

Review Article

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Unravelling the potential of synbiotics in ameliorating COVID−19 complications: A concise review

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ABSTRACT

The ongoing COVID-19 pandemic has highlighted the need for innovative strategies to mitigate the severe complications associated with infection caused by SARS-CoV-2. Developing empirical studies posited that the gut microbiota play a key role in modulating the immune response and overall health. This review explores the potential of synbiotics, a combination of probiotics and prebiotics, as a promising therapeutic approach to ameliorate COVID-19 complications. We conducted a comprehensive review of the literature to assess the impact of synbiotics on key aspects of the pathogenesis of this disease. Several studies indicate that synbiotics can bolster the gut microbiome, enhance mucosal barrier function, and regulate the immune system. These effects may be particularly beneficial in COVID-19, where immune dysregulation and cytokine storm are implicated in severe disease. We discuss the mechanisms through which synbiotics influence the gut axis, modulating the immune response and potentially reducing the risk of acute respiratory distress syndrome and other complications. Furthermore, synbiotics may help manage gastrointestinal symptoms often associated with COVID-19 and support the recovery of patients. While current research is promising, further clinical trials are needed to validate the safety and efficacy of synbiotics in the context of COVID-19. This review underscores the potential of synbiotics as an adjunctive therapy to conventional treatments for COVID-19, offering a novel and integrated approach to improve patient outcomes and reduce the burden of this health challenge worldwide.

KEYWORDS: SARS-CoV-2; COVID-19; Synbiotics; Prebiotics; Probiotics

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is an emerging public health pathogen worldwide[1]. SARS-CoV-2 exhibits a notably enhanced angiotensin-converting enzyme 2 (ACE2) receptor binding affinity in the pulmonary system, surpassing that of SARS-CoV by a magnitude of 1020 fold. In a practical clinical context, it has been observed that therapeutic interventions aimed at managing Coronavirus disease 2019 (COVID-19) in patients with severe manifestations may inadvertently render these individuals more susceptible to subsequent infections, one notable example is the use of corticosteroids, such as dexamethasone which have been employed to manage the severe inflammatory response often seen in severe COVID-19 cases. Among the multifarious challenges encountered in the clinical management of such cases, antibiotic-induced diarrhea has emerged as a particularly vexing issue[2].

The clinical presentation of COVID-19 encompasses a disease severity spectrum that ranges from mild respiratory symptoms that are non-specific flu-like to more pronounced manifestations, including fever, cough, fatigue, severe and potentially fatal pneumonia, as well as the development of acute respiratory distress syndrome and dysfunction multi-organs. Notably, individuals

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infected with SARS-CoV-2 frequently manifest gastrointestinal disturbances, such as diarrhea and dysbiosis[3]. Despite the primary mode of transmission being direct contact and respiratory aerosols, the detection of the virus in fecal specimens from both active and convalescent patients underscores the works of the human gut in the pathogenesis of COVID-19[4]. Moreover, a comprehensive array of infection and control measures has been globally implemented to mitigate the transmission of the COVID-19 pandemic. These strategies encompass hygiene practices, social distancing, lockdowns, the utilization of face masks, systematic screening, isolation of infected individuals, and quarantine protocols[5].

