistant dextrin. The majority of the investigated biotics exhibited positive effects on COVID-19 patients, manifesting in symptom alleviation, inflammation reduction, and notable decreases in mortality rates. Five studies reported death rates, showing an average mortality ranging from 0 % to 11 % in the intervention groups, as compared to 3 % to 30 % in the control groups. Specifically, probiotics, prebiotics, and synbiotics demonstrated efficacy in diminishing the duration and severity of symptoms while significantly accelerating viral and symptomatic remission. FMT emerged as a particularly effective strategy, successfully restoring gut microbiota and ameliorating gastrointestinal disorders.

Significance: The insights gleaned from this review significantly contribute to our broader comprehension of the therapeutic potential of biotics in addressing COVID-19-related gut dysbiosis and mitigating secondary multi-organ complications.

1. Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of the COVID-19, has presented a formidable global challenge, leading to a pandemic [1]. As of April 2023, the virus has been responsible for over 763 million confirmed cases and nearly a million deaths worldwide. Its primary mode of infection involves targeting cells in the respiratory system, resulting in significant inflammation and tissue damage [2,3]. The clinical presentation of COVID-19 is diverse, encompassing typical symptoms like fever, dry cough,

fatigue, and dyspnea. However, it may also extend to more complex physiological disruptions, including gut microbiota disruption, gastrointestinal issues, autoimmunity, blood clotting, endothelial function abnormalities, and dysfunctional neurological signaling [4,5]. A particularly noteworthy aspect of COVID-19 is its significant impact on the digestive system, with approximately half of the patients exhibiting digestive symptoms such as lack of appetite, abdominal pain, diarrhea, and vomiting. Research has connected the severity of these symptoms to various factors, notably the patient's age and comorbidities, which often correlate with a compromised immune system and changes in gut

composition [6]. The relationship between COVID-19 and gastrointestinal health has emerged as a focal point in the scientific discourse, given its demonstrable impact on both the clinical trajectory and therapeutic approaches for the disease. The integral role of gut microbiota in modulating immune responses and inflammatory pathways necessitates a deeper exploration into its interaction with SARS-CoV-2. Consequently, a comprehensive recognition of these interactions is imperative for advancing an integrative understanding of COVID-19 pathophysiology. Such an approach not only elucidates the extensive link between the virus and the gastrointestinal system but also propels the development of more effective therapeutic interventions.

The gut microbiota, comprising trillions of bacteria, archaea, and eukarya in the gastrointestinal tract, plays a crucial role in maintaining gut ecosystem balance and has become a key research focus due to its significant correlation with various aspects of human health [7]. A healthy gut microbiota not only supports digestion but may also play a role in boosting the immune system, lowering the risk of chronic diseases (e.g. obesity, type 2 diabetes, colorectal cancer), and influencing mental health [8–11].

COVID-19 management encompasses a range of preventative and disease-modifying treatments, such as vaccines, anti-inflammatory agents, antivirals, antithrombotic treatments, anti-SARS-CoV-2 antibody therapies, renin–angiotensin–aldosterone system (RAAS) modulators, and vitamins [12]. Vaccines have shown efficacy in preventing severe illness, hospitalization, and death, with effectiveness rates ranging from 72 % to 95 % ([13,158,160,162]). In symptom management, non-steroidal anti-inflammatory drugs (NSAIDs), have effectively mitigated symptoms such as anosmia, ageusia, or dysgeusia, thereby reducing hospitalization occurrences [14]. The administration of Vitamin D has markedly decreased the necessity for oxygen supplementation, intensive care unit (ICU) admissions, and overall mortality [15]. Additionally, therapies centered on anti-SARS-CoV-2 antibodies have demonstrated a substantial 70 % reduction in the incidence of severe disease or death compared to a placebo ("A neutralizing monoclonal antibody," [16]). RAAS modulators have also been noteworthy, particularly, in diminishing the risks of thrombosis and hospitalization [17]. However, while early treatments modalities have shown some efficacy, their impact on reducing the overall COVID-19 mortality remains limited [18].

While a range of COVID-19 treatments has been effective in managing various aspects of the disease, they are not without limitations and potential side effects. Vaccines, for example, can lead to short-term reactions like pain at the injection site, fatigue, headache, muscle aches, chills, and fever, though instances of severe side effects remain rare [155]. NSAIDs may lead to complications, such as those affecting the gastrointestinal, cardiovascular, and pulmonary systems [19]. Antiviral medications have been linked to central nervous system damage and neuropsychiatric complications [20]. Hemorrhaging is a major complication in antithrombotic therapy [21]. Similarly, RAAS inhibitors might exacerbate lung inflammation, potentially leading to further dysfunction [22,23]. Antibody therapies, while effective, carry risks of acute anaphylaxis, serum sickness, and various autoimmune conditions [24]. These side effects present considerable challenges in the management of COVID-19, particularly given the ongoing strain on global healthcare systems. Furthermore, despite their efficacy in certain respects, these treatments have yet to effectively address symptoms related to gut health, which may arise from alterations in the gut biome. This oversight underscores the need to consider the gut's significant role in overall health and disease management, especially in the context of COVID-19 [25–27].

Emerging research suggests that COVID-19, along with its treatment regimens, may disrupt the balance of the gut biome [28,29]. This disruption underscores the critical need for further research to explore the impact of gut microbes on health and identify strategies to enhance gut health through dietary modifications, biotics, and other therapeutic interventions. Potentially efficacious microbiome modulators, including probiotics, prebiotics, synbiotics, and fecal microbiota transplantation (FMT), are being investigated for their role in improving outcomes for COVID-19 patients. However, there remains a significant gap in research in this niche field. Considering the alteration of the gut microbiome in COVID-19 patients, the application of biotic interventions and FMT could offer viable routes for recovery. Here, we undertake a systematic review of existing literature to comprehensively assess the efficacy of various microbiome-modulating therapies as potential interventions for COVID-19 to provide a robust synthesis of existing evidence and shed light on the potential benefits of these therapies in COVID-19 management.

2. Effect of gut dysbiosis in COVID-19

Current research highlights a notable link between the gut and COVID-19. Evidence suggests that the virus not only presents in the fecal mucosa but also infiltrates immune cells within the gastrointestinal tract, impacting the gut biome [29–31]. Furthermore, the discovery of the Angiotensin-converting enzyme 2 (ACE2) receptor in gastrointestinal epithelial cells hints at a possible pathway for viral transmission beyond the lungs. The virus's impact extends to the induction of inflammatory responses that compromise gut integrity, potentially leading to bacterial translocation and systemic inflammation [32]. In the subsequent section, we investigate the relationships between the gut and different organ axes, placing them in the context of COVID-19 infection.

2.1. Gut-lung axis

Research findings suggest a profound interplay between gut and lung microbiota alterations, with discernible implications for both symptom severity and the trajectory of infection [28,33,34]. In the context of COVID-19 lung infection, proinflammatory cytokines such as IL-6 and IL-10 play a pivotal role in orchestrating immune responses, attracting immune cells, and intensifying the ongoing inflammation [35,36]. Meanwhile, dendritic cells activate immune responses in the gut, marshaling B and T cells to upregulate TNFα, IFN-γ and IL-6. IL-6, [35,37]. Furthermore, specific bacteria, like *Veillonella parvula*, in the gut of COVID-19 patients have been linked to higher TNF-α levels, intensifying inflammation [38]. This inflammation triggers oxidative production, draws leukocytes to pulmonary tissue, and prompts the production of adhesion molecules like ICAM-1 and VCAM-1, collectively contributing to the development of acute lung injury and asthma-like symptoms [38,39]. Concurrently, apoptosis of endothelial cells is also induced via caspase-3 pathways, resulting in a decrease in Treg cells and anti-inflammatory cytokines [39–41]. Evidence suggests that the gut and lungs share the mucosal immune system, primarily composed of gut-associated lymphoid tissue (GALT) and bronchial-associated lymphoid tissue (BALT). GALT, in particular, has been known to contribute more significantly, allowing immune cells and factor transfer from GALT to BALT in response to respiratory infections [42]. Furthermore, the gut and lung are interconnected through the systemic circulation via the mesenteric lymphatic system, establishing a link between initial immunization in the gastrointestinal tract and targeted action in the lungs [42,43]. This increased circulation of proinflammatory cytokines, upregulated VEGF angiogenic factor, reduced E-cadherin levels, and endothelial cell apoptosis collectively result in altered gut microbiome composition and increased gut and lung permeability, ultimately culminating in an exaggerated inflammatory response (Fig. 1).

Studies have revealed an increase in *Actinobacteria* in the gut microbiota of individuals with COVID-19 infection, linking it to elevated levels of gp130/sIL-6Rb associated with systemic inflammatory disorders ([28,44,159,45]). Additionally, researchers have observed higher levels of pathogenic *Enterobacteriaceae* in COVID-19 patients, which are known to produce endotoxins with inhibitory effects on protein synthesis in epithelial cells, facilitating lung damage [28,46,47]. Moreover, studies have documented a decrease in the *Clostridia* class of bacteria,
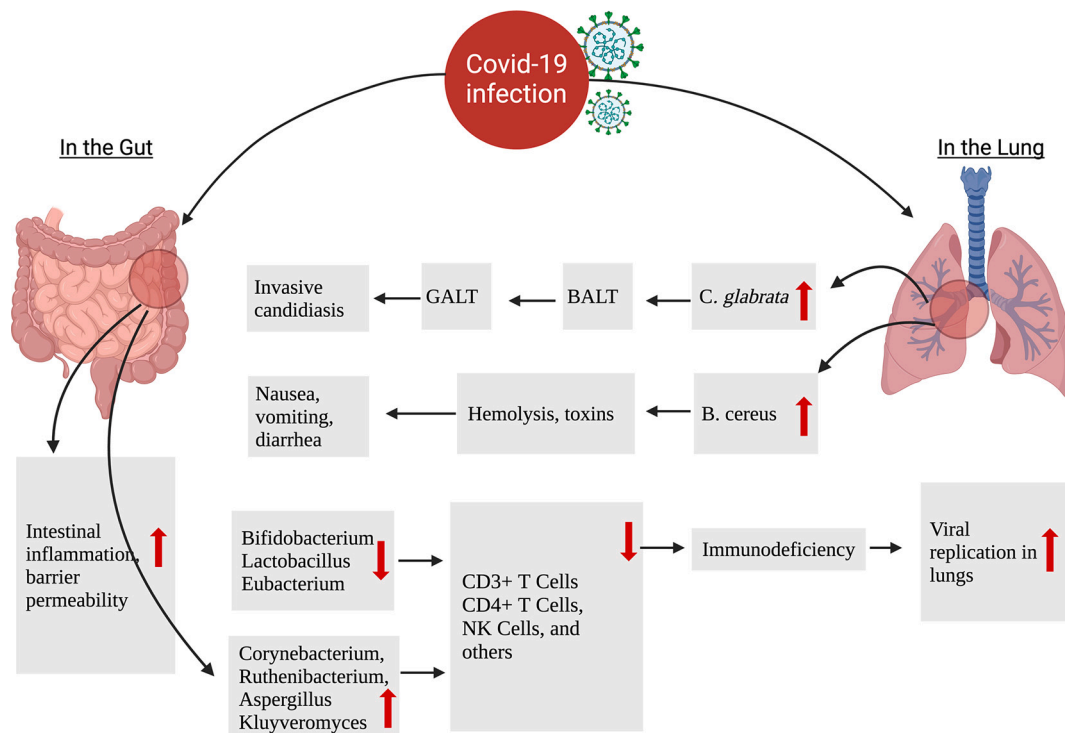
Fig. 1. Dysbiosis of the gut-lung axis in COVID-19 patients. In individuals infected with SARS-CoV-2, the gut microbiota may undergo changes, potentially resulting in a decrease in Bifidobacterium, Lactobacillus, and Eubacterium, while there may be an increase in Corynebacterium, Ruthenibacterium, Aspergillus, and Kluyveromyces. Similarly, alterations in the lung microbiota can occur, potentially leading to an increase in *C. glabrata* and *B. cereus*.

leading to diminished levels of butyrate, a critical short-chain fatty acid (SCFA) responsible for maintaining an anaerobic environment and regulating various intestinal functions (Mizutani et al., 2022; [48]). Typically, in a healthy individual's gut, butyrate is produced and then transported into the lungs through the bloodstream, where it plays a vital role in reducing pulmonary damage by inhibiting inflammation [49]. However, due to gut dysbiosis, COVID-19 patients experience a decline in butyrate levels, resulting in an inability to regulate lung inflammation and causing an increase in IL-8, IL-12, and (IFN)-γ and IL-28 A/IFN-I2 levels ([49]; Mizutani et al., 2022).

