Trends in Food Science & Technology 120 (2022) 174–192

Contents lists available at ScienceDirect

Trends in Food Science & Technology

journal homepage: www.elsevier.com/locate/tifs

Evidences and perspectives of the use of probiotics, prebiotics, synbiotics, and postbiotics as adjuvants for prevention and treatment of COVID-19: A bibliometric analysis and systematic review

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ARTICLE INFO

Keywords:
Diet
Functional foods
Gut-lung axis
Immunomodulation
Microbiome
Pandemic

ABSTRACT

Background: Coronavirus disease-19 (COVID-19) is an infectious disease transmitted by the virus responsible for the severe acute respiratory syndrome 2 (SARS-CoV-2), which exhibit several clinical manifestations including gastrointestinal symptoms.

Scope and approach: This review aimed to provide insights and perspectives for the use of probiotics, prebiotics, synbiotics, and postbiotics as adjuvants for prevention/treatment and/or modulation of the microbiota in COVID-19 patients. Eighty-four studies published in the Scopus database from the onset of the pandemic until December 2021 were assessed and submitted to a bibliometric analysis adapted from VOSviewer software.

Key findings and conclusions: Through bibliometric analysis, it might be suggested that the modulation of the gut/lung microbiome is promising as an adjuvant for the prevention/treatment of COVID-19 patients, due to immunomodulation properties related to probiotics and prebiotics. So far, few clinical studies involving the application of probiotics in COVID-19 patients have been completed, but reduction in the duration of the disease and the severity of symptoms as fatigue, olfactory dysfunction and breathlessness, nausea and vomiting and other gastrointestinal symptoms were some of the main findings. However, probiotics are not recommended to immunocompromised patients in corticosteroid therapy. The future perspectives point to the modulation of the intestinal microbiota by probiotics, prebiotics, synbiotics, and postbiotics represent a promising adjuvant approach for improving the health of patients with COVID-19.

1. Introduction

The global pandemic of coronavirus disease-19 (COVID-19), caused by severe acute respiratory syndrome 2 (SARS-CoV-2), has rapidly spread from China to around the world infecting more than 263,000,000 people across five continents until early December 2021. By that time, more than 5,200,000 deaths due to SARS-CoV-2 infection had occurred, while at least 8,000,000,000 vaccine doses had been administered in the same period, according to John Hopkins University (2021).

The International Committee on Taxonomy of Viruses (ICTV) recognized the symptomatic and biological likeness of the novel coronavirus with the severe acute respiratory syndrome coronavirus (SARS-CoV) (Al Noman et al., 2021). In this sense, the COVID-19 disease caused by SARS-CoV-2 infection is part of the variety of viruses associated to severe acute respiratory syndrome (Drosten et al., 2003; El-Anwar, Mohamed, & Sweed, 2021). Until the present moment, two serious disease outbreaks related to SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported in China

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https://doi.org/10.1016/j.tifs.2021.12.033
Received 11 September 2021; Received in revised form 3 December 2021; Accepted 28 December 2021
Available online 2 January 2022

(2002–2003) and in the Middle East (2012), respectively (Al Noman et al., 2021; Zaki, van Boheemen, Bestebroer, Osterhaus, & Fouchier, 2012; Zhong et al., 2003). SARS-CoV-2 is 96% identical to the entire genome of a coronavirus found in bats, so the domestication and/or consumption of these wild animals was initially pointed out as a likely origin for the outbreak (Wu et al., 2020). However, there is not a consensus on the outbreak's origin in the scientific community so far.

According to Li, Wang, Tracey, and Wang (2021), vaccines of mRNA and adenoviral are being responsible for encoding the spike protein (S), a fragment present on the viral surface, responsible for increasing the adaptive antibody liable in the combat against SARS-CoV-2 infection. Thus, antibodies potentially induced by vaccines might directly interact with the virus spike coat proteins and interfere in the binding of the virus to the angiotensin-converting enzyme 2 (ACE2) cell receptor for internalization (Miller et al., 2021). In this regard, a study with an animal model, utilizing mutant mice with ACE2 deficiency, showed the important function of this receptor in innate immunity modulation, balance of intestinal amino acid, synthesis of antimicrobial peptides, and maintenance of the intestinal microbiome (Infusino et al., 2020).

Gastrointestinal disorders are usual in COVID-19 patients and may impact the host's intestinal microbiota and, consequently, in the inflammatory process (d'Ettorre et al., 2020). Furthermore, studies have demonstrated that both gut and lungs are part of a shared mucosal immune system, and have inflammatory process and immune responses linked by the gut-lung axis (Antunes, Vinderola, Xavier-Santos, & Sivieri, 2020; Baindara, Chakraborty, Holliday, Mandal, & Schrum, 2021). In this sense, several studies have suggested that probiotics and/or prebiotics could improve host defense against SARS-CoV-2 infection by strengthening the mucosal barrier and modulating the host immune system (Brito et al., 2021; Conte & Toraldo, 2020; Dai, Han, & Lichtfouse, 2021; Din et al., 2021; Patra, Saxena, Sahu, Pradhan, & Roychowdhury, 2021).

In this regard, there is clinical evidence that modulation of the intestinal microbiota might positively control COVID-19 progression (Walton, Gibson, & Hunter, 2021). Akour (2020) proposed that the process of modulation through supplementation with probiotics or prebiotics as an adjuvant therapy might decrease the risk of secondary infection in these patients by helping to restore the altered microbiota. Nevertheless, according to an ongoing clinical trial, the supplementation of synbiotics could reduce the duration of diarrhea, ameliorate stool consistency and may prevent the process of dysbiosis and intestinal inflammation, in addition to the gastrointestinal symptoms of COVID-19 (US National Library of Medicine, ClinicalTrial.gov, Identifier: NCT04420676, 2021). Besides, Anwar et al. (2021) showed in a computational docking study that some plantaricins synthetized by *Lactiplantibacillus plantarum* have potential to avoid the binding of SARS-CoV-2 to ACE2 receptors proposing an antiviral property of these compounds against infection caused by SARS-CoV-2.

Although many patients with COVID-19 show mild symptoms of the disease, an expressive number of individuals experience a worsening of their clinical condition due to a series of factors, particularly, the risk of secondary infection. In this study, a new outlook on research on dietary intervention as an adjunct in the control of these infections becomes necessary. Therefore, the present study aimed to provide insights and perspectives for the administration of probiotics, prebiotics, synbiotics, and postbiotics related to prevention/treatment and/or modulation of the microbiota of COVID-19 patients. This is an unprecedented study to identify the scientific perspectives of dietary interventions that may collaborate to immunomodulation and constrain the damage promoted by SARS-CoV-2 infection through a bibliometric analysis associated to a systematic review.