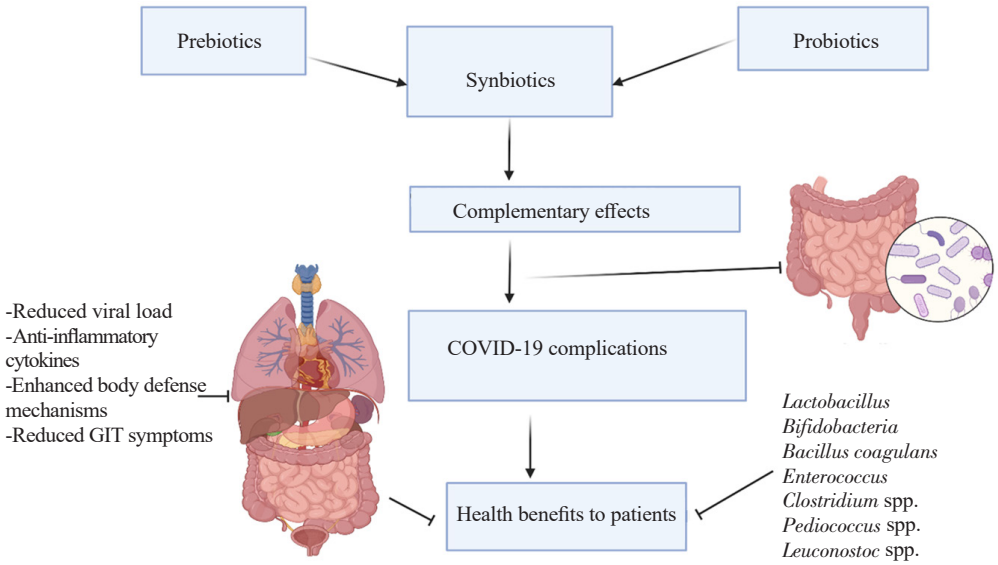
Recently, there has been an escalating scientific direction in the utilization of indigenous gut microbiota and exogenous microorganisms as probiotic agents, intended for the prevention and treatment of various infectious and non-infectious conditions[6]. Probiotics, defined as living microorganisms, when administered in adequate quantities, bestow advantageous health effects upon the host. Lactic acid bacteria (LAB) represent a category of bacteria frequently encountered in fermented food products, spanning dairy, meat, vegetables, and cereals. Strains of LAB, particularly Bifidobacterium and Lactobacillus, have been locally utilized as probiotics to eliminate infections related to the gastrointestinal tract (GIT) and vagina as well as to decrease colonization of pathogenic organisms. Probiotics typically confer advantageous attributes using competitive exclusion or pathogen antagonism, host-microbiota modulation, the release of antibiotics and the elicitation of responses by the immune cells[7].

Given a comprehensive comprehension of the viral agent pathogenicity and its interaction with the gut microbiota (GM), it becomes evident that employing probiotics as a therapeutic intervention to regulate the intestinal microbiota and alleviate COVID-19 and its related comorbidities is an imperative component of the comprehensive strategy in combating the COVID-19 pandemic[7]. Several studies have reported success in using probiotics in reducing or eliminating respiratory tract-related viruses in mice models and human species[8].

Clearly, the utilization of probiotics and prebiotics as countermeasures against COVID-19 holds promise for diminishing the disease's impact and its accompanying comorbidities. It is anticipated that a scientifically sound application of prebiotics, probiotics, and synbiotics may offer a viable and alternative strategy in the context of microbial infections, particularly during the COVID-19 pandemic and its aftermath (Figure 1). Ongoing scientific research is imperative for the continual refinement of our knowledge in this domain, with a focus on investigating the potential utility of synbiotics in alleviating human-related diseases. Therefore, this concise review looked at potential synbiotics and how they ameliorate COVID-19 complications.

2. The attractiveness of modulating synbiotics for COVID–19 amelioration

The attractiveness of modulating synbiotics for COVID-19 amelioration lies in their potential to influence the host's immune response and improve overall health outcomes during viral infections as shown in Figure 1 which summarizes the synergistic potentials of prebiotics, probiotics and synbiotics in ameliorating COVID-19 complications by the help of microbes especially beneficial bacteria that ensure the viral loads is suppressed, GIT symptoms is ameliorated, the immune defense system is enhanced,



GIT: Gastrointestinal tract

Figure 1. The synergistic effects of prebiotics, probiotics and synbiotics in ameliorating COVID-19 complications.

and inflammation is drastically reduced by anti-inflammatory cytokines. Figure developed with BioRender. Firstly, synbiotics can enhance the gut microbiota composition. A balanced gut microbiome is linked to improve immune function, and dysbiosis, often observed in COVID-19 patients, may contribute to disease severity. Probiotics in synbiotics can introduce beneficial microorganisms, while prebiotics serve as nourishment for these microbes, promoting a healthier gut environment.

Secondly, synbiotics might modulate the immune cell responses. They can stimulate the synthesis of anti-inflammatory cytokines and enhance the body's defense mechanisms against viral infections. This modulation may reduce the excessive immune response often associated with severe COVID-19 cases, known as a cytokine storm.

Furthermore, this therapeutic approach may mitigate gastrointestinal symptoms commonly observed in COVID-19 patients. Probiotics can help maintain gut barrier integrity, potentially preventing the translocation of viral particles from the gut to other organs. While research in this area is ongoing, the potential benefits of this approach in COVID-19 are promising. However, it's important to note that synbiotics should complement, not replace, established preventive measures and medical treatment lines. Their use should be guided by rigorous clinical trials and tailored to individual patient needs. As our understanding of the interplay between GM and COVID-19 evolves, synbiotics hold considerable appeal as a supportive therapeutic avenue in the battle against this global pandemic.