Pathogenic bacteria in the guts of COVID-19 patients, such as those from the *Streptococcus* and *Rothia* genera, may impact lung health through the gut-lung axis [50]. These bacteria play a role in developing secondary bacterial lung infections, with *Rothia* mainly promoting pneumonia pathogenesis [50,51]. Genera like *Bacteroides, Parabacteroides, Enterocloster, and Flavonifractor* are elevated in the guts of COVID-19 patients, leading to the production of putrefactive compounds as a result of protein fermentation [52,53]. This metabolic activity results in putrefactive dysbiosis, characterized by the buildup of ammonia and amine. Accumulation of Polyamine in the pulmonary epithelium can lead to lung edema and hemorrhaging [54]. Finally, Putrefactive dysbiosis, driven by increased catabolism of amino acids like tryptophan, phenylalanine, lysine, and tyrosine, and reduced carbohydrate metabolism through pathways such as glyoxylate, sucrose, galactose, and decarboxylate, may ultimately result in excessive systemic inflammation, intensifying dysbiosis severity [55].

Elevated levels of pathogenic bacteria (e.g., Corynebacterium and Ruthenibacterium) and fungi (e.g., Aspergillus and Kluyveromyces), combined with lower levels of beneficial probiotics (e.g., Bifidobacterium, Lactobacillus, and Eubacterium), can reduce the numbers of critical immune cells like CD4+ T cells, CD8+ T cells, and CD16 + 56+ NK cells [45,56]. This gut dysbiosis-induced immunodeficiency significantly amplifies viral replication in the lungs, potentially hindering the clearance of the virus [35,45]. In one study, gut dysbiosis-induced

immunodepletion resulted in hypoxemia and hypoxia in severe cases of COVID-19 [45]. The microbial imbalance within the lungs may contribute significantly to the progression of COVID-19. Pathogenic bacteria such as *Bacillus cereus* can proliferate, releasing hemolysin BL and nonhemolytic toxins, which are associated with severe gastrointestinal symptoms including nausea, vomiting, and diarrhea [57]. Additionally, *Candida glabrata*, a fungal pathogen found in the respiratory tracts of intubated COVID-19 patients, can lead to life-threatening mucosal infections in immunocompromised individuals, potentially disseminating into the GI tract and causing invasive candidiasis, resulting in morbidity and mortality [58–60]. This underscores the critical need to understand and address the complex interplay between pulmonary microbial imbalances and systemic disease manifestations in COVID-19.

2.2. Gut-brain axis

A growing body of research has highlighted neurological manifestations associated with COVID-19. For instance, a study conducted in Wuhan, China, found that 36.4 % of 214 individuals infected with COVID-19 showed neurological symptoms [61]. Another study reported that approximately 33 % of discharged patients experienced symptoms such as inattention, confusion, or impaired coordination [62]. Additionally, recent research has established a connection between neurological symptoms in COVID-19 patients and gastrointestinal (GI) issues. It was observed that 66 % of individuals with GI symptoms during COVID-19 later developed disorders affecting both the gut and brain [5]. In addition, COVID-19 infections have been found to induce psychological effects such as anxiety, stress, and depression in patients. These mental health issues can worsen gut dysbiosis and inflammation, which is often exacerbated by the release of pro-inflammatory cytokines like IL-6 and TNF-alpha from mast cells, a process influenced by corticotropin-releasing hormone [63].

Studies have linked COVID-19 to gut microbial dysbiosis, including a

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reduction in SCFA-producing bacteria like *Ruminococcaceae*, the genus *Faecalibacterium*, and *Eubacterium hallii* in COVID-19 patients [64,65]. A deficiency in SCFAs, which are linked to brain inflammation, is also a common feature in neuropsychiatric disorders [66]. COVID-19 infections disrupt the blood-intestinal barrier and lead to a decrease in ACE2 expression, a protein highly expressed in the respiratory and gastrointestinal systems [67,68]. Patients reporting gastrointestinal symptoms have been found to have increased levels of IL-6 and fecal calprotectin, markers indicative of gut inflammation and compromised gut integrity [69]. A compromised gut barrier allows bacteria and inflammatory molecules to move into the body, potentially causing sepsis and failure of multiple organs [70]. Furthermore, the downregulation of ACE-2 negatively impacts the tryptophan transporter B^0AT1, affecting the activation of mTOR, the expression of antimicrobial peptides, and ultimately altering the intestinal microbiota [71]. The disruption of the gut barrier in COVID-19 also leads to the movement of microbial metabolites like LPS into the system, causing unusual systemic inflammation [72]. This results in an unregulated rise in proinflammatory cytokines, such as IL-6, TNF-α, CRP, IL-1, and IL-2, potentially impacting the blood-brain barrier's permeability and causing neuroinflammation [29] (Fig. 2).

Lipopolysaccharides (LPS) are linked to neurodegenerative diseases like Alzheimer's and Parkinson's, where they are known to promote the creation and aggregation of Aβ and α-Synuclein deposits in enteric neurons [161]. Additionally, the invasion of the central nervous system (CNS) by SARS-CoV-2 stimulates microglia, leading to sustained neuroinflammation and neurodegeneration [73]. Furthermore, the gut microbiome plays a crucial role in modulating CNS functions by producing various neurotransmitters, including serotonin, histamine, melatonin, acetylcholine, and catecholamines [74]. The loss of smell and taste often experienced by COVID-19 patients may be attributed to an infection in the olfactory system. This occurs as the virus penetrates the brain through the neural-mucosal interface within the olfactory mucosa [75]. Once inside, SARS-CoV-2 can affect the medulla, which is critical for regulating respiratory and cardiovascular functions [76]. Consequently, neurological symptoms observed in COVID-19 patients, such as recurrent headaches, disorientation, cerebrovascular illness, muscular discomfort, ataxia, seizures, and dizziness, could be a result of these infections and alterations [77]. In summary, studies indicate that COVID-19 is linked to neurological and gastrointestinal symptoms in many patients, leading to gut-brain interaction disorders and exacerbating neuroinflammation and neurodegeneration. This relationship is influenced by the virus's impact on the central nervous system and the gut microbiome.

2.3. Gut-heart axis

Patients with pre-existing cardiovascular disease are at a higher risk of experiencing moderate to severe COVID-19. Furthermore, these patients continue to have an increased chance of major cardiovascular complications and higher mortality rates for at least 18 months following infection [78,79]. The link between COVID-19 and heart disease is significantly influenced by gut dysbiosis caused by the infection, highlighting the crucial connection between gut microbiota and cardiovascular health during viral infections.

SARS-CoV-2 infects cells by binding its spike protein to ACE2 receptors, which are key regulators of the renin-angiotensin system [80]. This interaction results in decreased ACE2 expression, decreased TGF-β expression, suppression of the ERK/NFκB pathway and the NLRP3 inflammasome, and inhibition of NADPH oxidase [81,82]. The downregulation of ACE 2 receptors triggers a pro-inflammatory, pro-fibrotic state, producing inflammatory cytokines such as TNF-α, IL-1β, IL-13, and IFN-γ. These cytokines create an environment in the gut that is hostile to some beneficial bacterial species like *Ruminococcus obeum* and the
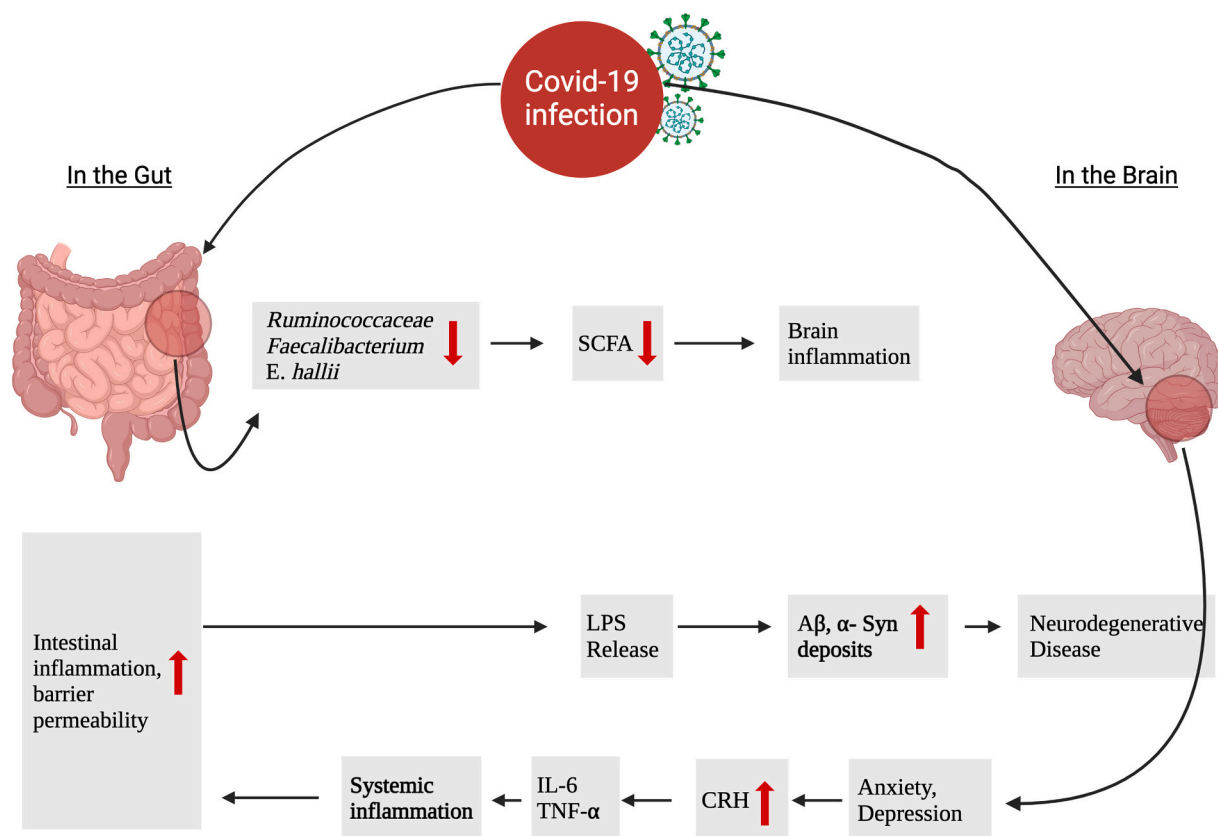

Fig. 2. Dysbiosis of the gut-brain axis in COVID-19 patient. *In individuals infected with SARS-CoV-2, there is a decrease in Ruminococcaceae, facalibacterium and E. halli in the gut. Additionally, hormone levels associated with the brain are altered, marked by an increased level of CRH.*

butyrate producing *Bifidobacterium adolescentis*, while favoring the growth of harmful bacteria such as *Enterobacteriacea* and *Escherichia* ([83,165,30,31]). This inflammation, coupled with changes in gut microbiota composition, increases the risk of heart disease [83].

ACE 2 receptors, widespread throughout the body but highly expressed in enterocytes and the gut lining, facilitate direct COVID-19 infection [84]. This might explain why gastrointestinal symptoms like diarrhea often precede respiratory symptoms in COVID-19 patients [85]. ACE2 plays a vital role in absorbing intestinal amino acid, and its downregulation may result in a deficiency of essential amino acids, particularly tryptophan [86]. Tryptophan and its metabolites, produced by bacterial species like *Streptococcus* and *Clostridium sporogenes*, are key in regulating intestinal inflammation and permeability [87]. Since tryptophan transport is downregulated in COVID-19, this may in turn alter the composition of the gut microbiota, affecting the abundance of bacteria like *Clostridium perfringens* that rely on the host for amino acids synthesis [88].