2. Methodology

The methodological approach utilized was based on bibliometric tracking to review the scientific papers found on similar previous studies (Melo et al., 2021; Sweileh, 2021; Trager & Dusek, 2021; Zhong, Wang, & Cui, 2021). All relevant data on modulation of microbiota with probiotics, prebiotics, synbiotics, and postbiotics associated to prevention and/or treatment of patients with COVID-19 were downloaded from the Scopus, considered by the academic community, the largest citation database of peer-reviewed literature (Falagas, Pitsouni, Malietzis, & Pappas, 2008; Kulkarni, Aziz, Shams, & Busse, 2009; Mongeon & Paul-Hus, 2016; Zyoud & Al-Jabi, 2020). The present study used a systematic process of four principles, adapted from Randhawa, Wilden, and Hohberger (2016). First, discussions were held to recognize the theme and relevant concepts to the researched topic. Terms were identified to shape three cores: the supplement (i.e., probiotics, prebiotics, synbiotics, and postbiotics); the pathology, in this case was included the illness (COVID-19) and the virus (SARS-CoV-2 and Coronavirus) and; the main problem/discussion, in this case, were included descriptors for microbiota, clinical trials, prevention, and treatment. Second, based on the identified terms, a search procedure was performed. For the Scopus the following terms were utilized: ("probiotics" OR "prebiotics" OR "synbiotics" OR "paraprobiotics" OR "postbiotics") AND ("COVID-19" OR "Coronavirus" OR "SARS-CoV-2") AND ("microbiota" OR "clinical trials" OR "prevention" OR "treatment" OR "therapy").

In the third step, three authors reviewed, independently, the title, abstract, and keywords to define the studies' relevancy. The Scopus database returned 323 articles. Lastly, the full-text of 183 studies was read. In this section, 99 studies were foreclosed for several reasons: not explicitly discussing the use of these supplements in the prevention and/or therapy in COVID-19 patients; the modulation of microbiota addressed other pathologies not associated with SARS-CoV-2 infection; insufficient information about the topic; no adequate relation to the global pandemic of COVID-19 in the discussion of the articles. All the citations and references from the selected publications were reviewed to prevent any vital reference loss.

Data collected in the Scopus database were then accomplished utilizing the VOSviewer v.1.6.17 (https://www.vosviewer.com/) in order to gather information related to countries network, co-occurrence networks of author keywords, and co-occurrence networks of terms in title/abstract. The data extracted from Scopus to obtain the terms present in titles and abstracts were processed utilizing binary counting without considering a repeated item in the same publication, according to the network view map. The software enables the elaboration of a map of co-occurrence terms from data exported in an Excel file format.

Only scientific papers from 2020 to 2021 were included. The entire review process was done during the month of December 2021. Results and discussion were organized into four sections. The first section introduces bibliometric analysis and scientific production; the second summarizes the main findings and discussion on the importance of reinforcing the gut-lung axis through administration of probiotics against COVID-19; the third highlights the clinical evidence in relation to the use of probiotics aiming at COVID-19 treatment and prevention; finally, the fourth discusses the potential role and the advantages of using postbiotics in minimizing and preventing COVID-19.

3. Bibliometric analysis and scientific production

This bibliometric analysis aims to provide an approach of how scientific production associated to potential preventive and therapy measures by the administration of probiotics, prebiotics, synbiotics, and postbiotics has evolved throughout the pandemic of COVID-19. In this study, eighty-four scientific papers published from the beginning of the global pandemic until December 2021 were analyzed. The main papers reporting the effects of these supplements on the health of COVID-19 patients are described in Table 1. The results reported that the three journals with the highest number of citations are Virus Research (210), The Lancet Gastroenterology and Hepatology (74), and Nutrients (74). It is also noted that these three most cited periodicals express 56.9% of the 629 total citations, and that more than 50% of these publications have

Table 1
Main scientific articles reporting the effects of probiotics, prebiotics, synbiotics, and postbiotics in health of COVID-19 patients.

Authors	Country	Type of document	Supplement	Outcomes of interest
Ailioaie and Litscher (2021)	Austria and Romania	Review	• Probiotic	• Probiotics might have the capacity to modulate the action of cytokine storm, an exacerbated immune response in COVID-19 patients
Akatsu (2021)	Japan	Review	• Probiotic • Prebiotic • Postbiotic	• Modulation of the intestinal microbiota with probiotics, prebiotics or postbiotics is a viable manner to improve the effects of vaccination in older people • It could improve immune responses, including sustainable activities of natural killer cells and antibodies, in addition to preventing the process of dysbiosis
Akour (2020)	Jordan	Review	• Probiotic • Prebiotic	• Consumption of prebiotics and probiotics as modulating agents of the intestinal microbiota may offer a new and economical methodology to reduce the risk of viral infections • The antiviral and anti-inflammatory effect of the use of probiotics can potentially collaborate, at least partly or in conjunction with other medications to prevent and/or relieve the symptoms of COVID-19.
Allali et al. (2021)	Morocco	Review	• Probiotic	• The administration of probiotics, as a new therapeutic approach, to balance the composition of the intestinal microbiota can favor the intestine-lung axis towards a more diverse microbiome could favor the immune system and regulate inflammation, which is one of the main COVID-19 symptoms
Antunes et al. (2020)	Argentina and Brazil	Review	• Probiotic • Prebiotic • Synbiotic	• Probiotics, prebiotics, and synbiotics are able to modulate the intestine, helping with intestinal dysfunctions presented by patients with severe cases of COVID-19 • The administration of probiotics in the diet of patients with gastrointestinal symptoms related to COVID-19 and those with mild-to- moderate systemic symptoms can be an alternative for preventing cytokine storm
Anwar et al. (2021)	Saudi Arabia, Australia, and India	Original	• Probiotic	• The computational representation depiction and molecular dynamics study demonstrated that postbiotics, plantaricin compounds, resulting from the metabolism of *Lacticaseibacillus plantarum* showed antiviral activity • They block the viral entry by binding with RNA-dependent-RNA polymerase (RdRp) enzymes, SARS-CoV-2 receptor-binding domain (RBD) and angiotensin-converting enzyme 2 (ACE2)
Baindara et al. (2021)	United States and India	Review	• Probiotic	• Evidences suggest that probiotics strains may have a beneficial effect to forestall or relieve COVID-19 symptoms due to anti-inflammatory and immunomodulatory properties • Probiotics may collaborate against SARS-CoV-2 infection through synthesis of peptides and antimicrobial metabolites. • The use of probiotics may alleviate symptoms associated to the dysbiosis process, promote anti-inflammatory effect, immunomodulation, and microbial activity. Consequently, supplementation with these probiotic strains may contribute to avoid the secondary infection process.
Balmeh et al. (2021)	Iran	Original	• Postbiotic	• Products resulting from the metabolic activity of *Lactococcus lactis* and *Lactiplantibacillus plantarum* such as glucocin F and lactococcine G, respectively, may be administrated as a therapy for inhibiting SARS-CoV-2 infection
Bottari et al. (2021)	Italy	Review	• Probiotic	• Modulation of the intestinal microbiota is among the prevention and treatment approaches against COVID-19 due to evidence of the gut-lung axis, making the use of probiotics a strategy to be considered by health professionals • Probiotic potentially attenuates COVID-19 through immunomodulatory actions in systemic inflammation
Chattopadhyay and Shankar (2021)	India	Review	• Probiotic • Prebiotic	• Prebiotics can decrease pro-inflammatory IL-6 which is related to the severe prognosis in COVID-19, and increase anti-inflammatory IL-10 • Combined approaches including probiotics and prebiotics could be useful to improve the immune response and prevent a microbiota dysbiosis induced by drugs such as Azithromycin
Conte and Toraldo (2020)	Italy	Letter to the Editor	• Probiotic • Prebiotic	• Evidences suggest that probiotics strains may have a beneficial effect to forestall or relieve COVID-19 symptoms due to anti-inflammatory and immunomodulatory properties • Probiotics may collaborate against SARS-CoV-2 infection through synthesis of peptides and antimicrobial metabolites. • The use of probiotics may alleviate symptoms associated to dysbiosis process, promote anti-inflammatory effect, immunomodulation, and microbial activity. Consequently, supplementation with these probiotic strains may contribute to avoid the secondary infection process.
Dai et al. (2021)	China and France	Review	• Probiotic • Prebiotic	• Proposes alternative therapies, including probiotics and prebiotics, to prevent/treat viral infections, including SARS-CoV-2 • Probiotics and prebiotics could promote an enhanced expression of tight junction proteins to maintain the intestinal barrier integrity; prevent opportunistic infections and boost human immune functions by stimulating the immune cells, besides contribute to gut modulation
	Brazil	Review	• Probiotic	