3. Literature review

3.1. Prebiotics

Prebiotics refer to dietary components that are indigestible and exert effects that benefit the host organism by discerningly promoting the proliferation and functional activity of specific bacteria within the colonic microbiota, ultimately enhancing the host's well-being. The definition of prebiotics underwent a comprehensive review by a panel of specialists affiliated with the International Scientific Association for Probiotics and Prebiotics (ISAPP)[9]. This panel expanded refined the description to encapsulate a more comprehensive perspective, characterizing prebiotics as a "selectively substrate that is metabolized by indigenous microbes within the host, resulting in health benefits"[9]. This refined definition extends the prebiotic concept to potentially encompass non-carbohydrate substances, potential applications beyond the GIT, and a wide range of categories extending beyond the domain of dietary consumption. These typically involve short-chain carbohydrates that resist enzymatic breakdown but serve as substrates for the proliferation of probiotic microorganisms in the upper GIT. Additionally, certain non-carbohydrate compounds, such as cocoa-derived flavanols, have been suggested as candidates for prebiotic classification[10]. The underlying mechanism involves the stimulation of preexisting metabolic activities within the colon through the facilitation of bacterial growth in the intestinal microbiota. Observations have indicated a marked increase in the population of bifidobacterial in fecal matter after the consumption of Fructooligosaccharides (FOS)[11]. These compounds are typically subject to hydrolysis within the intestinal environment and are characterized by a relatively low degree of polymerization, typically consisting of 2 to 20 monomeric units. These monomers predominantly include glucose, galactose, fructose, and xylose. Among the most extensively investigated prebiotics are omalto-oligosaccharides, FOS, and xylooligosaccharides as shown in Figure 2. FOS, encompassing inulin and neosugar, are valuable dietary fibres known for their capacity to augment fecal volume, alleviate constipation, and elevate fecal acidity. Inulin, prevalent in numerous plant sources and commercially available, is often derived from chicory roots and is recognized for its promotion of *Bifidobacterium* proliferation. Omalto-oligosaccharides, on the other hand, is naturally present in foods that are fermented like honey, soy sauce, and miso. It serves as a substrate for both bifidobacterial and bacteriodes groups, fostering the growth of species of *Bifidobacterium* and *Lactobacillus* (Figure 2). This in turn contributes

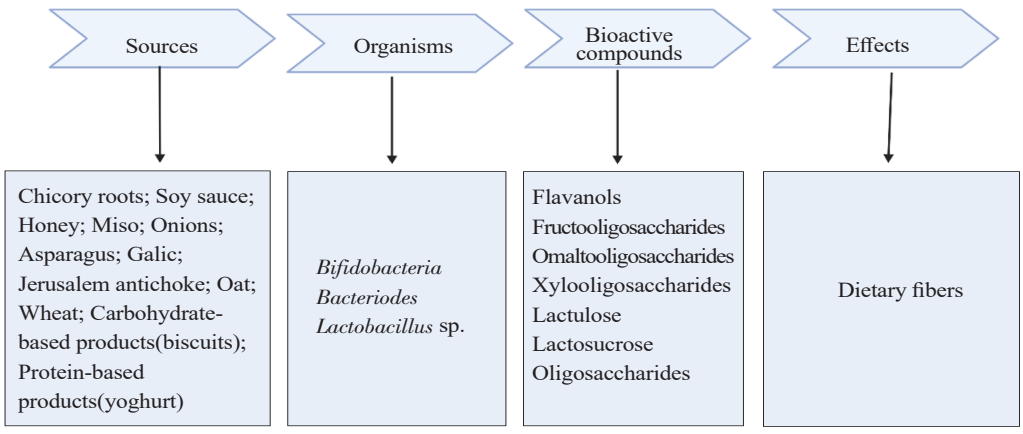


Figure 2. Different sources of prebiotics, organisms involved, compounds produced and its effects in the system.