COVID-19-induced gut dysbiosis significantly reduces the population of butyrate producing bacteria (e.g. *Dorea formicigenerans, Faecalibacterium prausnitzii, Eubacterium rectale, Lachnospiracea bacterium 5_1_63FAA,* and *Eubacterium ventriosum*), which are typically abundant and vital for gut health [30,31,89]. This reduction in butyrate producers leads to decreased butyrate levels, contributing to gut barrier dysfunction and the release of pro-inflammatory bacterial metabolites like LPS, PAGln, and TMAO into the bloodstream, thereby causing systemic inflammation [90,91]. Additionally, butyrate plays a role in downregulating cholesterol absorption, which can reduce the formation of atherosclerotic plaques [92] (Fig. 3).

Individuals with cardiovascular diseases, metabolic syndrome, and obesity often have higher levels of biomarkers like PAGln, LPS, and TMAO, which can lead to systemic inflammation [34]. Additionally, direct viral infection can exacerbate inflammation by targeting ACE-2 receptors in the myocardium. TMAO, in particular, can disrupt iron homeostasis, leading to anemia in patients with cardiovascular disease

[93]. The interaction of PAGln′ with β2-adrenergic receptors in the heart may result in the hyperstimulation of the sympathetic nervous system, a factor contributing to heart failure [94,95]. Furthermore, LPS leakage from the gut barrier can activate inflammasomes, triggering a cascade of events that intensify inflammation [96,97]. Gut dysbiosis can lead to inflammation with significant implications for cardiac health, particularly pronounced in the context of atherosclerosis, a prevalent cardiac condition. Atherosclerosis is associated with systemic inflammation, dyslipidemia, and compromised endothelial barrier function, all of which can be exacerbated by the pathological effects of gut dysbiosis [98,99]. In summary, individuals with pre-existing cardiovascular disease face an elevated risk of severe COVID-19, leading to increased mortality rates and persistent cardiovascular complications, as the virus induces gut dysbiosis, disrupting the balance of beneficial and harmful bacteria and triggering a pro-inflammatory state that contributes to heart disease through mechanisms involving ACE2 downregulation, altered gut microbiota composition, and reduced levels of protective butyrate-producing bacteria.

2.4. Gut-liver axis

While COVID-19 predominantly affects the lungs, it can also lead to elevated levels of alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase [100,101]. The mechanisms behind this liver damage are intricate. One key factor contributing to this complexity is the limited expression of ACE2 receptors in hepatocytes, which suggests that direct viral damage to liver cells is relatively uncommon [102]. This low expression of ACE2 receptors in the liver makes it less likely for the virus to directly harm liver cells. Consequently, understanding the precise reasons behind liver damage in the context of COVID-19 becomes a challenging puzzle to solve, given the relative rarity of direct viral impact on liver cells. Different factors like diet, genes, and the environment can influence the communication between gut microbiota and the liver. Endogenous and exogenous substances are metabolized by the
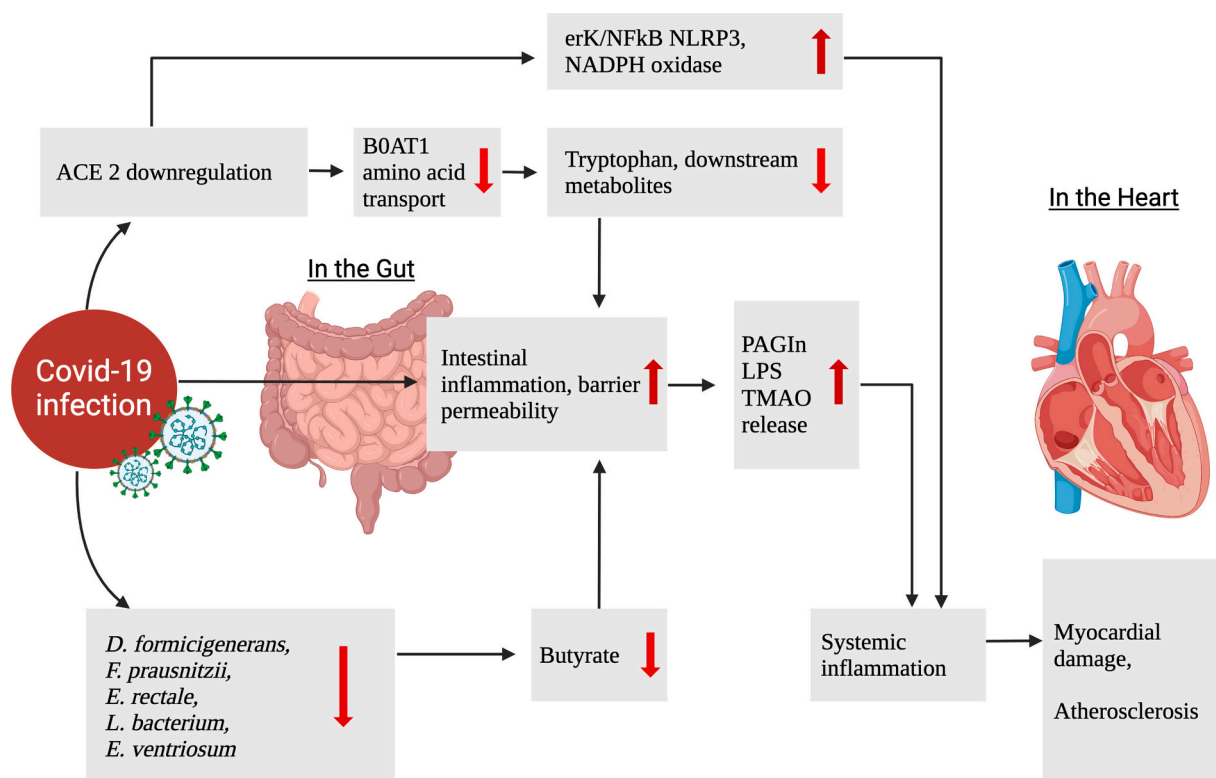

Fig. 3. Dysbiosis of the gut-heart axis in COVID-19 patient. *In individuals infected with SARS-CoV-2, there is a decrease in D. formicigenerans, F. prausnitzii, E. recatle, L. bacterium and E. ventriosum in the gut, accompanied by a downregulation of ACE 2.*

gut microbiome and facilitate communication [103]. In this context, research on animal models suggests that dysbiosis may play a crucial role in liver disease progression, resulting in intestinal inflammation, increased intestinal permeability, and ultimately translocation of microbial products into the bloodstream [104].

Liver damage resulting from COVID-19 infection is marked by changes in gut barrier permeability and tissue damage. These effects are typically identified through elevated calprotectin levels, which may be associated with the growth of opportunistic bacteria like Enterobacteriaceae and *Escherichia coli*. Consequently, this cascade of events leads to systemic inflammation, potentially precipitating conditions such as systemic inflammatory response syndrome (SIRS) [105–107]. Inflammatory mediators such as granulocyte-macrophage colony-stimulating factor (GM-CSF) and IL-6 may play a role in activating CD8+ cytotoxic T cells, TNF-α, and cytokine storms, contributing to hepatocyte apoptosis (Chichoz et al., 2021; [108]). In turn, bacteria and their by-products may translocate to the liver through the hepatic portal vein, interacting with the innate sensors (TLRs and NLRs) of hepatocytes and Kupffer cells, prompting further production of inflammatory cytokines [109]. Additionally, certain opportunistic pathogens, such as *Clostridium* and *Peptostreptococcus*, may further disrupt nitrogen homeostasis by producing high levels of ammonia, leading to hepatocellular metabolic dysfunction and liver injury [110]. The result of this event cascade may be one such mechanism leading to the elevated levels of bilirubin and hepatic enzymes, such as alanine aminotransferase and aspartate aminotransferase, in the blood [111] (Fig. 4).

Liver chemistry abnormalities (LCA) serve as independent indicators of severe COVID-19, especially in individuals with chronic liver disease [112]. Furthermore, the increasing severity of LCA is a robust predictor of early in-hospital mortality among COVID-19 patients [113]. The second mechanism of liver damage in COVID-19 patients involves the depletion of SCFA-producing bacteria, leading to reduced SCFA production, which in turn affects glucose tolerance and contributes to cytokine-mediated inflammatory injury [30,31,114,115]. For example, butyrate inhibits LPS-induced production of nitric oxide and pro-inflammatory cytokine (IL-6, IL-12) release. Therefore, the reduced production of butyrate and other SCFAs contributes to cytokine-mediated inflammatory liver injury [116]. A study conducted on mouse models of immune-mediated liver injury ascertained similar results [117]. Additionally, post-COVID patients show a significant decrease in bile acid and bile salt transporters, suggesting potential bile acid dysregulation with adverse effects on the gut microbiota [118,119]. In addition, liver cirrhosis stands out as a notable risk factor for severe COVID-19, risk marked by a reduced *Bifidobacteriaceae/Enterobacteriaceae* (B/E) ratio [120]. A separate study found lower levels of immunomodulatory microbiota, such as *Bifidobacteria* and *Faecalibacterium prausnitzii*, persisting for up to 30 days after recovering from COVID-19 [32]. These lower microbe levels were associated with the severity of the disease and a weakened immune response [32]. In summary, liver damage in COVID-19 involves intricate mechanisms, including dysbiosis-induced intestinal inflammation, increased permeability, translocation of microbial products, and activation of inflammatory pathways, with liver cirrhosis and altered gut microbiota further exacerbating the severity of the disease.

3. Material and methods

3.1. Search strategy

The reporting of the study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [121]. Literature sources across PubMed, Scopus, and Web of Science were searched for studies published by September 28, 2023. The full and comprehensive search strategy and keyword string is provided in the Supplementary Materials.
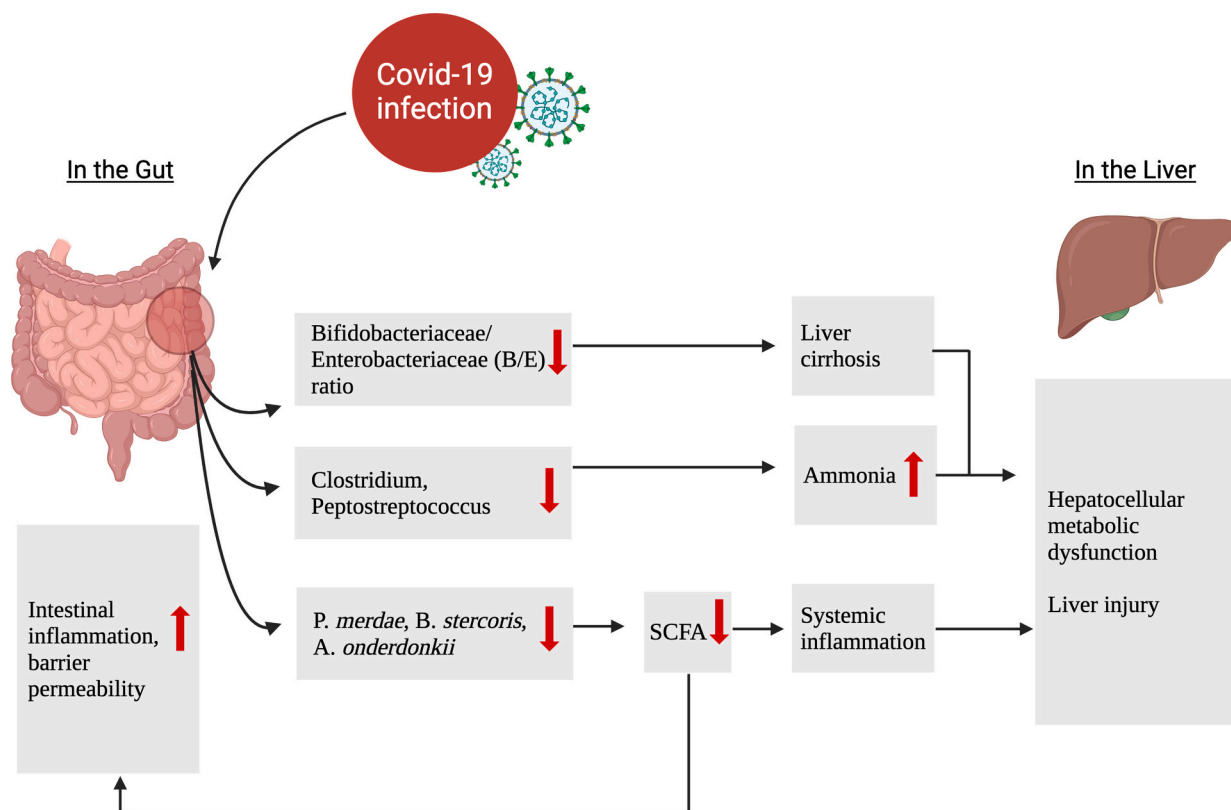

Fig. 4. Dysbiosis of the gut-lung axis in COVID-19 patient. *In the gut of SARS-CoV-2 infected patients, Bifidobacteriacae/Enterobacteriaceae (B/E) ratio, Clostridium, Peptostreptococcus, P. merdae, B. stercoris and A. onderdonkii was decreased which are associated with hepatocellular metabolic dysfunction and liver injury.*

3.2. Inclusion and exclusion criteria

Randomized clinical trials (RCTs) were included to review the effects of probiotics, prebiotics, synbiotics and FMT on COVID-19 patient outcomes. Additionally, we limited our search to publications in English only. No exclusion criteria were applied based on age, sex, ethnicity, region, or publication year. Papers related to other respiratory tract infections, reviews, conference proceedings, abstracts, editorials, animal studies, and non-clinical papers were excluded; additionally, duplicate papers were removed. Title and abstract screening was conducted, which was followed with a full text screening. Any conflicts during either screening stage were resolved through consensus. Additionally, at least two independent authors screened each paper to ensure accuracy and rigor.