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Table 1 (*continued*)

Authors	Country	Type of document	Supplement	Outcomes of interest
de Oliveira, Oliveira, Pinzan, de Salis, and Cardoso (2021)			• Synbiotic	• Adjuvant therapies including the use of prebiotics and/or probiotics aimed at restoring the state of eubiosis may show an alternative approach to improve or prevent worsening of the symptoms of COVID-19 • Regular consumption of fermented foods containing probiotic strain support to the immunomodulation of the intestinal microbiota • Probiotics supplementation and synbiotic therapy may contribute to treat diarrhea related to SARS-CoV-2 infection or to use of antibiotics • Adjunctive treatment focused on the modulation of the intestinal-lung crosstalk may be a relevant instrument to support the intense inflammatory process that generally worsens the diagnosis of COVID-19
Dhar and Mohanty (2020)	India	Review	• Probiotic • Prebiotic	• The impact of SARS-CoV-2 infection might be minimized in older adult and immunocompromised patients with a diet composed of probiotics and prebiotics as a complement to current routine therapies to improve the overall immune response
Di Pierro (2020)	Italy	Letter to the Editor	• Probiotic	• *Streptococcus salivarius* K12 might be considered an option by healthcare professionals as an adjunct to control viral lung secondary infections and those related to pneumonia of COVID-19 patients
Di Renzo, Merra, Esposito, and De Lorenzo (2020)	Italy	Letter to the Editor	• Probiotic • Prebiotic • Postbiotic	• Malnutrition contributes to the worsening of immunity already impaired by COVID-19 • The use of probiotic strains, such as *Lacticaseibacillus rhamnosus* and *Bifidobacterium lactis* HN019, promote anti-inflammatory effects, balance of the gut microbiota, and prevent of secondary bacterial infections in patients with nutritionally deficient and COVID-19 • Immunomodulation with prebiotics, probiotics, postbiotics, polyphenols, and zinc, restores innate and adaptive immunity and it might be an adjunctive therapeutic option for COVID-19
Di Stadio et al. (2020)	Italy, Israel, and United States	Review	• Probiotic	• The supplementation of probiotics might be considered as an adjunctive treatment to modulate the immune response against COVID-19 • Probiotics can effectively modulate the immune system and have antiviral capabilities, which seems more appropriate to combat SARS-CoV-2 infection • Intestinal dysbiosis increases the possibility of infection, so the use of probiotics can positively modulate the microbiota, being an adjuvant treatment to COVID-19
Dicks and Grobbelaar (2021)	Africa	Review	• Probiotic	• Probiotics could be utilized to interfere with virus–target cell identification or interact with virions to make viral infection more difficult
Din et al. (2021)	China and Pakistan	Review	• Probiotic	• Probiotics can reduce the inflammation, improve the immune response, enhance the gut barrier function, as well as prevent opportunistic infections by harmful bacterial strains • Studies and trials for probiotics use in COVID-19 are essential
Fanos et al. (2020)	Italy	Review	• Probiotic	• The maintenance of a well-established intestinal microbiota with the presence of commensal microorganisms might significantly influence the need for ventilation in the treatment of SARS-CoV-2 patients • Probiotic strains belonging to *Bifidobacterium* and *Lactobacillus* genera are the most recommended for treatment of patient with COVID-19
Garofolo, Qiao, and Maia-Lemos (2021)	Canada and Brazil	Review	• Probiotic	• Probiotics could be utilized as an adjunctive measure in the prophylaxis of COVID-19 for host immunomodulation and microbiota antiviral activity • The nutritional approach may promote anti-inflammatory activity and it should be proposed to patients with cancer in order to decrease the physiological damages of pro-inflammatory states to prevent and minimize the severity of COVID-19
Gasmi et al. (2021)	France, Thailand, India, Italy, Luxembourg, Iran, and Norway	Review	• Probiotic • Prebiotic	• Dietary interventions, including the supplementation with pre and probiotics can prevent severe outcomes in COVID-19 patients • Prebiotics and probiotics can mediate the microbiota antiviral immunity by their potential immunomodulation effects • More evidence is required to conclude the role of specific probiotic strains in therapeutic management of COVID-19
Gautier et al. (2021)	France and Lebanon	Review	• Probiotic • Postbiotic	• Disorders in the process of immune homeostasis stimulated by SARS CoV-2 infection may be induced by intestinal microbiota • The ingestion of non-toxinogenic *Bacteroides fragilis*, *Faecalibacterium prausnitzii*, *Akkermancia muciniphila*, *Clostridium butyricum*, *Propionobacterium freundenreichii,* and *Staphylococcus epidermidis* can collaborating to immunomodulation or synthesis of metabolites that may reduce the inflammation process in the lungs
Gohil, Samson, Dastager, and Dharne (2021)	India	Review	• Probiotic	• The administration of probiotics will help boosting the host-immunity, and it may reduce the incidence and symptoms of COVID-19
Hamida et al. (2021)	Egypt and Saudi Arabia	Review	• Probiotic • Postbiotic	• Kefir may act as a protective agent against viral infections to Inhibitor of expression of pro-inflammatory cytokines in COVID-19 patients