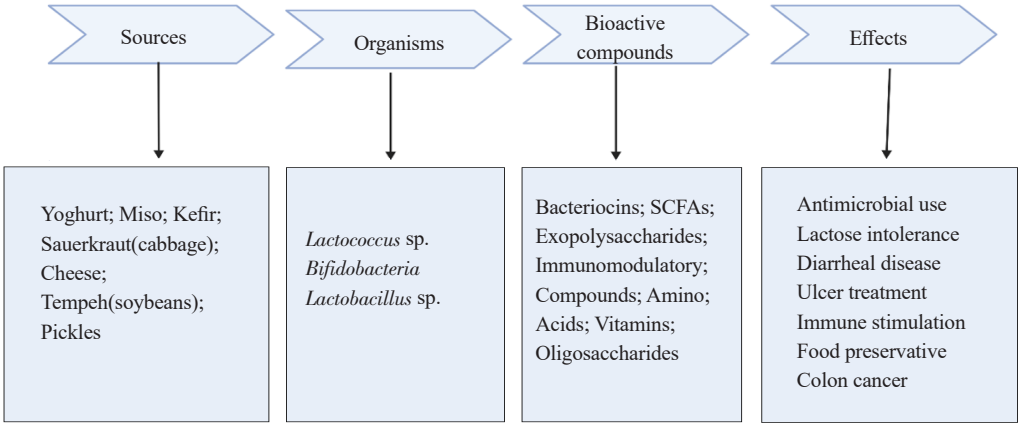


Figure 3. Different sources of probiotics, organisms involved, compounds produced and its effects in the system.

to the initiation of Th-1-like immunological triggers, locally and systematically, while also modulating immune response.

The industrial-scale synthesis of prebiotics holds a paramount position in the enhancement of food quality and human well-being. Diverse functional food products, including biscuits, confections, tabletop sweeteners, and frozen yogurt, have been formulated with the incorporation of prebiotics[12]. These prebiotics can be naturally sourced from a variety of vegetables like garlic, asparagus, onion, oat, Jerusalem antichoke (*Helianthus tuberosus*), wheat and chicory as summarized in Figure 2. Furthermore, they are intentionally integrated into a wide spectrum of food items, including yogurts, cereals, cakes, condiments, beverages, infant formula foods, pasta, cereal bars, bread products and different fruit juices[13].

3.2. Probiotics

The origins of probiotics trace back to ancient human civilizations, marked by the consumption of fermented food products[14]. Notably, Elie Metchnikoff introduced the notion that health could be improved through the intentional manipulation of the gut microbiota with beneficial microorganisms found in yogurt. This pioneering concept laid the foundation for the usage of probiotics in the medical world[15]. These microorganisms can pull a positive modulatory effect on the gastrointestinal microflora while concurrently mitigating the proliferation of pathogenic bacteria and the release of toxic compounds within the human intestinal milieu.

A significant milestone in the evolution of probiotics was reached with the development of the first probiotic product, designed as a therapeutic agent for *Escherichia coli* infections elimination in pigs[16]. The WHO has maintained a conviction that probiotics represent a prominent frontier in the realm of immune defense, particularly in cases where conventional antibiotics demonstrate limited efficacy against certain microorganisms[17]. Various intestinal bacteria, including *Lactobacillus*, *Bifidobacterium*, and *Lactococcus* confer beneficial effects by enhancing GIT stability as summarized in Figure 3. Probiotics offer multiple advantages for human health, encompassing areas such as antimicrobial applications, mitigation of lactose intolerance, management of diarrheal conditions, ulcer treatment, immune system stimulation, food preservation, and the potential role in addressing colon cancer, among other domains[18]. Probiotics exert protective effects against gastrointestinal diseases using colonization, an efficient mechanism that initiates the probiotic effectiveness of these microorganisms. Furthermore, probiotics demonstrate the inhibition of pathogenic agents through the secretion of inhibitory substances, including organic origin substances, short-chain fatty acids (SCFAs), CO_2, H_2O_2, acetoin, diacetyl, and bacteriocin-like inhibitory substances among others (Figure 3).

Of particular significance, the bacteriocins produced by probiotic bacteria have garnered attention due to their safe applications in a range of domains, including the food industry, pharmaceuticals, veterinary medicine, and human healthcare[19,20]. These bacteriocins effectively curtail the viability of a spectrum of bacteria, exerting an influence on bacterial cell metabolism and toxin production[21]. It is worth noting that probiotics demonstrate a unique capability to inhibit pathogens that actively consume nutrients and, in doing so, compromise the host's nutritional resources[22].