All relevant data related to the study, including author names, publication years, and geographical locations, were extracted and organized. Information about the study's design, including the study period, population type, population size, age, BMI, sex ratio, and vaccination status, was also recorded. Finally, the type of nutraceutical administered was recorded, and further details, including the nutraceutical, placebo, dose, delivery method, intervention duration, and biomarkers affected were extracted. We also discuss the implications of the results.

4. Results

4.1. Study characteristics

We initially identified 502 search results for studies investigating the effects of biotics on COVID-19 symptoms and biomarkers. After applying the inclusion criteria, we retained 27 studies originated from various countries, including Spain (3), Italy (6), Mexico (2), China (7), Turkey (1), Iran (1), Pakistan (1), Egypt (1), Belgium (1), Sweden (1), Russia (1), England (1), and Argentina (1) (Fig. 5). The total number of patients across these studies was 3428, with 1827 in the intervention groups and 1601 in the control groups. All individuals were diagnosed with COVID-19. Data regarding the severity of the COVID-19 patients was only reported in 6 of the 27 studies. 2 studies each reported on mild [122,123], moderate [124,125] and severe [100,126,127] cases. 5 of the 27 studies reported death rates. Average mortality rates from these studies range from 0 % to 11 % in the intervention groups, as compared to 3 % to 30 % in the control groups [124,126–129].

The median year of publication was 2022 (Range: 2021–2023). In the intervention groups, the median age was 52 years (IQR 48–62), and the median BMI was 27 (IQR 25–30). The median duration of the intervention was 21 days. Among the interventions, some studies used prebiotics (1), single-species probiotics (5), multi-species probiotics
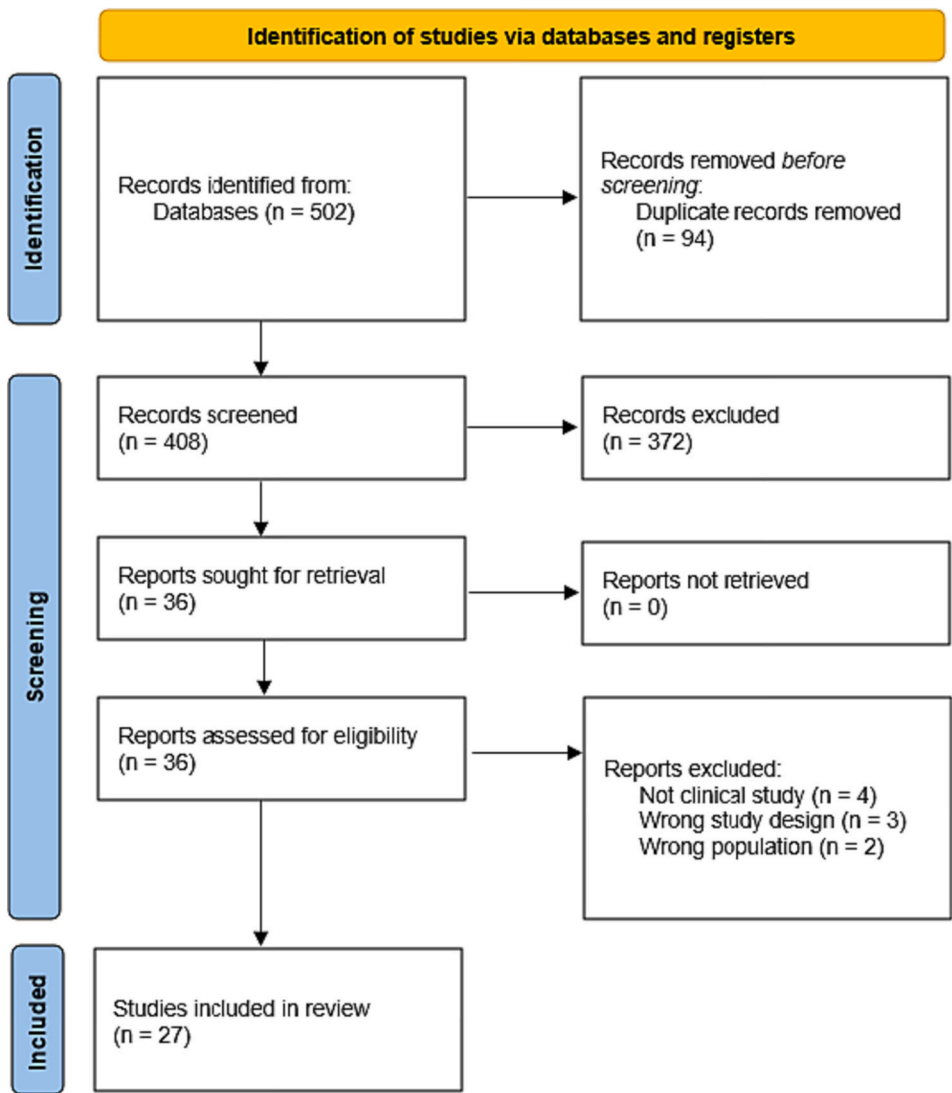

Fig. 5. PRISMA Flowchart of the screening strategy and included studies.

(11), oropharyngeal probiotics (4), synbiotics (5), and FMT (1). The probiotics and synbiotics employed various genera of bacteria and fungi, including *Lactobacillus, Bifidobacterium, Streptococcus, Enterococcus, Pediococcus, Bacillus, Saccharomyces,* and *Kluyveromyces.* Specific bacterial and fungal species administered included *Lactobacillus salivarius, Bifidobacterium animalis, Streptococcus salivarius, Bifidobacterium Bifidum, Saccharomyces boulardii, Streptococcus thermophilus, Bifidobacterium lactis, Lactobacillus acidophilus, Lactobacillus helveticus, Lactobacillus paracasei, Lactobacillus plantarum, Lactobacillus brevis, Pediococcus acidilactici, Bifidobacterium infantis, Dung enterococcus, Bacillus cereus, Bifidobacterium longum, Lactobacillus bulgaricus, Enterococcus faecium, Bacillus subtilis, Kluyveromyces marxianus, Lactobacillus rhamnosus, Lactobacillus casei, Limosilactobacillus reuteri, Bifidobacterium breve* and *Lactobacillus gasseri.* The prebiotics used included in the analyzed studies were quebracho and chestnut tannin, inulin, galactooligosaccharides, fructooligosaccharides, xylooligosaccharides, and resistant dextrin.

Table 1 summarizes the studies investigating the effects on COVID-19 patients following interventions with probiotics, prebiotics, synbiotics, and fecal microbiota transplant.

4.2. Effects of single-strain probiotics

Here, we review recent studies that explore the impact of various probiotics on immune responses, microbiota composition, and overall health outcomes following COVID-19 infection. Among these, the research conducted by Mozota et al.'s studies in 2021 and 2022 involved the use of 9.3 $\log_{10}$ CFU of *L. salivarius* over four months. In their 2022 study, they observed a significant increase in gut microbiota *Lactobacillus* ($p < 0.001$), along with decreases in *Eubacterium halii* ($p < 0.01$) and *Actinobacteriota* ($p < 0.01$). However, no significant differences were found in α and β diversity, nor in the levels of acetate, butyrate, propionate, or their sum [131]. In their 2021 study, Mozota et al. found that nasal samples had significantly lower levels of immune biomarkers such as BAFF/TNFSF13B, IL-12p70, L11, IL32, MMP-1, Osteopontin, and sTNF-R1, but significantly elevated levels of APRIL/TNFSF13, IL-19, IL-35, pentraxin 3 and chitinase 3-like 1. Fecal samples showed increased levels of IL-19, IFN2, MMP-2, Pentraxin 3, sCD163, and IL-35, but reduced levels of APRIL/TNFSF13, BAFF/TNFSF13B, IL32, IL34, gp130/sIL-6Rb, sTNF-R1, and sTNF-R2. Additionally, improvements were noted in the Barthel index, a measure of the functional state assed by ability to perform 10 essential activities of daily life, and the Mini Nutritional Assessment score, which measures nutritional status [130]. In another study, Leal-Martinez et al. administered *Saccharomyces boulardii* at a dosage of 500 mg daily for six days, resulting in a reported overall lower mortality ($p < 0.027$). Additionally, the study found that fewer patients required home oxygen, had fewer days of home oxygen use, and achieved higher blood saturation without supplementary oxygen ($p = 0.030$). There was also a decrease in the administered oxygen flow needed to maintain spO2 > 90 % from baseline to day three ($p = 0.014$). However, while there was a reduction in body weight among fewer participants, this did not reach statistical significance ($p = 0.135$) [129]. In a parallel study, Hegazy et al. administered $1·4 \times 10^9$ CFU of *Bifidum* and observed increased levels of ferritin, C-reactive protein (CRP), and D-dimer. Additionally, this study reported a lower incidence of diarrhea, but a higher risk and severity of SARS-CoV-2 infection [123]. Conversely, the 2023 study by Forsgård et al., which administered $1*10^8$ CFU L. *reuteri* DSM 17938 twice daily for six months, found no statistically significant differences in serum anti-SARS-CoV-2 specific antibody titers compared to probiotics [132]. In summary, the findings from these studies underscore the significant role of probiotics in altering gut microbiota composition, modulating immune responses, and ultimately affecting overall health. Notably, using single-strain probiotics has been linked with reductions in inflammation, shorter disease durations, and lessened severity of symptoms.

4.3. Effects of multi-strain probiotics

Here, we review studies that explore the impact of multi-strain probiotics on health outcomes following COVID-19 infection. Li et al.'s study used 3 capsules: 1) *Bifidobacterium infantis, Lactobacillus acidophilus, Dung enterococcus, Bacillus cereus;* 2) *Bifidobacterium longum, Lactobacillus bulgaricus, Streptococcus thermophiles;* 3) *Enterococcus faecium, Bacillus subtilis* over an average duration of 12.94 days. They observed no significant change in total T lymphocytes, NK cells, B lymphocytes, CD4 + T cells, CD8 + T cells, or the CD4/CD8 ratio, but found higher levels of ESR ($P = 0.049$) and IL-6 ($P = 0.001$) [100]. Ceccarelli et al. conducted a trial with SLAB51 (2.4×10^{12} CFU *Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961) administered three times daily for 23 days, leading to decreased levels of biomarkers albumin, CRP and LDH [126,127].