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Table 1 (*continued*)

Authors	Country	Type of document	Supplement	Outcomes of interest
				• Secondary metabolites acidic resulting from metabolism of microorganisms presents in kefir grains create an acidic pH environment, change the pH in a specific area when it is consumed. The SARS CoV-2 replication dependents in mildly alkaline pH, so the kefir may hamper the activity of this pathogenic viral
Harper et al. (2021)	United Kingdom, Finland, United States, France, Spain, Canada, and India	Review	• Probiotic	• Probiotics could avoid the microbiota disorders noted in some cases of COVID-19 by prevent the growth of pathogenic bacteria and/or facilitating the recovery of beneficial microorganisms • Probiotics could increase immune system activity through crosstalk with immune cells and/or strengthening the gut barrier
Hegazy et al. (2021)	Egypt	Original	• Probiotic • Prebiotic	• Modulation of the intestinal microbiome may have contributed to reduce the severity of COVID-19
Hu et al. (2021)	China	Review	• Probiotic • Prebiotic • Synbiotic	• Microbiota disturbance is observed in cases of SARS-CoV-2 infections and it may be associated with disease severity • Dietary interventions, including probiotics or selected prebiotics during COVID-19 pandemic could positively impact host immune functions during SARS-CoV-2 infection, strengthening the intestinal barrier and pro-inflammatory states • Identify bacterial species and prebiotics, or a combination that can boost the immune activity, and better understand the mechanisms related to the anti-viral immunity for SARS-CoV-2 infection are required.
Hung, Lee, Lee, Tsai, and Ko (2021)	Taiwan	Review	• Probiotic	• Evidence demonstrates that the effect of supplementation with commercial probiotics in the treatment of patients with COVID-19 may have antiviral effects and reach homeostasis through the gut-lung axis
Infusino et al. (2020)	Italy	Review	• Probiotic	• The administration of probiotics may represent a complementary alternative to reduce the inflammation caused by the SARS-CoV-2 infection • Modulation of the microbiota would favor the recovery of the intestinal mucosa due to viral infection
Kullar, Johnson, McFarland, and Goldstein (2021)	United States	Review	• Probiotic	• The use of specific or mixtures probiotic strains may prevent antibiotic-associated diarrhea, *Clostridioides difficile* infections and ventilator-related pneumonia in patient with COVID-19
Lee and Hong (2021)	Republic of Korea	Review	• Probiotic	• The administration of probiotics as an adjuvant in respiratory infection, including COVID-19, can improve host immune responses
Liu et al. (2020)	China	Review	• Probiotic	• The supplementation of probiotics is an effective and safe intervention for combat the diarrhea symptoms related to COVID-19
Mackiewicz, Lemieszek, and Dutkiewicz (2021)	Poland	Review	• Probiotic • Prebiotic	• Supportive therapy with supplementation of COVID-19 patients with probiotics, prebiotics, vitamins, and microelements is a safe and inexpensive strategy for treating SARS-CoV-2 infection with antiviral drugs, anti-inflammatory drugs, and immunomodulators
Mak, Chan, and Ng (2020)	China	Letter to the Editor	• Probiotic	• Probiotics are improbable to act directly on SARS-CoV-2 infection. Nevertheless, intestinal–lung axis has been suggested in the pathogenesis of some respiratory conditions • Lactobacilli and Bifidobacteria can really modulated the gut ecosystem in combating COVID-19 • The indiscriminate application of traditional probiotics for COVID-19 is not encouraged until we have further comprehension about the pathogenesis of SARS-CoV-2 and its action on intestinal microbiota
Manna, Chowdhury, Chakraborty, and Mandal (2021)	India	Original	• Postbiotic	• Subtilisin, curvacin A, sakacin P and lactococcin Gb, which are lipopeptides resultant from distinct probiotic strains, demonstrated a higher affinity to bind S-protein of SARS-CoV-2 and human ACE2. The amphiphilic nature of lipopeptides might act to competitively restrain the interaction of SARS-CoV-2 with the host ACE2 inhibiting its cell infection
Mirzaei et al. (2021)	Iran and Australia	Review	• Probiotic	• Probiotics may be an option for the prevention/amelioration of COVID-19 disease • Probiotics approach in COVID-19 seems to be promising in terms of treatment and vaccination
Moradi-Kalbolandi, Majidzadeh-A, Abdolvahab, Jalili, and Farahmand (2021)	Iran	Review	• Probiotic	• Recombinant probiotics have been suggested as a promising vector for live oral vaccines. Clinical studies are required to evaluate the prophylactic and therapeutic effects of the recombinant probiotics against infection by SARS-CoV-2
Morais, Passos, Maciel, and Silvia-Maia (2020)	Brazil	Review	• Probiotic	• Adjunct nutritional therapies as the use of *Lactobacillus gasseri* and diets with low purine content, especially in individuals with hyperuricemia, could enhance the immune system and hamper viral replication, helping in the treatment of COVID-19 patients
Morais et al. (2021)	Brazil	Review	• Probiotic	• Probiotics may be used as additional nutritional therapy against the SARS-CoV-2 infection by stimulate the immune system patient • A wholesome diet allied to adequately ingestion of micronutrients, bioactive compounds and probiotic strains can be alleviate symptoms of COVID-19 in patients as adjuvant agents
Mulak (2021)	Poland	Letter to the Editor	• Probiotic	• The interaction between SARS-CoV-2 and gut ACE2 might be associated to the gastrointestinal symptoms and increased COVID-19 severity