3.3 Synbiotics

Synbiotics represent a combined therapeutic regimen encompassing both prebiotics and probiotics, aimed at augmenting the well-being of lower animals and humans[23]. Within symbiotic food products, probiotic microorganisms selectively employ prebiotics as substrates to support their growth and functional activities[24]. There are two primary categories of synbiotics: complementary and synergistic. Complementary synbiotics incorporate both probiotics and prebiotics, each independently conferring one or more health benefits without necessitating co-dependent interactions[25]. In contrast, synergistic synbiotics entail a substrate that is selectively used by the co-delivered microorganisms, resulting in a combined therapeutic effect[25].

Scientific investigations have consistently documented the favourable impact of symbiotic foods on the overall health and nutritional status of the host. Notably, these studies have observed

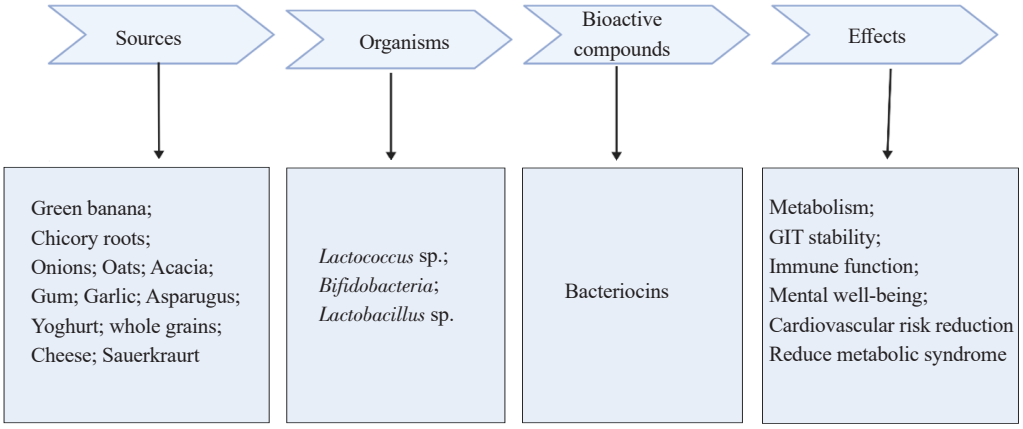


Figure 4. Different sources of synbiotics, organisms involved, compounds produced and its effects in the system.

that the consumption of synbiotics led to a notable rise in the population of probiotic bacteria, specifically *Bifidobacterium* and *Lactobacillus*, within fecal samples, concomitant with a reduction in coliform bacteria[26]. Furthermore, it was noted that symbiotic supplementation significantly elevated the activity levels of key digestive enzymes in the test cohort such as isomaltase, sucrase, lipase and lactase. In addition to these gastrointestinal effects, there is compelling evidence suggesting that synbiotics can exert a substantial impact on reducing various cardiovascular risk factors, lowering the prevalence of metabolic syndrome, and ameliorating resistance of insulin, particularly in older people(Figure 4)[27]. These findings underscore the multifaceted health-promoting potential of symbiotic interventions.

The capability of bifidobacterial to metabolize prebiotic compounds exhibits species-specific variations, a pivotal characteristic in the context of gut microbiota modulation via selective prebiotic utilization. For instance, β-fructofuranosidase from *Bifidobacterium(B.) adolescentis* GI demonstrates reactivity with fructooligomers other than inulin, a characteristic shared by *Bifidobacterium bifidum*[27]. In contrast, *B. longum* and *B. animalis* exhibit the ability to hydrolyze a broad spectrum of prebiotics, encompassing FOS and xylooligosaccharides, inclusive of inulin. Research studies have consistently identified the highest counts of viable bifidobacterial in various food products[27]. In relation, *B. longum* viability, when incorporated with FOS, is notably enhanced in fermented dairy products like curd. *B. lactis* probiotic is equipped with β-glucosidase and β-fructofuranosidase enzymes, facilitating the metabolism of oligosaccharides within fermented milk, thereby promoting its development and metabolic activity[28]. Moreover, a study reported that the synergistic combination of *Bacillus coagulans* MTCC5856 and sugarcane fibre as a symbiotic yielded more profound effects than this individual administration of *B. coagulans* and sugarcane fibre. This combination exhibited enhanced efficacy in mitigating inflammation and inducing the synthesis of SCFAs within a colitis model[29].