Gutierrez-Castrellon et al.'s reported reduced serum CRP levels on day 15 (but not on day 30), decreased hsCRP, D-Dimer levels, nasopharyngeal viral load ($P < 0.001$), and higher serum titers of SARS-CoV2-binding IgG and IgM, following treatment with *Lactiplantibacillus plantarum* KABP022, KABP023, KAPB033 and *Pediococcus acidilactici* KABP021 at 2×10^9 CFU [134]. Saviano et al. found lower CRP and fecal calprotectin levels after administering twice a day for 10 day 40×10^9 CFU of Lactibiane Iki®, which includes 6×10^9 CFU of *Bifidobacterium lactis* LA 304, 28×10^9 CFU of *Lactobacillus salivarius* LA 302, and 6×10^9 CFU of *Lactobacillus acidophilus* LA 201 [139]. However, Li et al. noted higher CRP but a lower incidence of cough phlegm. Ceccarelli et al. reported a longer hospital stay ($p = 0.0012$) but a lower death rate. In another study using SLAB51, Ceccarelli et al. found that fewer patients were admitted to the ICU, more experienced increased blood oxygenation levels ($p = 0.002$), with significantly reduced FiO2 ($p = 0.002$), and no deaths were reported [126,127]. Zhang et al. observed fewer hospital days ($p = 0.009$), a shorter duration for viral shedding, and quicker clinical improvement with a 630 mg dosage of *Bifidobacterium, Lactobacillus,* and *Enterococcus* [125]. Conversely, Li et al. reported longer inpatient stays and a lower discharge rate, with similar severity of pneumonia. Additionally, they observed no significant change in lymphocytes, PLT, WBCs, neutrophils, monocytes, D-dimer, hospitalization length, ICU admissions, bloodstream infections, lung superinfections, or fungal infections. D'Ettorre et al. administered SLAB51 for 14 days and observed a reduced mortality rate [135].

Navarro-Lopez et al. observed an improvement in global symptoms, particularly gastrointestinal, after administering 1×10^9 CFU of *Kluyveromyces marxianus* B0399 and 1×0^8 CFU of *Lactobacillus rhamnosus* CECT 30579 for 30 days. In this study, none of the patients in the intervention group experienced abdominal pain, pyrosis or musculoskeletal pain [133]. Zhang et al. reported the elimination of gastrointestinal complaints without adverse effects. Gutierrez-Castrellon et al. also observed fewer days of cough, headache, myalgia, dyspnea, nausea, diarrhea, abdominal pain, loose stools in intervention patients, with more experiencing full remission ($p < 0.001$). This study also noted reduced median time to symptomatic clearance, decreased radiographic grading in patients with lung infiltrates ($p < 0.001$), and improvement in other COVID-19 symptoms, but no significant change in α or β diversity. Similarly, d'Ettorre et al. reported a significantly higher percentage of patients cured of diarrhea, fever, asthenia, headache, myalgia, and dyspnea ($p < 0.001$), along with a lower probability of developing respiratory failure requiring resuscitation ($p < 0.001$) and less need for ICU mechanical ventilation. Navarro-Lopez et al. observed fewer non-digestive symptoms in patients. Zhang et al. and Gutierrez-Castrellon et al. both reported fewer fever days. Santinelli et al. used SLAB51 for a median duration of 23 days and showed decreased chronic fatigue [136]. The study also saw substantially lower fatigue assessment scores ($p = 0.02$) and increase in levels of arginine, asparagine and lactate

Table 1

Studies investigating effects on COVID-19 patients following intervention with probiotics, prebiotics, synbiotics and fecal microbiota transplant. Statistically significant mortality benefits have been highlighted in bold.

Study design and country	Participant* demographics Sample size and sex (n, F/M) Age (mean ± SD or median [IQR]) BMI (mean ± SD or median [IQR])		Interventional nutraceutical administered	Intervention duration	Effects$^{\Phi}$	References
	Control/placebo	Intervention				
Probiotics (single species)						
RCT (Mexico)	n = 33 (22 M/11 F) 53.9 ± 10.3 29.35 ± 3.89	n = 39 (24 M/15 F) 51.5 ± 11.4 29.98 ± 4.07	*Saccharomyces boulardii* 500 mg orally	6 days	↓ **Death rate (1/40 vs. 7/40) (I, B).** ↓ Oxygen flow needed to maintain SpO2 > 90 % from baseline to day three (6 ± 3.2 L to 4.5 ± 3.5 L vs. 5.9 ± 3.8 L to 6 ± 4.4 L) (I, B). ↑ Saturation without supplementary oxygen (92.08 ± 2.5 vs. 90.39 ± 3.4) (I, B, 40d). ↓ Patients requiring home oxygen use (66.7 % vs. 85.2 %) (I, B). ↓ Days of home oxygen use (43.8 ± 16.2 vs. 57.6 ± 24.6) (I, B) ↓ Patients with post-COVID syndrome (23.5 % vs. 37.5 %) (I, B). ↓ Decrease in body weight (44.4 % vs. 72.2 %) (I, B).	[129]
Longitudinal (Egypt)		n = 122 mild (50 M/72 F) 37 29 ± 5.8 n = 78 Moderate (44 M/ 34 F) 45 31.1 ± 6.1	Probiotic yoghurt containing *Bifidum.* 1·4 × 10^9 CFU (in 135 g) Fiber rich prebiotics	Never to daily	↓ Diarrhea. ↑ Ferritin, CRP, D-dimer. ↑ Risk of severe SARS-CoV-2 infection. ↑ Risk of severity.	[123]
Open-label single group (Spain)		n = 22 (11 M/ 11F) 84.95 ± 3.54 24.82 ± 1.94	Yoghurt containing *Ligilactobacillus salivarius* MP101 9.3 log$_{10}$ CFU per unit	4 months	↓ BAFF/TNFSF13B, IL-12p70, L11, IL32, MMP-1, Osteopontin, sTNF-R1 in nasal samples. ↓ APRIL/TNFSF13, BAFF/TNFSF13B, IL32, IL34, gp130/sIL-6Rb, sTNF-R1, sTNF-R2 in fecal samples. ↑ APRIL/TNFSF13, IL-19, IL-35, pentraxin 3, chitinase 3-like 1 in nasal samples. ↑ IL-19, IFN2, MMP-2, Pentraxin 3, sCD163, IL-35 in fecal samples. ↑ Barthel index, Mini Nutritional Assessment score.	[130]
Open-label single group (Spain)		n = 15 (7 M/8 F) 84.73 ± 8.87 24.61 ± 3.97	*L. salivarius* CECT 30632 9.3 log$_{10}$ CFU	4 months	↓ *Eubacterium halii, Actinobacteriota, Streptococcus.* ↑ *Lactobacillus (L.salivarius).* α & β diversity not significantly different. No statistically significant difference in the change of levels of acetate, butyrate, propionate, or their sum.	[131]
TB, PC, RCT (Sweden)	Intention to treat: n = 41 (8 M/33 F) 48 (29–60) BMI (23 normal, 14 overweight, 4 obese) Per-protocol: n = 34 (5 M/29 F) 49 (29–60) BMI (19 normal, 11 overweight, 4 obese)	Intention to treat: n = 48 (7 M/41 F) 51.5 (21–60) BMI (28 normal, 18 overweight, 2 obese) Per-protocol: n = 43 (5 M/38 F) 52 (21–60) BMI (25 normal, 16 overweight, 2 obese)	*L. reuteri* DSM 17938 (1*10^8 CFU) + 10 µg of vitamin D3 (Protectis, BioGaia, Lund, Sweden) orally	Twice daily for 6 months	No statistically significant difference in serum anti-SARS-CoV-2 specific antibody titers and probiotic use.	[132]
Probiotics (multi-species)						
RCT (Spain)	n = 15 (5 M/10 F) 46.33 ± 10.91 BMI NR	n = 24 (13 M/11 F) 48.88 ± 12.35 BMI NR	*Kluyveromyces marxianus* B0399 (1 × 10^9 CFU) *Lactobacillus rhamnosus* CECT 30579 (1 × 10^9 CFU)	30 days	↑ Patients without pyrosis (100 % vs 33.3 %) (I, B). ↑ Patients without abdominal pain (100 % vs 62.5 %) (I, B). ↑ Patients without non-digestive symptoms (41.7 %, vs 13 %) (I, B). ↑ Patients with improved digestive	[133]

Table 1 (*continued*)

Study design and country	Participant* demographics Sample size and sex (n, F/M) Age (mean ± SD or median [IQR]) BMI (mean ± SD or median [IQR])		Interventional nutraceutical administered	Intervention duration	Effects$^\Phi$	References
	Control/placebo	Intervention				
					symptoms (88 % vs. 65 %) (I,B). ↑ Patients with improvement of global symptoms (digestive and non-digestive) (88.6 % vs. 70.8 %) (I, B). ↑ Complete resolution of symptoms (10/24 (41.7 %) vs. 2/15 (13 %)). ↑ Patients with improved musculoskeletal pain (100 % vs. 69.2 %).	
QB, R, CT (Mexico)	n = 146 (69 M/ 77 F) 39 (27–49) 29.4 (27.1–32.9)	n = 147 (67 M/ 80 F) 34 (26–45) 27.5 (23.3–31.8)	*Lactiplantibacillus plantarum* KABP022, KABP023, KAPB033; *Pediococcus acidilactici* KABP021 2 × 10^9 CFU	30 days	↓ At least 1 adverse event (27.3 % vs. 42.0 %) (I, B). ↓ Days of fever, cough, headache, myalgia, dyspnea, nausea, diarrhea, abdominal pain, loose stools. ↓ Nasopharyngeal viral load (15d, 30d). ↓ Lower radiographic scoring in subjects with lung infiltrates at baseline (15d, 30d). ↓ hsCRP, D-Dimer (15d, not on 30d). ↓ Median time to symptomatic clearance (5d shorter). ↑ Complete remission (53.1 % vs. 28.1 %) (I, B). ↑ Serum titers of SARS-CoV2-binding IgG and IgM (15d, 30d). No difference in α or β diversity.	[134]
Retrospective (China)	n = 188 (83 M/ 105 F) 60.20 ± 12.67 BMI NR	n = 123 (67 M/ 56 F) 62.019 ± 10.88 BMI NR	*Bifidobacterium infantis, Lactobacillus acidophilus, Dung enterococcus, Bacillus cereus*-oral combined tablets *Bifidobacterium longum, Lactobacillus bulgaricus, Streptococcus thermophiles*- Live Combined Tablets *Enterococcus faecium, Bacillus subtilis*- Live Combined Coated Capsules	Mean 12.94 days	↓ Cough phlegm. ↓ Discharge rate (75.61 % vs. 78.19 %) (I, B). ↑ CRP, IL-6, ESR. ↑ Total T lymphocytes, NK cells, B lymphocytes. ↑ Median inpatient stay (17 vs. 32 days) (I, B). ↑ Mean virus clearance days (17 vs 20 days) (I, B). CD4+/CD8 + ratio remained within the normal range. No significant difference in levels of IL-6, CRP, total T lymphocytes, NK cells, B lymphocytes, CD4 + T cells, CD8 + T cells, CD4/CD8 ratio.	[100]
Retrospective (China)	n = 150 (16 M/ 12 F) 50 (37–62) 23.3 (21.4–25.6)	n = 150 (16 M/ 12 F) 49 (35–60) 23.2 (21.3–25.3)	Live combined *Bifidobacterium, Lactobacillus*, and *Enterococcus* 630 mg	Time from probiotic initiation to viral shedding/death	↓ Time to improvement (18.0 (14.0–28.0) vs. 21.0 (17.0–29.0)) (I, B). ↓ Hospitalization length (19.0 (15.0–25.0) vs. 22.0 (16.0–31.0)) (I, B). ↓ Duration of viral shedding (15.0 (10.0–20.0) vs. 18.0 (13.0–24.0) (I, B)). ↓ Duration of fever days (6.0 (3.0–9.0) vs 7.0 (4.0–10.0)) (I, B). GI symptoms improved. No side effects.	[125]
RCT (Italy)	n = 28 (16 M/12 F) 60.5 ± 14.2 23.4 ± 3.5	n = 42 (25 M/17 F) 59 ± 14.4 24.7 ± 3.4	*Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961 2400 billion bacteria	14 days	↓ Diarrhea, fever, asthenia, headache, myalgia, and dyspnea. ↓ Risk of evolving into respiratory failure requiring resuscitation support. ↓ ICU admission rates for mechanical ventilation or death (0/28 vs 4/42) (I, B).	[135]
Retrospective (Italy)	n = 112 (64 M/ 48 F) 64 ± 16 BMI NR	n = 88 (49 M/39 F) 62 ± 15 BMI NR	*Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243,	23 days	↓ Albumin <32 (mg/dl) detected (7 % vs. 20 %) (I, B) ↓ CRP (mg/L) (63,540 (22,375–160,770) to 34,900 (12,375–113,970)) (I) ↓ LDH (U/L) (272.0 (211–379) vs. 310	[126,127]

Table 1 (*continued*)