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Authors	Country	Type of document	Supplement	Outcomes of interest
				• Potential modulation of the ACE2 expression by probiotics affects the SARS-CoV-2 entry into cells and the inflammatory response
Olaimat et al. (2020)	Jordan, United Arab Emirates, Australia, Singapore, and China	Review	• Probiotic • Prebiotic	• Probiotics could be a potential inhibitor to the ACE receptor by bioactive peptides production and help to prevent COVID-19 by stabilize the gastrointestinal tract and lung microbiota, since dysbiosis plays a major role in the opportunistic infectious diseases • Prebiotics may have a potential effect against COVID-19 by promote the probiotics growth and resistance and a direct effect on gastrointestinal symptoms caused by COVID-19
Patra et al. (2021)	India	Review	• Probiotic	• Probiotics may be a potential alternative strategy to prevent mild and severe stages of COVID-19 by producing antimicrobial peptides or bacteriocins, short-chain fatty acids, and ACE inhibitory peptides. These probiotics related compounds could modulate the immune system leading to the downregulation of inflammatory pathways and secretion of proinflammatory cytokines • Probiotics and bacteriocins are suggested to balance pro- and anti-inflammatory cytokine levels and increase the T-cell count in the SARS-CoV-2-infected individuals. The probiotic ability to degrade hyaluronan has been suggested to improve the acute respiratory distress syndrome
Peng, Zhang, Yao, Kwok, and Zhang (2021)	China	Review	• Probiotic	• The administration of probiotics contributes for modulation of the gut-lung axis as an adjunctive treatment for COVID-19
Reuben, Makut, and Adogo (2021)	Germany and Nigeria	Commentary	• Probiotic	• Probiotic strains have been effectively used over the last years to reduce the incidence and severity of different intestinal and respiratory tract viral infections. There is substantial evidence for the positive effect of the use of probiotics against COVID-19 to reduce the disease severity and its related comorbidities thereby mitigating the pandemic
Şahin (2020)	Turkey	Letter to the Editor	• Probiotic	• Probiotics may contribute to strength the immune system and be an important prophylaxis to be implemented against COVID-19 • Probiotics might also have an effective management of gastrointestinal symptoms, which is an important factor in reducing the transmission and mortality from COVID-19 pandemic
Santacroce (2020)	Italy	Letter to the Editor	• Probiotic • Postbiotic	• Probiotics synthesize antimicrobial compounds and bioactive molecules such as short-chain fatty acids that can modulate the immune system, as well as restore intestinal homeostasis • The interaction between SARS-CoV-2 and other viruses in a dysbiosis process can infect intestinal cells and spread more easily through the body in a dysbiosis process. Thus, this fact reinforces the importance of maintenance of intestinal homeostasis with the supplementation of probiotics in the diet with a protective factor against COVID-19
Santacroce et al. (2021)	Italy and Albania	Review	• Probiotic	• Strains belonging to the *Lactobacillus* and *Bifidobacterium* genera are the main probiotics used to reestablish the microbiota disturbance associated with the SARS-CoV-2 infection • By restoring the eubiosis of the gut microbiota, probiotics might collaborate with an anti-inflammatory effect, and reduce the translocation of pathogens preventing opportunistic infections • The use of probiotics to treat SARS-CoV-2 comes from few clinical studies and indirect evidence; however, it is recommended to use probiotic strains, and their metabolites, to strengthen innate and adaptive immunity in patients with SARS-CoV-2, as an adjunct strategy against complications
Shahbazi, Yasavoli-Sharahi, Alsadi, Ismail, and Matar (2020)	Canada	Review	• Probiotic	• Considering the strong links between the immunity and severity of viral infections, the development of strategies to reinforce the immune system might be useful in prevent infection by SARS-CoV-2 or reduce the COVID-19 severity • The administration of probiotics in infection by SARS-CoV-2 prevention or treatment comes from indirect observations
Singh, Shaik, Mehra, Kashyap, and Surani (2021)	India and United States	Review	• Probiotic	• The probiotic strains can be used as an adjunct in the prevention of Acute Respiratory Distress Syndrome, a significant complication of COVID-19 • Intake of probiotics modulate the balance between pro-inflammatory and anti-inflammatory cytokines that assist in viral clearance and, at the same time, reduce lung damage mediated by the immune response • Probiotics could inhibit the cytokine storm that occurs as a result of SARS-CoV-2 infection
Spagnolello et al. (2021)	Italy and Brazil	Review	• Probiotic	• A more successful symptoms control and consistent reduction in mortality were found in COVID-19 patients pneumonia receiving oral bacteriotherapy as an adjuvant treatment • Advantages for probiotic therapy include mostly cheap, freely available, and with limited/no adverse effects
Stavropoulou and Bezirtzoglou (2020a)	Switzerland and Greece	Opinion	• Probiotic	• Probiotics can take a therapeutic approach against COVID-19 by stimulation the immune system, improvement the mucosal barrier function, and preclude the accession of the microorganism pathogenic • Probiotic should be administered with attention, particularly, in critically patients. The probiotics are not suggested in cases of patients with immunologically compromised or who use prosthetic valves, since the high

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Table 1 (*continued*)

Authors	Country	Type of document	Supplement	Outcomes of interest
				risk of invasive infections. Furthermore, certain strains may influence in medication metabolism and bioavailability
Stavropoulou and Bezirtzoglou (2020b)	Switzerland and Greece	Review	• Probiotic • Postbiotic	• The intestinal microbiota acts, through the intestine-lung axis, as a protective mediator during pneumonia. Because of this, probiotics can alleviate gastrointestinal and respiratory symptoms in a patient with COVID-19 • Polyphosphates derived from probiotics strengthen the epithelial barrier and promote intestinal homeostasis • Probiotics can prevent or reduce inflammation in respiratory infectious diseases
Tian and Rong (2020)	China	Letter to the Editor	• Probiotic	• Probiotics can be more efficient in treat patient with critical symptoms of COVID-19 since to the elevated degree of inflammation or in the patients at considerable chance of co-infection through mechanical ventilation • Supplementation with probiotic strains in the routine treat in cases of mild symptoms of COVID-19 patients or asymptomatic is not necessary, since the process of intestinal dysbiosis was less intense in most cases
Walton et al. (2021)	United Kingdom	Review	• Synbiotic	• The modulation of the intestinal microbiota through dietary agents (prebiotics and probiotics) may be used as an adjunct in the treatment of this pathology, since immunomodulation might contribute to prevent secondary bacterial infection in patients with COVID-19 • The supplementation with synbiotic can be a relevant factor before vaccination against COVID-19, especially, in the parcel of the population with metabolic diseases and in relation to elderly population who may have unbalanced intestinal microbiota

an impact factor range of 4.813–18.486. Among the 10 most cited publications, 7 were review articles, followed by letters to the editor and original articles with 2 and 1 publications, respectively. A total of 5 subject areas were identified in all the top 10 publications. Each subject area was selected according to the source titles appertains to; in some cases, the periodicals had more than one subject area. The most pertinent subject area in the selected topics relates mainly to the Medicine area, accounting for 37.4% of the chosen publications. This subject area includes the following research fields and the number of papers: Infectious Diseases (1), Gastroenterology (1), Hepatology (1), General Medicine (1), Public Health, Environmental and Occupational Health (1), Pediatrics, Perinatology and Child Health (1), Pulmonary and Respiratory Medicine (1), and Pharmacology (medical) (1). The second most relevant subject areas are "Agricultural and Biological Sciences" and "Immunology and Microbiology" with 18.8% each, and the third areas were "Biochemistry, Genetics and Molecular Biology" and "Nursing" with 12.5% each. Those results show how to what extend probiotics, prebiotics, synbiotics, and postbiotics studies have multidisciplinary approaches. Thus, the multidisciplinary research of COVID-19 represents a great scientific progress and its approach is fundamental due to the virus newness, impact, and uncertainty. On other hand, the journals with most CiteScore among top the 10 are: The Lancet Gastroenterology and Hepatology (22.2), Applied Microbiology and Biotechnology (6.7), and Virus Research (5.9), i.e., two from the top 3 (Table S1). Therefore, the most cited papers are not necessarily those with the largest number of cite scores.