3.4. Current clinical trials

Several clinical trials are underway to investigate the potential of synbiotics in mitigating COVID-19 complications, focusing on their immunomodulatory and anti-inflammatory effects. These trials aim to elucidate the impact of synbiotics, which combine probiotics and prebiotics, on the gut microbiota and immune response, ultimately influencing disease severity and outcomes in COVID-19 patients.

Lau *et al.* randomized, double-blind and placebo-controlled trial carried out in Hong Kong where synbiotic preparation (SIM01) was evaluated for its efficacy in treating post-acute COVID-19 syndrome. Results showed no significant differences between SIM01 and placebo groups in improving symptoms or clinical outcomes among participants with persistent COVID-19 symptoms[30].

In another development, a randomized placebo-controlled trial investigating synbiotic adjunct therapy effects on clinical and paraclinical outcomes in hospitalized COVID-19 patients showed no significant differences between the synbiotic and placebo groups. The study aimed to assess the impact of synbiotics on various parameters associated with COVID-19 illness severity and recovery[31]. Wischmeyer *et al.* double-blinded, placebo-controlled randomized trial examining the efficacy of probiotic treatment as post-exposure prophylaxis for COVID-19 outcome showed no significant differences between the probiotic and placebo groups[32]. Overall, current clinical trials investigating synbiotics against COVID-19 complications are shedding light on the potential of these microbial-based interventions to modulate immune responses, reduce inflammation, and improve clinical outcomes in affected individuals. As research in this field progresses, further insights into the role of synbiotics in combating COVID-19 may pave the way for novel therapeutic strategies and public health interventions aimed at mitigating the impact of the pandemic.

4. Discussion

Research has demonstrated a substantial elevation of both proinflammatory and anti-inflammatory cytokines, encompassing T helper cytokines, interferon-γ, IL-2 and IL-17, chemokines, and lymphocytes producing tumour necrosis factor (TNF) in COVID-19 patients[20]. Consequently, interventions aimed at modulating T cells and cytokines could serve as an excellent treatment approach, potentially reducing COVID-19-related mortalities. Notably, certain probiotic LAB isolates have exhibited the ability to diminish the levels of proinflammatory cytokines, specifically, IL-1β, IL-6, and TNF-α, while also inhibiting the phosphorylation of Mitogen-Activated Protein Kinases (MAPKs) in LPS-triggered RAW 264.7 cells[33].

As of now, there is a lack of empirical evidence supporting the direct inhibition of coronaviruses by probiotics. Nonetheless, it is well-established that certain probiotic strains exhibit inhibitory effects against various other viruses, for example Influenza A virus, respiratory syncytia virus, Norovirus among others[19]. Consuming probiotics tends to reduce the viral loads and enhances immune response, which is paramount during the peak of the pandemic. Based on existing data, specific probiotic strains, including *Lactobacillus(L.) rhamnosus* CRL1505, *B. subtilis*, *L. gasseri* SBT2055, and *B. bifidum* hold promise for their potential function in mitigating the severity of COVID-19 disease[19]. Additionally, probiotic organism shows antioxidant properties, offering a unique avenue for COVID-19 amelioration, as redox homeostasis plays a pivotal role in impeding disease progression[34]. Interestingly, SARS-CoV-2 relies on the binding of ACE2 for cellular internalization and requires the action of transmembrane protease serine 2 precursors for priming and replication within the host[35]. Consequently, ACE inhibitors are suggested as potential contributors to COVID-19 management[36]. It is worth noting that several probiotics, particularly LAB, are recognized for their capacity to generate bioactive peptides that function as ACE inhibitors[36]. Furthermore, the lung-gut axis, in conjunction with microbiota influenced by probiotics, warrants investigation as a potential approach to COVID-19 management[35].

Numerous research investigations have presented compelling evidence supporting the potential of probiotics to mitigate the occurrence, duration, and severity of upper respiratory infections[37,38]. Several studies have indicated that probiotics can reduce the incidence of upper respiratory infections, their temporal extent, and the gravity of associated illnesses[38]. Of particular interest, a comprehensive review conducted by Cochrane has suggested that probiotics outperform placebos in ameliorating the frequency of acute upper respiratory tracts infections, the average duration of such episodes, antibiotic utilization, and instances of school absenteeism[39]. In a related development, Sly and colleagues demonstrated that the administration of the immunostimulant OM-85 to infants resulted in a notable reduction in the total occurrence of lower respiratory tract infections(RTIs) severity and the days count characterized by symptomatic manifestations compared to a placebo group[40]. This observation implies a potential decrease in the cumulative inflammatory load within the lungs and lower airways.