Study design and country	Participant* demographics Sample size and sex (n, F/M) Age (mean ± SD or median [IQR]) BMI (mean ± SD or median [IQR])		Interventional nutraceutical administered	Intervention duration	Effects$^\Phi$	References
	Control/placebo	Intervention				
			Lactobacillus plantarum DSM 32244, and *Lactobacillus brevis* DSM 27961 2400 billion bacteria		(242.3–419.3)) (I, B) ↓ **Death (11 % vs 30 %) (I, B).** ↑ Hospital stay (23 ± 14 vs. 18 ± 13) (I, B). Severity of pneumonia remained similar. No significant change in lymphocytes, platelets (PLT), white blood cells (WBCs), neutrophils, monocytes, D-dimer, length of hospitalization, ICU admissions, bloodstream infections, lung superinfections, or fungal infections.	
Prospective (Italy)	n = 29 (25 M/4 F) 70 (60–77) 20 (18.8–22)	n = 33 (18 M/15 F) 61 (51–74.3) 20 (20–22)	*Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961 2400 billion bacteria		↑ pO2/FiO2 ratio (6 h), pO2 (6 h). ↑ O2Hb, SaO2 (6 h). ↑ Blood oxygenation. ↓ FiO2 (6 h). ↓ ICU (1/40 vs. 4/29) (I, B). ↓ **Death (0 vs. 1) (I, B).**	[126,127]
RCT (Italy)	n = 34 (23 M/11 F) 62 (52–63) BMI NR	n = 24 (14 M/10 F) 64 (56–69) BMI NR	*Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961 2400 billion bacteria	Median 23 days (19–38 days)	↑ Arginine, Asparagine, Lactate. ↓ Fatigue (41.7 % (10/24) vs. 91 % (31/34)). ↓ Extreme (4.2 (1/24) vs. 29.4 (10/34)). ↓ 3-Hydroxyisobutirate. ↓ Fatigue assessment scores (24 (22.5–26) vs. 34 (31.5–38)) (I, B). No significant differences in clinical variables (discharge).	[136]
RCT (Italy)	n = 21 (15 M/6 F) 66 (60–68) BMI NR	n = 15 (5 M/10 F) 64 (54–73) BMI NR	*Streptococcus thermophilus* DSM 32245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lactobacillus paracasei* DSM 32243, *Lactobacillus plantarum* DSM 32244, and *Lactobacillus brevis* DSM 27961 2400 billion bacteria		↓ Fatal events (1/21(4.8 %), vs. 3/14 (21.4 %)) (I, B) (30d) ↓ Need of CPAP (4/21, 19 % vs. 12/14, 85.7 %)(I, B) (7d) ↑ pO2 (3d) ↑ P/F ↑ Platelets counts (3d) Homogeneous for SaO2 (3d) No difference in CaO2 (3d)	[137]
Open-label, RCT (Russia)	n = 101 (48 M/53 F) 64 (54–70) 31.2 (27.1–33.5)	n = 99 (44 M/55 F) 65 (59–71) 30.5 (27.4–35.3)	Florasan-D containing ~ 10^9 CFU of *Lacticaseibacillus rhamnosus* PDV 1705, ~10^9 CFU of *Bifidobacterium bifidum* PDV 0903, ~10^9 CFU of *Bifidobacterium longum* subsp. *infantis* PDV 1911, ~10^9 CFU of *Bifidobacterium longum* subsp. *longum* PDV 2301 orally	No >14 days	No significant differences were observed in the survival rates, total duration of disease, length of hospital stay, incidence of intensive care unit admission, need for mechanical ventilation or oxygen support, volume of the affected lungs, serum levels of CRP, erythrocyte sedimentation rate, ferritin, fibrinogen, WBC, neutrophils, lymphocytes, creatinine, ALT, AST, albumin, and total bilirubin.	[138]
CT	n = 40 (23 M/17 F) 60.1 ± 15.2 BMI NR	n = 40 (21 M/19 F) 59.2 ± 17.8 BMI NR	40×10^9 Lactibiane Iki® containing 6×10^9 *Bifidobacterium lactis* LA 304, 28×10^9 *Lactobacillus salivarius* LA 302, and 6×10^9 *Lactobacillus acidophilus* LA 201	Twice a day for 10 days	↓ Mean fecal calprotectin (Days 3–5: 191.8 vs. 404.04) (I, B); (Days 7–10: 124.9 vs. 339.0) (I,B). ↓ CRP levels (Days 3–5: 18 vs. 27) (I, B); (Days 7–10: 5 vs. 9) (I,B).	[139]
Oropharyngeal probiotics						
RCT (China)	n = 95 (26 M/69 F) 35.74 ± 8.88 BMI NR	n = 98 (30 M/68 F) 36.13 ± 8.62 BMI NR	*S. thermophilus* ENT-K12 oral lozenges No <1 billion CFU		↓ Number of infections (8 vs. 22) (I, B). ↓ Incidence of respiratory tract infections (reduced by 64.8 %). ↓ Key symptoms such as sore throat (reduced by 61.3 %) low fever (reduced by 80.6 %). ↓ Days experiencing respiratory tract infection symptoms (23 days (0.23 days/person) vs. 100 days (1.05 days/person)) (I, B). ↓ Average duration of infection episodes (2.88 days/episode vs. 4.67	[140]

Table 1 (*continued*)

Study design and country	Participant* demographics Sample size and sex (n, F/M) Age (mean ± SD or median [IQR]) BMI (mean ± SD or median [IQR])		Interventional nutraceutical administered	Intervention duration	Effects^Φ	References
	Control/placebo	Intervention				
					days/episode, a reduction of 38 %) (I, B).	
R, CT (Pakistan)	n = 25 (16 M/9 F) 51.3 ± 16.0 BMI NR	n = 25 (13 M/12 F) 45.8 ± 14.6 BMI NR	*S. salivarius* K12 oral-dissolving tablet >1 × 10⁹ CFU	14 days	↓ Requirement supplementary oxygen (8 vs. 17) (I, B). **↓ Death (3 % vs. 8 %) (I, B).** ↓ Ferritin. No statistical difference in CRP, D-Dimer, LDH, oxygen saturation, or fever.	[128]
RCT (Turkey)	n = 23 (sex NS) age NS BMI NR	n = 20 (11 M/9 F) 53.55 BMI NR	*Bifidobacterium* BB-12 dissolved in water 1 trillion CFU	3 days	**↓ Death (5 % vs. 20.83 %) (I, B).** ↓ Mean hospital stay (7.6 vs. 13.6 days) (I, B). ↓ IL-6 (6.2 vs. 33.6) (I, B).	[124]
DB, PC, RCT (Belgium)	n = 27 (22 M/5 F) 43 ± 12 26.1 ± 5.5	n = 33 (26 M/7 F) 42 ± 12 BMI NR	*Lacticaseibacillus casei* AMBR2, *Lacticaseibacillus rhamnosus* GG, *Lactiplantibacillus plantarum* WCFS1 throat spray 9.5 × 10⁸ CFU	21 days	↓ Tested positive (2/30 (6.7 %) vs. 7/27 (26 %)). ↓ Acute symptom score. ↓ *Dolosigranulum* ASV1 (*D. pigrum*) (effect size of −1.99), *Streptococcus* ASV7 (*S. gordonii*) (effect size of −5.8), *Streptococcus* ASV6 (*S. crispatus*, *S. oligofermentans*, and *S. sinensis*) (effect size of −3.3). ↑ Mean relative abundance of *L. casei* ASV, *L. plantarum* ASV, *L. rhamnosus* ASV (1.6 %, 1.3 %,0.5 % vs. <0.01 %, <0.01 %, <0.01 %) (I, B) ↑ *Moraxella* ASV4 (*M. lacunata*) (effect size of 0.95), *Rothia* ASV14 (*R. amarae*) (effect size of 4.86), several commensal *Streptococcus* ASVs (*S. thermophilus*, *S. rubneri*, and *S. sanguinis*, among others) No statistically significant decrease in symptoms.	[122]
Prebiotics						
DB, RCT (Argentina)	n = 61 (21 M/40 F) 55 ± 14 29.32 (27.10–33.18)	n = 58 (26 M/32 F) 55 ± 16 30.30 (27.89–34.89)	Capsules of 240 mg of quebracho and chestnut tannin extract blend +0.72 µg B12 vitamin	14 days	↑ *Enterococcus* (LDA score 3.095), *Allisonella* (LDA score 2.733), *Burkholderiaceae* (14d). ↓ *Lachnospiraceae* (LDA score 2.676). ↓ MIP-1α (−0.21) (I) (14d). ↓ TNF-α (−6.99 vs. -1.99) (I, B). ↓ IL-1β (−0.21 vs. -0.04) (I, B). No statistically significant difference in IL-1rα IL-2 IL-4 IL-5 IL-6 IL-7 IL-8 IL-9 IL-10 IL-12(p70) IL-13 IL-15 IL-17, Eotaxin, FGF ba1c, G-CSF, GM-CSF, IFN-g, IP-10, MCP-1(MCAF), MIP-1β, PDGF-ββ, RANTES, and VEGF.	[141]
Synbiotics (multi-species)						
Longitudinal (China)	n = 10 (5 M/5 F) 49.2 (37–61) BMI NR	n = 22 during infection (12 M/10 F) 53.1 (41–62) n = 20 after viral clearance (9 M/11 F) 48.5 (35–61) BMI NR	2 × 10¹¹ CFU of 3 lyophilized *Bifidobacteria*, 3 prebiotics (galactooligosaccharides, xylooligosaccharide, resistant dextrin)	28 days	↓ Number and relative abundance of antibiotic resistance genes (ARGs) (12 weeks). ↓ Reduced resistome (2 weeks), with no rebound observed (12 weeks).	[142]
Longitudinal (China)	n = 30 (9 M/21 F) 46.5 (29.5–56) BMI NR	n = 25 (14 M/11 F) 50 (39–59) BMI NR	100 billion CFU of 3 lyophilized *Bifidobacteria*, 3 prebiotics (galactooligosaccharides, xylooligosaccharide, resistant dextrin)	28 days	↓ IL-18, CXCL-10, MIG, IL-6, MCP-1, M-CSF, TNF-α, IL-1RA (5w). ↓ *E. coli* in Proteobacteria, *Bacteroides* spp. in Bacteroidetes (5w). ↓ SARS-CoV-2 viral load. ↑ Number of patients developing anti-SARS-CoV-2 antibodies (16 days). ↑ Relative abundance in fecal samples of probiotic species contained in synbiotics. ↑ *Actinobacteria* and *Firmicutes* (*Bifidobacterium* spp. (*Bifidobacterium*	[143]

Table 1 (*continued*)