Of all these articles, the scientific articles that address probiotics, prebiotics, synbiotics, and postbiotics account for 73.2, 14.3, 3.6, and 8.9%, respectively (Fig. S1). Reviews and original articles account 69% (n = 58) and 19% (n = 16), respectively, totalizing 88% of all publications. Other publications were represented by letter to editor (n = 8; 10%), opinion (n = 1; 1%), and commentary (n = 1; 1%).

The global distribution of the scientific papers was divided by continent (Table S2). In this sense, Asia (n = 58; 43%) was the continent with the highest number of publications, followed by Europe (n = 53; 39%); Americas (n = 17; 13%); Africa (n = 4; 3%); and Oceania (n = 3; 2%).

Considering our research topic, in Asia the country with the highest number of contributions was India (n = 16; 28%), in Europe it was Italy (n = 17; 32%), and in America it was Brazil (n = 6; 35%), as showed in Table S2. Australia and countries from the African continent had lower numbers of publications. Indeed, India has shown the highest number of cases reported in Southeast Asia to date (WHO, 2021), and from June 2020, Brazil has been among the 10 countries most affected by the pandemic (Sharma, Bansal, Yadav, Jain, & Garg, 2021), which may have boosted research in this topic. On the other hand, the pandemic has had a very low impact on countries from Oceania (WHO, 2021), whereas African countries have been suffering political and economic instability for many years (Mwelwa, Boulton, Wafula, & Loucoubar, 2020), which could be the reason for the low number of studies.

Despite being among the most affected country by the pandemic, according to John Hopkins University (2021), Spain had only one publication in collaboration with the United Kingdom, Finland, the United States, France, Canada, and India, considering the topic covered by our study (Harper et al., 2021).

In Fig. 1, co-authorship network of countries, India, Italy and China are arranged in a position of influence of the network of countries by authorship affiliations, since these countries presented the highest number of publications (16, 17, and 10, respectively) and co-authorship network (17, 13, and 3 co-occurrences networks, respectively). Despite a lower number of scientific publications, other countries such as France and the United States presented a relevant number of connections (13 and 8, respectively), evidencing an extensive collaboration network of these countries, considering the present research topic.

The first publications date from April 2020 (Di Pierro, 2020; Fanos, Pintus, Pintus, & Marcialis, 2020, Table 1) and start gaining prominence from mid-2020, after the "first wave" of the pandemic (Fig. 1). Italy, India, Iran, China, and Brazil were the countries with more contributions in terms of number of publications, accounting for around 78% of total papers published in 2020. More articles were published from that date until December 2021, and France was the country which more recent papers.

The top 10 keywords most frequently used are shown in Fig. S2. "COVID-19" and "Probiotics" were cited in 48 and 42 papers, respectively accounting for 54% of the top 10 keywords, whereas, "SARS-CoV-2", "Gut-lung axis", "Microbiota" and "Gut microbiome" were cited in 54 papers, totalizing 32% of the top 10 keywords. The term "Prebiotic" was present in four papers. Indeed, probiotics, prebiotics, gut microbiome, microbiota, as well as the gut-lung axis are the most studied topics related to the prevention or treatment of COVID-19 in our search. Since postbiotics (including the old term "paraprobiotics") is a more recent approach as a research topic, it was less frequent in the keyword terms, present in one paper, although five papers addressed postbiotics.

In this sense, a more detailed bibliometric analysis was performed on the current trends to address microbiome-modulation through supplements (probiotics and prebiotics) administrated in the diet of patients with COVID-19, with the objective of identifying the frequency of the keywords in the articles found. Fig. 2a–b shows the analysis of co-occurrence networks of keywords from the selected publications. Some studies report that in a bibliometric analysis, the analysis of keywords is a fundamental part of the methodology, since it plays a crucial and furthering role in areas such as co-word analysis and information consultation, serving as a filter in study searches (Li, 2018; Melo et al., 2021; Rodríguez-Rojas, Ospina, Rodríguez-Velez, & Arana-Florez, 2019).

According to Fig. 2a, it was possible to check that the most frequent author keywords (largest circles) were: "covid-19", "probiotics", "sars-cov-2", and "gut-lung axis". From the bibliometric mapping originated by the software, the terms were separated and classified into eight clusters. The red cluster contains the largest number of items, including keywords more focused on prevention of COVID-19 (coronavirus disease 2019, cytokine storm, gut microbiome, immunotherapy, prevention, and therapy). In this regard, the blue and yellow cluster grouped keywords associated to process of immunomodulation (gut microbiota, immunomodulation, lactic acid bacteria, probiotics, SARS-CoV-2, and vaccines) and treatment through modulation of the intestinal microbiota (adjunctive therapy, anti-inflammatory, *Bifidobacterium*, immune system, and *Lactobacillus*). The violet cluster, which contains 5 items, grouped terms focused on immune response against SARS-CoV-2 infection (elderly, immunity, immunomodulatory, influenza, and probiotic). Moreover, the green cluster contained terms mostly concerning dietetics aspects (diet, fermented foods, microbiota, nutrition, pandemic, prebiotics, SARS-CoV-2, and viral infection). Lastly, the orange and clusters contained terms more related to gut and lung microbiome (gut, lung, microbiome, and pneumonia) and inflammation process resultant of COVID-19 (ACE2, COVID-19, inflammatory, and plantaricin).

Through observation of these data in Fig. 2a–b, it might be asserted that the microbiome modulation is promising for prevention/treatment in COVID-19 patients, since it showed immunomodulation properties as a result of supplementation with probiotics and prebiotics. These properties can be influenced by the presence of a microbiota commensal established in a eubiosis process (Ballan, Battistini, Xavier-Santos, & Saad, 2020). Specialized cells release immunoglobulins and specific antibodies and mediate host defense by eliminating intracellular pathogens and virus infected cells (Gill & Guarner, 2004). Thus, it is explicit that although there is little information in the literature on the relation between microbiome modulation and COVID-19, the functional properties of these supplements have been studied in some ongoing clinical studies (Table 2).