Probiotics usually shows an immunomodulatory impact that is strain-specific character. Numerous clinical trials involving *Lactobacillus plantarum*, *L. rhamnosus* GG, *L. casei* and paracasei and few *Bifidobacterium* spp. has shown potential prophylactic properties against respiratory infections[39]. These scientific insights underscore the exploration of distinct probiotic strains possessing immunomodulatory capabilities, particularly immunobiotics, aimed at bolstering antiviral defenses within the respiratory tract. This focus primarily accentuates the synergistic interplay of prebiotics and probiotics. Moreover, Baud *et al.*, have presented evidence demonstrating the efficacy of certain probiotic formulations in diminishing the burden of SARS-CoV-2 across various demographic cohorts[41]. While vaccination efforts are widespread in numerous nations, the imperative for additional strategies to mitigate viral impact remains crucial, particularly considering the enduring presence of the virus, especially within high-risk groups like the elderly, children, and immunocompromised individuals. Villena *et al*. comprehensively reviewed the data about the immunomodulatory effects of *L. rhamnosus* CRL1505 on mucosal antiviral immune responses. Their analysis suggests the potential utility of this strain in preventing and mitigating infection severity induced by SARS-CoV-2[42].

In the context of COVID-19, certain patients exhibit dysbiosis of the intestinal microbiota characterized by diminished levels of probiotic species like *Bifidobacterium* and *Lactobacillus*, indicative of compromised immunity. The introduction of synbiotic supplementation has shown promise in re-establishing a balanced intestinal microbiota and reducing infection risk[43]. The beneficial effects of these microbial interactions encompass fortifying the coverage of the gut epithelial, outcompeting pathogenic microbes for attachment and nutrition sites, synthesizing antimicrobial agents, and modulating the host immune system[44]. Additionally, a study has suggested that synbiotic interventions can lead to a 16% reduction in the incidence of RTIs and a concurrent 16% decrease in the study participant numbers that shows RTIs symptoms[45]. It is noteworthy that synbiotic interventions demonstrate an infection due to virus decrease, even among pediatric patients with asthma[46]. A particular study has shown that individuals receiving synbiotics experienced a decrease in gastrointestinal symptoms[47]. This aspect is of peculiar significance around COVID-19, as diarrhea is a prevalent illness observed in 10%-30% of patients infected with SARS-CoV-2. For instance, In China, Mak *et al.* reported that 58% to 71% of COVID-19 patients received antimicrobes, with antibiotic-related diarrhea occurring in 2% to 36% of cases[48]. Administration of probiotics has been posited to potentially reduce the susceptibility of patients with COVID-19 to secondary infections.

Epidemiological investigations have revealed varying incidence

rates of olfactory challenges in patients with COVID-19, ranging from 33.9% to 68%, with a predominance among female patients[49]. In summary, while probiotics and synbiotics are primarily positioned as preventive measures against this disease, emerging evidence suggests their potential utility in aiding patients' post-infection.

5. Conclusions and future perspectives

Synbiotic combinations offer numerous health benefits by enhancing the intestinal microbiota and boosting host immune function, potentially impeding COVID-19 attachment, and invasion. Probiotics positively impact human health through immune stimulation and pathogen inhibition, generating considerable interest in healthcare and consumer products. Nevertheless, there remains limited information on certain probiotics and prebiotics.

Ample evidence suggests a potential role for probiotics and their derivatives in managing COVID-19, necessitating clinical validation for treatment approaches. Leveraging novel methods like molecular biology, system biology, genetic engineering, multi-omics, nanobiology, and immunological approaches is essential to comprehend the microbiome's structure and function in relation to probiotics and prebiotics. Further research should investigate the interplay between human physiological functions and the microbiome. Collaborative translational research between academia, clinicians, and industry is crucial to bridge the gap between lab insights and practical applications.

Given the safety of synbiotics, large-scale clinical analysis should be expedited, independent of universally accepted COVID-19 vaccines.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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Data availability statement

The data supporting the findings of this study are available from the corresponding author upon request.

Authors' contributions

Oti VB designed the study, performed literature search, and wrote the first draft. Oti VB, Adah OF, Dzator J, Omoloye NAY and Kandagor B read the manuscript, made corrections to the manuscript, reviewed, and edited the content of the entire manuscript. All authors approved the final copy of the manuscript before submission.

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