Study design and country	Participant* demographics Sample size and sex (n, F/M) Age (mean ± SD or median [IQR]) BMI (mean ± SD or median [IQR])		Interventional nutraceutical administered	Intervention duration	Effects$^\Phi$	References
	Control/placebo	Intervention				
					adolescentis), *Eubacterium* spp., *Faecalibacterium prausnitzii*) (5w). ↑ Pathways related to ʟ-lysine biosynthesis, 5-aminoimidazole ribonucleotide biosynthesis, and pyruvate fermentation (5 weeks).	
DB, PC, RCT (China)	$n = 229$ (120 M/ 109 F) 67.6 ± 8.0 BMI NR	$n = 224$ (106 M/ 118 F) 67.4 ± 8.3 BMI NR	20 billion CFU SIM01 (3 lyophilized *Bifidobacteria* and 3 prebiotics (galactooligosaccharides, xylooligosaccharide, and resistant dextrin)) orally	3 months	↓ Percentage of patients experiencing adverse effects. At 30 days: 2.9 % (5/6 had GI issues and 1/6 had dermatitis) vs. 12.6 % (14/25 had GI issues, 5 had rashes and allergic reactions, and 6 had infections including 1 with an infected liver cyst, 4 with infected wounds, and 1 with septic shock) (I, B). At 90 days: 0 % vs. 3.1 % (2/5 had GI issues, 2 had wound infections, and 1 had COVID-19) (I, B). ↓ Pathogenic bacterial species enriched in COVID or long COVID. ↑ *Bifidobacterium adolescentis*. ↓ *Bacteroides nordii*.	[144]
DB, R, CT (England)	$n = 21$ (sex NR) Age NR BMI NR	$n = 126$ (sex NR) Age NR BMI NR	*Lactobacillus* probiotic and inulin prebiotic	Twice daily for 30 days	↓ Cough score (1.4 ± 0.6 to 0.6 ± 1.4). ↑ SWS (from 24.5 ± 8.3 to 28. ± 7.2). ↓ Fatigue score (from 21.2 ± 5.7 to 16.5 ± 6.7).	[145]
DB, PC, RCT (Iran)	$n = 38$ (20 M/18 F) 51.54 ± 15.26 BMI NR	$n = 38$ (23 M/15 F) 52.08 ± 16.08 BMI NR	Fructooligosaccharides prebiotic and 10^9 CFU *Lactobacillus (L.) rhamnosus, L. helveticus, L. casei, Bifidobacterium (B.) lactis, L. acidophilus, B. breve, L. bulgaricus, B. longum, L. plantarum, B. bifidum, L. gasseri,* and *Streptococcus (S.) thermophilus* orally	Twice daily for 14 days	↓ IL-6 (12.24 ± 14.34 vs. 88.67 ± 247) (I, B). ↓ ESR, CRP (14d). ↓ WBC. No statistical differences in the duration of clinical symptoms, hospital stay, respiratory rate, level of SpO2 with or without oxygen therapy, AST, ALT, ALP, BUN, creatinine, platelets, hemoglobin, PMN, or lymphocytes (14d). Significant differences were observed in level of SPO2 with or without oxygen therapy during the follow-up period.	[146]
Fecal microbiota transplant (FMT) Prospective (China)		$n = 11$ (6 M/55 F) 49.82 BMI NR	Oral capsule	4 days	↓ Total B cells, naïve B cells. ↓ *Proteobacteria* (2.5 %). ↑ Naïve B cells, immature regulatory B cells, non-switched B cells, double-positive T cells. ↑ *Actinobacteria, Bifidobacterium, Faecalibacterium, Collinsella*. Improved GI symptoms such as constipation, diarrhea, stomach discomfort, gastralgia, and acid reflux. Improved psychological problems such as weariness, sadness, and sleeplessness. Pre-FMT: *Bacteroides* (28.3 %), *Prevotella* (13.0 %), *Faecalibacterium* (6.5 %), *Lachnospiraceae* (6.2 %), *Phascolarctobacterium* (5.7 %). Apost-FMT: *Bacteroides* (31.1 %), *Faecalibacterium* (11.7 %), *Prevotella* (6.6 %), *Bifidobacterium* (10.4 %), *Collinsella* (4.5 %). No significant change detected in erythrocyte count, hemoglobin, platelets, ALT, AST, AST/ALT, albumin, globulin, A/G, blood urea nitrogen, serum creatinine, T cell	[147]

Table 1 (*continued*)

Study design and country	Participant* demographics Sample size and sex (n, F/M) Age (mean ± SD or median [IQR]) BMI (mean ± SD or median [IQR])		Interventional nutraceutical administered	Intervention duration	Effects$^\Phi$	References
	Control/placebo	Intervention				
					count, helper T cells, Killer T cells, Th to Tc ratio, γδT cells, NK cells, Immature NK cells, mature NK cells, immature/mature NK cells	

* All participants are COVID19-diagnosed patients, unless otherwise stated. Φ Order of markers compared = those of intervention (I) group first, control (C) or baseline (B) second. NS, not specified; NR, not reported; spp., species; DB, double-blinded; TB, triple-blinded; QB, quadruple-blinded; R, randomized; RCT, randomized controlled trial; PC, placebo-controlled; CT, clinical trial.

while decrease in 3-Hydroxyisobutirate. The study however showed no significant difference in clinical variables. Trinchieri et al., using SLAB 51, found higher pO2 and platelet count, fewer fatal events, and reduced need for continuous positive airway pressure (CPAP) in patients. The study also showed that SaO2 and CaO2 were not significantly different [137]. However, Ceccarelli et al. reported decreased ICU admittance and deaths, and significantly increased O2Hb and SaO2. Ivashkin et al., which administered 10^9 CFU each of *Lacticaseibacillus rhamnosus* PDV 1705, 10^9 CFU of *Bifidobacterium bifidum* PDV 0903, 10^9 CFU of *Bifidobacterium longum* subsp. *infantis* PDV 1911 and 10^9 CFU of *Bifidobacterium longum* subsp. *longum* PDV 2301 reported no significant differences in survival rates, total duration of disease, length of hospital stay, incidence of ICU admission, need for mechanical ventilation or oxygen support, volume of affected lungs, serum levels of CRP, erythrocyte sedimentation rate, ferritin, fibrinogen, WBC, neutrophils, lymphocytes, creatinine, ALT, AST, albumin, and total bilirubin [138]. In summary, the findings from these studies suggest that multi-strain probiotic therapies can play a crucial role in mitigating gastrointestinal discomfort, enhancing immune responses, and improving respiratory conditions in individuals recovering from COVID-19. These findings suggest a consistent pattern of benefit across various health parameters, including symptom remission, reduction in inflammatory biomarkers, and improved respiratory function, offering a promising adjunct treatment strategy for managing the complexities of post-COVID-19 recovery.

4.4. Effect of oropharyngeal probiotics

Here, we review studies that explore the impact of oropharyngeal probiotics on health outcomes following COVID-19 infection. DiPierro et al. administered 1×10^9 CFU of *S. salivarius* K12 for 14 days to modulate the oral microbiota of hospitalized COVID-19 patients. They observed a reduction in overall mortality and a fewer patients requiring supplementary oxygen in the intervention group, though these results were not statistically significant. Additionally, they reported a reduction in ferritin levels, but they found no statistical differences in CRP, D-Dimer, LDH, oxygen saturation or fever levels [128]. In a parallel study, Wang et al. administered 1×10^9 CFU of *S. thermophilus* ENT-K12, which resulted in fewer infections and a reduced incidence of respiratory tract infections ($p < 0.005$). This trial also demonstrated a decrease in the incidence of symptoms like fever and sore throat ($p < 0.1$), as well as a reduction in the duration of respiratory tract infection symptoms ($p < 0.005$) [140]. In another study, Bozkurt et al. administered Bifidobacterium BB-12 for 3 days and reported a decrease in the death rate. Additionally, hospital stays were shorter, and IL-6 levels were reduced [124]. In a 3-week trial, De Boeck et al. administered 9.5×10^8 CFU of *Lactobacilli*. Following the experiment, fewer patients remained positive for the virus ($P = 0.07$). Although there was no statistically significant difference in overall symptoms, they reported a significant difference in the acute symptom score related to the *Lactobacilli* used. The intervention group showed a positive association with *Moraxella* ASV4 (*M. lacunata*), *Rothia* ASV14 (*R. amarae*), and several commensal

Streptococcus ASVs (e.g. *S. thermophilus*, *S. rubneri*, and *S. sanguinis*). Conversely, they found a negative correlation between the intervention group and *Dolosigranulum* ASV1 (*D. pigrum*), *Streptococcus* ASV7, and *Streptococcus* ASV6 (*S. crispatus*, *S. oligofermentans*, and *S. sinensis*) [122]. Overall, our analyses suggest that using oropharyngeal probiotics in COVID-19 patients presents a complex yet promising field. Although not all results reached statistical significance, the studies indicate potential benefits, including reduced mortality, lower infection rates, and enhanced symptom scores.

4.5. Effect of prebiotics

Few studies have investigated the effect of prebiotics on COVID-19 gut-dysbiosis. Molino et al. administered a blend of 240 mg of quebracho and chestnut tannin extracts to patients infected with COVID-19. After 14 days of treatment, they found an increase in *Enterococcus*, *Allisonella*, and *Burkholderiaceae* levels in the patient's fecal samples, while Lachnospiraceae were present in lower quantities. Additionally, there was a decrease in the levels of MIP-1 ($p < 0.03$), TNF-α ($p < 0.06$), and IL-1β ($p < 0.09$). However, they found no statistically significant differences in the levels of a wide array of other cytokines and growth factors, including IL-1rα, IL-2, IL-4 through IL-10, IL-12(p70), IL-13, IL-15, IL-17, Eotaxin, FGF basic, G-CSF, GM-CSF, IFN-γ, IP-10, MCP-1 (MCAF), MIP-1β, PDGF-ββ, RANTES, and VEGF [141]. Thus although promising, more studies are required before effective adoption of prebiotics against COVID-19.

4.6. Effect of synbiotics

Many studies have investigated the effects of synbiotic mixtures on COVID-19 patients. Zhang et al. demonstrated that a 28-day administration of 10^{11} CFU, comprising a blend of three lyophilized *Bifidobacteria* strains and three prebiotics (galactooligosaccharides, xylooligosaccharide, resistant dextrin) significantly reduced opportunistic stomach infections by pathogens like *E. coli* and *Bacteroides* spp. Moreover, this treatment led to an increase in beneficial commensal bacteria abundance, specifically *Bifidobacterium adolescentis*, and in the Actinobacteria and Firmicutes phyla,. They also reported significant reductions in inflammatory markers such as IL-6 ($p < 0.0005$), MCP-1 ($p < 0.014$), M-CSF ($p < 0.0018$), TNF-α ($p < 0.0005$), and IL-1RA ($p < 0.0008$), IL-18, CXCL-10 and MIG [143]. In a parallel study, Vaezi et al. administered fructooligosaccharides prebiotic and 10^9 CFU of *Lactobacillus (L.) rhamnosus, L. helveticus, L. casei, Bifidobacterium (B.) lactis, L. acidophilus, B. breve, L. bulgaricus, L. longum, L. plantarum, B. bifidum, L. gasseri,* and *Streptococcus (S.) thermophilus* twice daily for 14 days. Similar to Zhang et al., this regimen also resulted in lower levels of IL-6. Furthermore, they found a reduction in ESR, CRP and WBC levels. However, they found no statistical differences in the duration of clinical symptoms, hospital stays, respiratory rates, or SpO2 levels with or without oxygen therapy, AST, ALT, ALP, BUN, creatinine, platelets, hemoglobin, PMN or lymphocytes. Nevertheless, significant differences were observed in the levels of SpO2 with or without oxygen therapy

during the follow-up period [146]. In another study, Zhang et al. found that a larger proportion of the participants in their study developed antibodies against SARS-CoV-2 ($P = 0.037$) and the SARS-CoV-2 viral load decreased significantly over time ($p = 0.0082$). Their study indicated an enhancement in metabolic pathways related to ʟ-lysine biosynthesis, 5-aminoimidazole ribonucleotide biosynthesis, and pyruvate fermentation. Su et al. reported that a 28-day dosage of 2×10^{11} CFU of three lyophilized *Bifidobacteria* and three prebiotics (galactooligosaccharides, xylooligosaccharide, resistant dextrin) resulted in a significant reduction in the resistome after two weeks and a decreased relative abundance of antimicrobial resistance genes. However, they also found that enlarged resistomes in post-COVID-19 patients did not seem to diminish after six months [142]. Wong et al. [144] reported fewer adverse effects in their study participants, who also exhibited lower pathogenic levels of pathogenic bacterial species associated with COVID-19 and an increase in beneficial bacteria such as *Bifidobacterium adolescentis* [144]. Thomas et al. reported that patients in the intervention group of their study experienced reduced cough and fatigue, alongside improved subjective well-being scores [145].

4.7. Effect of fecal microbiota transplant

Fecal transplant is an emerging therapeutic intervention that has been studied for its effectiveness against COVID-19 induced gut dysbiosis. Liu et al. reported that administering ten oral FMT capsules over four days led to improvements in GI symptoms, including constipation, diarrhea, stomach discomfort, gastralgia, and acid reflux. Interestingly, they also observed improvements in psychological issues such as weariness, sadness, and sleeplessness. They noted significant decrease in *Proteobacteria* and significant increase in *Actinobacteria, Bifidobacterium, Faecalibacterium* and *Collinsella*. Pre-FMT, they identified *Bacteroides* (28.3 %), *Prevotella* (13.0 %), *Faecalibacterium* (6.5 %), *Lachnospiraceae* (6.2 %), and *Phascolarctobacterium* (5.7 %) as the most common genera. Post-FMT, the most prevalent genera shifted to *Bacteroides* (31.1 %), *Faecalibacterium* (11.7 %), *Prevotella* (6.6 %), *Bifidobacterium* (10.4 %), and *Collinsella* (4.5 %). The study also showed an increase in naïve B cells, immature regulatory B cells, non-switched B cells and double-positive T cells ($P < 0.012$), along with a decrease in total and naïve B cells. They found no significant changes in erythrocyte count, hemoglobin, platelets, ALT, AST, AST/ALT ratio, albumin, globulin, A/G ratio, blood urea nitrogen, serum creatinine, T cell count, helper T cells, killer T cells, Th to Tc ratio, γδT cells, NK cells, immature NK cells, mature NK cells, and the immature/mature NK cell ratio [147]. In summary, FMT is a novel strategy that has shown promising effects in positive modifying COVID-19 induced gut dysbiosis.