The main research hot topics for publications associated to prevention/treatment and/or microbiota-modulation in COVID-19 patients were visualized and shown by mapping of co-occurrence networks of terms in the title/abstract of selected scientific articles (Fig. 3a and b). Thus, 24 terms were inserted into the network and clustered into three groups (red, green, and blue), that are showed with different colors.

Moreover, the blue cluster involved terms associated to clinical aspects such as "inflammation", "patient", "death", "impact", or "mortality". On the other hand, the blue cluster included terms related to

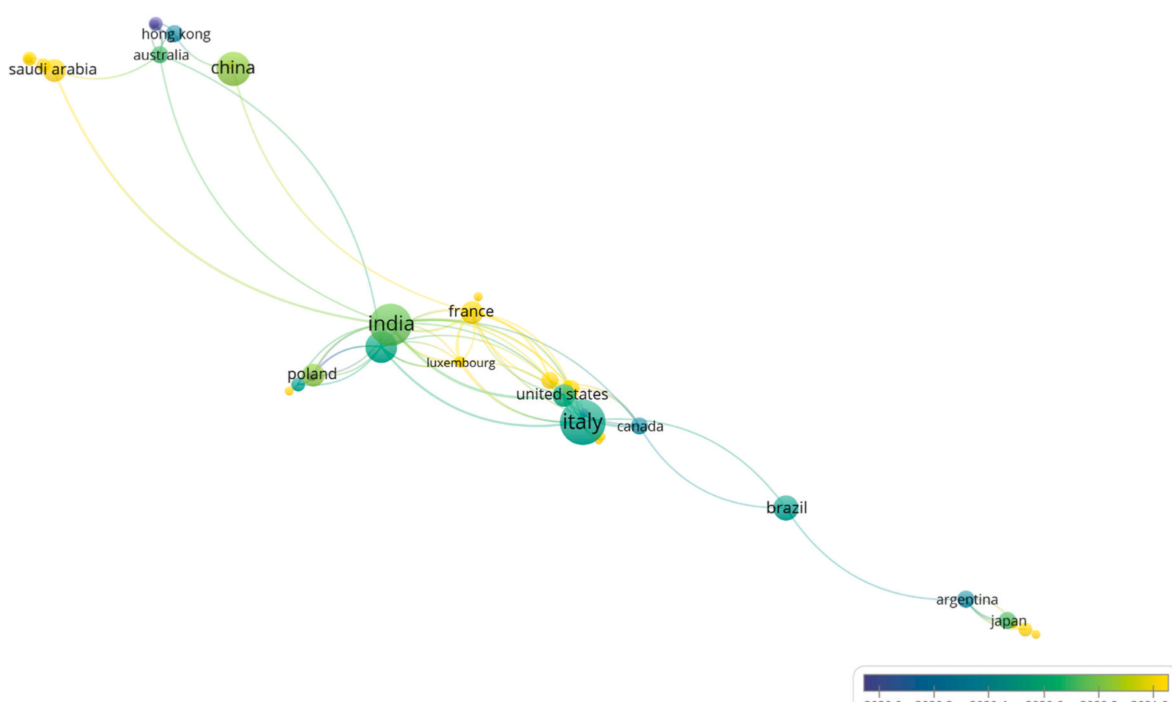

Fig. 1. Countries network according to authorship affiliations. Forty-seven countries were included in the network. Greece, Iraq, Morocco, Russian, South Africa, Taiwan, and Turkey were identified, but showed no co-occurrence network.

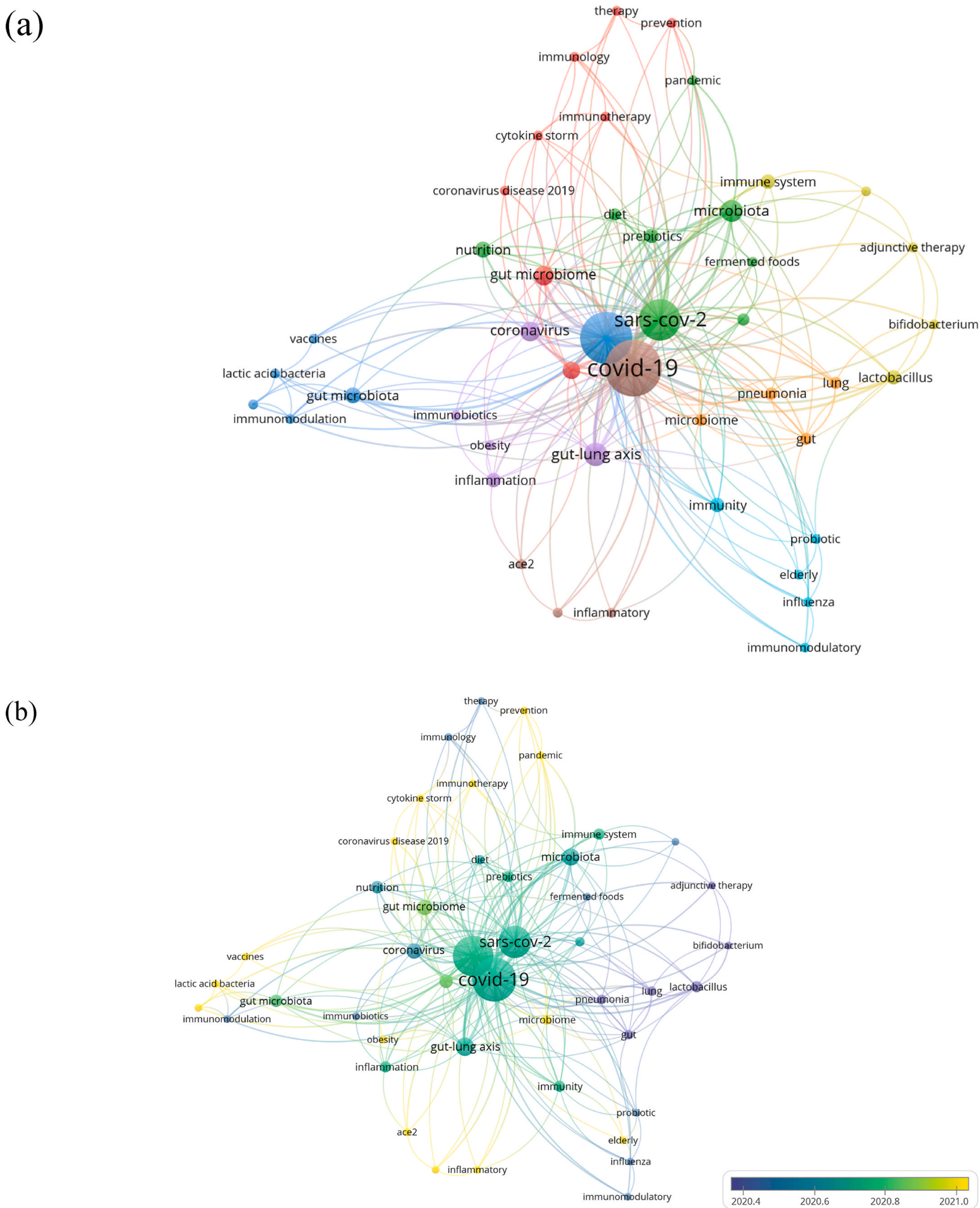

Fig. 2. Co-occurrence networks of 45 author keywords which appeared at least two times. The keywords-networks are colored according to the five generated clusters (a) and gradient color (b) which indicates the period of the keywords occurrence from 2020 (blue) to 2021 (yellow). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