5. Discussion

The COVID-19 pandemic has presented continuous challenges in optimizing treatment protocols and strategies. The studies examined in this systematic review have consistently reported favorable outcomes spanning various health aspects, including respiratory and gastrointestinal health, cognitive function, mortality rates, oxygen saturation, length of hospital stays, and immune response. These findings support the notion that adjunctive probiotic could play a significant role in severity of COVID-19 infections. For example, the study by Leal-Martinez et al. demonstrated significant improvements in mortality and the need for oxygen supplementation among 72 COVID-19 patients, where a subgroup of 39 received a probiotic regimen, as opposed 33 who were given a placebo. The mortality rate in the probiotic group was notably lower (1/40) compared to the control group (7/40) in the control group. The probiotic administered was *Saccharomyces boulardii*, which is recognized for its potential to substantially curb the progression of inflammatory response [129]. Similarly, probiotics containing *Bifidobacterium*, known for their SCFAs production, exhibit anti-inflammatory effects. Such mechanisms may account for the reduced

decreased mortality rates observed in several studies included in this review [15,128,129,135]. Probiotics, including strains like *L. salivarius* have been identified as key players in the suppression of various pro-inflammatory mediators [148]. The subsequent reduction in inflammatory factors in the bloodstream is thought to confer a protective effect against acute lung injury and symptoms similar to asthma, potentially clarifying the enhanced respiratory outcomes associated with probiotic use [38]. Moreover, this anti-inflammatory action is believed to contribute to the significant decreases in chronic fatigue, depression, and insomnia, as observed in the treatments involving probiotics and synbiotics [136,145,147]. In the realm of oxygenation, the research conducted by Cecceralli et al. highlighted that the 33 patients receiving intervention showed improved blood oxygen levels compared to the 29 patients in the control group. The SLAB51 synbiotic formula is noted for its potential to boost arterial oxygen availability, a crucial factor for vital organs like the brain, kidneys, and heart. This effect is attributed to the inhibition of inducible nitric oxide synthase activity, a mechanism that has been detailed in both past and recent studies [117,126,127,157]. Oropharyngeal probiotics containing lactic acid bacteria, such as *Streptococcus*, have been shown to generate peptides with ACE inhibitory properties that prevent SARS-CoV-2 virus interactions [163,164]. In support of this, the oropharyngeal probiotic studies analyzed in the current review measured decreased incidence rates, length of hospitalization, and mortality rates. Another bacterium found in oropharyngeal probiotics is *Bifidobacterium BB-12*. Many of the metabolic products it secretes, such as hydrogen peroxide, are toxic and harmful to surrounding pathogenic bacteria, allowing for effective colonization of the surrounding area [149]. Furthermore, *B. BB-12* produces antibacterial compounds known as bacteriocins [149]. Similarly, to *B. BB-12*, the bacterial strain *Streptococcus salivarius K12* is mainly characterized by its release of two specific antibiotics: Salivaricin A2 and Salivaricin B, which target the membranes of opportunistic bacteria and helps the growth of beneficial bacteria [128]. In a review conducted by [147], it was shown that the increased bacteria levels of bacteria established by FMT treatment have positive effects on the body. For example, *Faecalibacterium* inhibits the activation of the anti-inflammatory pathway, while *Prevotella* assists in the recruitment of neutrophils [150–152]. Another bacterium that increases following FMT treatment is *Bacteroides* spp., which provides nutrients to other commensal bacteria [153]. A healthy gut microbiome enhances immune response, reduces inflammation, and potentially improves outcomes in COVID-19 patients [154].

One of the major protective mechanisms utilized by probiotics is the maintenance of gut wall integrity. A study was conducted in which *L. salivarius* was administered to piglets exposed to high level of inflammation and oxidative stress. The study found that a high dose of this probiotic was capable of regulating oxidative stress and inflammatory responses that occurred as a result of exposure to LPS [148]. As previously discussed, intestinal LPS significantly increases in patients experiencing COVID-induced dysbiosis, mainly due to the proliferation of bacteria such as Enterobacteriaceae [28,46]. *L. salivarius* was found to result in increased levels of Claudin-1, Occulidin, and ZO-1, which are essential structural components of tight junctions, which in turn reduces gut permeability. The decreased gut permeability prevents LPS and other PAMPs from translocating from the intestinal lumen to mesenteric lymph nodes. PAMPs induce inflammatory reactions, resulting in the production of downstream pro-inflammatory mediators such as TNF-α, IL-6, IL-1β, IFN-γ. In the brain, the overproduction of IL-6 and TNF-α caused by COVID-19-induced gut dysbiosis leads to inflammation through mast cells. This could potentially explain the decrease in patients experiencing headaches and other neurological symptoms observed in this review [134,135].

Another major mechanism through which probiotics improve the course of COVID-19 infections is by producing SCFAs. Multiple studies have demonstrated the efficacy of the synbiotic formula SIM01 [142–144], which contributes to alleviating gut dysbiosis by producing SCFAs. Through the fermentation of dietary fibers, major SCFAs like

butyrate, propionate, and acetate are utilized by colon epithelial cells to support the integrity of tight junctions, reinforcing the physical barrier. Moreover, SCFAs not only serve as fuel for colonocytes, promoting overall cell health and function, but they also play a pivotal role in preventing the translocation of toxins into the bloodstream. This dual function of SCFAs contributes to reducing the risk of systemic inflammation.

6. Limitations and future perspectives

While our findings contribute meaningful insights into the interplay between various organ systems and the gut microbiome and the potential role of microbiome-modulating therapies, the scope of our analysis was bound by specific parameters that future studies may wish to expand. Firstly, the studies that we included reported diverse primary and secondary outcomes, encompassing specific symptoms such as coughing and abdominal pain, measurements of the gravity of the disease like morbidity and mortality, or measurements of immune factors and inflammatory biomarkers such as CRP, disallowing unified homogeneous comparisons across studies. Additionally, there were significant variations in dosages, delivery methods, and types of administered nutraceuticals. For example, Wong et al. administered 20 billion CFU lyophilized Bifidobacteria for three months, while Bozkurt et al. administered only 1 million CFU of Bifidobacterium dissolved in water for three days. This lack of homogeneity limited the comparability of the studies. Furthermore, factors such as age, region, ethnicity, BMI and comorbidities could not be explored due to study heterogeneity. Additionally, our inclusion criteria for prebiotics focused solely on studies explicitly mentioning the term "prebiotics," potentially excluding studies on natural prebiotic substances. Lastly, our findings reveal a paucity of research on FMT, prebiotics, and postbiotics. The limited availability of studies on these interventions underscores the necessity for further research to gain a comprehensive understanding of microbiota modulation in COVID-19 management. Future investigations should prioritize the exploration of the efficacy and safety of FMT, prebiotics, and postbiotics, offering essential insights into their potential as adjunctive therapies for COVID-19 patients.

7. Conclusion

This systematic review provides compelling evidence supporting the potential use of various biotics as therapeutic interventions for COVID-19. The reviewed studies demonstrate that the administration of probiotics, prebiotics, synbiotics, and FMT can alleviate COVID-19 induced dysbiosis. By modulating the gut microbiota, these interventions can mitigate the severity of the disease and improve clinical outcomes. Interventions aimed at restoring gut dysbiosis may have far-reaching implications, benefiting various organs impacted in gut axes. Multiple organizations recommend the use of probiotics. For example, the European Pediatric Association strongly recommends the use of strictly specified strains to prevent upper respiratory tract infections in children in Europe [156]. In February 2023, the World Gastroenterology Organization authorized the use of probiotics and prebiotics that proved to be beneficial in at least one randomized, controlled experiment. However, there are no formal recommendations for the use of microbiota-modulating therapies in COVID-19 patients. Results from this study and many others have shown that probiotics and synbiotics can be a safe and potent adjunctive therapy for COVID-19 patients, highlighting the importance of incorporating them into recommendations and guidelines. However, it is worth noting that while the findings of this review are promising, further research is needed to fully understand the mechanisms through which biotics affect the human body. Additionally, more clinical trials on various biotics are necessary to establish their efficacy in diverse populations and across different severities of COVID-19.

Abbreviations used

FMT	Fecal Microbiota Transplantation
COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
RNA	Ribonucleic Acid
ICU	Intensive Care Unit
RAAS	Renin-Angiotensin-Aldosterone System
ACE	Angiotensin-Converting Enzyme
NSAID	Non-Steroidal Anti-Inflammatory Drug
IL	Interleukin
MIP	Macrophage Inflammatory Protein
MCP	Monocyte Chemoattractant Protein
TNF-α	Tumor Necrosis Factor-alpha
IFN-γ	Interferon-gamma
VEGF	Vascular Endothelial Growth Factor
ICAM-1	Intercellular Adhesion Molecule-1
VCAM-1	Vascular Cell Adhesion Molecule-1
MALT	Mucosa-Associated Lymphoid Tissue
GALT	Gut-Associated Lymphoid Tissue
BALT	Bronchus-Associated Lymphoid Tissue
gp130	Glycoprotein 130
sIL—6Rb	Soluble Interleukin-6 Receptor beta
LPS	Lipopolysaccharide
SCFA	Short-Chain Fatty Acid
IFN-I2	Interferon Iota-2
CD16 + 56+ NK cells	Cluster of Differentiation 16-positive 56-positive Natural Killer cells
Hemolysin BL	Hemolysin L2/Bacillus-like
GI	Gastrointestinal
B0AT1	Broad-spectrum amino acid transporter 1
mTOR	Mammalian Target of Rapamycin
CRP	C-Reactive Protein
BBB	Blood-Brain Barrier
Aβ	Amyloid-beta
α-Syn	Alpha-Synuclein
CNS	Central Nervous System
AT2R	Angiotensin II Receptor Type 2
TGF-β	Transforming Growth Factor-beta
ERK/NFκB	Extracellular Signal-Regulated Kinase/Nuclear Factor-kappa B
NLRP3	NOD-like Receptor Protein 3
IL-1β	Interleukin-1 beta
PAGln	Plasma Amino Acid-Linked Glycine
TMAO	Trimethylamine N-Oxide
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
SIRS	systemic inflammatory response syndrome
GM-CSF	granulocyte-macrophage colony stimulating factor
LCA	Liver Chemistry Abnormalities
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
URTI	Upper Respiratory Tract Infections
BMI	Body Mass Index
CFU	Colony Forming Unit
BAFF	B cell Activating Factor
MMP	Matrix Metallopeptidase
APRIL	A Proliferation Inducing Ligand
sCD163	Soluble CD163
PLT	Platelet Count
hsCRP	High Sensitivity C Reactive Protein
Ig	Immunoglobulin
FiO2	Fraction of Inspired Oxygen
pO2	Partial Pressure of Oxygen
O2Hb	Oxygenated Hemoglobin
CaO2	Oxygen Content

SaO2 Arterial Oxygen Saturation
CPAP continuous positive airway pressure
WBC White Blood Cells
ASV Amplicon Sequencing Variants
FGF Fibroblast Growth Factor
RANTES Regulated upon Activation, Normal T Cell Expressed and Presumably Secreted
PDGF Platelet Derived Growth Factor
G-CSF Granulocyte Colony Stimulating Factor
GM-CSF Granulocyte-Macrophage Colony stimulating factor
IP-10 Gamma Induced Protein 10
MCP-MCAF Monocyte Chemotactic and Activating Factor
MIP Macrophage Inflammatory Protein
CXCL Chemokine (C-X—C) motif ligand
MIG B Lymphocyte Antigen Receptors
ESR Erythrocyte Sedimentation Rate
ALP Alkaline Phosphatase
BUN Blood Urea Nitrogen
PMN Polymorphonuclear Neutrophils
SPO2 Oxygen Saturation
PAMP Pathogen Associated Molecular Pattern

CRediT authorship contribution statement

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Declaration of competing interest

The authors declare that there are no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lfs.2024.122535.

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