prevention/therapy topic such as "gut lung axis", "immune system", "severe acute respiratory syndrome", or "vaccine", while the cluster green involved terms associated to microbiota modulation in COVID-19 patients topic such as "covid", "diet", "gut microbiota", "gut", "immunity", "prebiotic", "probiotic", or "severity".

In addition to contributing to explain publication trends, Fig. 3b revealed that the principal goals of intestinal microbiota modulation in patients with COVID-19 are related to immunomodulatory properties and their respective beneficial impact on health. However, it is possible to note that the terms present in this network are concentrated in the year 2020. This may indicate that clinical trials, many of which are still ongoing, may bring robust scientific evidence and support information reported in this bibliometric analysis (Table 2).

In this study, the bibliometric analysis reported above, provided as a basis for leading the systematic review, approached the topics of highest relevance for microbiome modulation by means of these supplements as an adjunctive therapy, safe, effective, and a low-cost strategy to support prevention or and treatment of COVID-19.

4. Gut-lung axis, pre- and probiotics supplementation and COVID-19 prevention/treatment

Arguably the COVID-19 pandemic has changed the way people live. After almost two years of pandemic, we are still learning how to prevent and treat it, and strategies to mitigate the spread of the virus and severity of the infection are extremely necessary (Tang et al., 2021). In this way, it is known that the intestine and the lung, are organs that shares a relationship by influencing immune responses and inflammatory processes through the gut-lung axis, and both may respond to the treatment with pre and/or probiotics (Baindara et al., 2021).

Recently, probiotic supplementation has been suggested as adjunctive treatment against COVID-19 due to its current administration for preventing and treating several viral infections (Conte & Toraldo, 2020; Olaimat et al., 2020; Patra et al., 2021; Santacroce et al., 2021; Stavropoulou & Bezirtzoglou, 2020a). In this sense, some general mechanisms of probiotics are inhibition of microbial adherence, enhancement of the gut barrier function and boosting of the immune system (Stavropoulou & Bezirtzoglou, 2020b). More specifically, probiotics can influence intestinal epithelial cells to modulate cytokines; provide IgA secretion; activate phagocytosis; modulate the function of regulatory cells; induce dendritic cell maturation; strengthen the mucosal barriers and minimize viral entry (Bottari, Castellone, & Neviani, 2021; Patra et al., 2021). Those mechanisms may favor viral clearance, as well as to prevent/combat bacterial co-infections associated with COVID-19 (Patra et al., 2021).

The secretion of bioactive peptides with angiotensin converting enzyme (ACE) inhibitory activity by some lactic acid and probiotic strains was proposed to act blocking the active site of infection of SARS-CoV-2 (Olaimat et al., 2020). The effect of those bioactive peptides in modulating blood pressure, due to the inhibition of angiotensin-I to angiotensin-II conversion, is well-known. Presently, those peptides have been prospected to act also by reducing the progression of COVID-19 (Mulak, 2021). Prebiotics also have potential effect against this disease by stimulating probiotics growth and blocking ACE enzymes (Conte & Toraldo, 2020).

The lung microbiota is less studied than the gut microbiota. It is known that to be a dynamic and transient ecosystem with microorganisms belonging to this niche coming mostly from the mouth, inhaled air and the digestive tract due to microaspiration (Allali, Bakri, Amzazi, & Ghazal, 2021). Respiratory inflammation caused by SARS-CoV-2 is able to cause local dysbiosis and allows translocation of microbial metabolites and toxins to the gut and other organs, as long as antibiotics and antivirals used for the COVID-19 treatment could also result in further intestinal microbiota imbalance (Conte & Toraldo, 2020; Santacroce et al., 2021).

Santacroce et al. (2021) described in COVID-19 a dysregulation of four biological communication axes: gut/lung, gut/brain, gut/skin and skin/brain microbiota. Beneficial microbes delivered by water/-food/environment may access the gut, lung, skin and other tissue, compose the local microbiota, compete with pathogens and promote protection (Antunes et al., 2020; Conte & Toraldo, 2020). On the other hand, the gut-lung axis enables the migration of immune cells from the gut to the lung (Patra et al., 2021). Not only can immune cells be exchanged through this axis, but also intact bacteria and their metabolites (such as short-chain fatty acids) can enter the systemic circulation via the mesenteric lymphatic system and influence the pulmonary immune response (Olaimat et al., 2020; Patra et al., 2021; Santacroce et al., 2021). Besides, probiotics are able to restore dysbiosis and maintain gut immune homeostasis by intra and extra cellular molecules like peptidoglycan, lipoteichoic acid and phospho-polysaccharides (Bottari et al., 2021).

Patra et al. (2021) reaffirmed that the resident gut microbiota is able to modulate the immune system and improve lung infections. This group identified candidate genes associated to COVID-19 and probiotic treatment. The tools used by this group were systematic biological network and meta-analysis. During SARS-CoV-2 infection, loss of equilibrium between IL-10 and IL-17 and pulmonary acute damage known as "cytokine storm" are observed (Santacroce et al., 2021). Probiotics could improve the inflammatory condition by regulating oxidative stress (Patra et al., 2021). In this context it is important to emphasize that probiotic supplementation needs to be carefully evaluated because there are many different strains and multistrain products, whose profile of immune modulation is not likely to be the same. Some probiotic strains may promote anti-inflammatory response, but the opposite response is also possible to be observed. Although a proinflammatory state can be useful to accelerate viral clearance, in a context of cytokine storms, this strategy can put the lung function at risk, greatly hindering gas exchange at the alveolar level. According to Stavropoulou and Bezirtzoglou (2020b) special attention should be given to patients immunocompromised receiving corticosteroid therapy. In this situation probiotics should not be recommended.

Using a machine learning model (Gou et al., 2021), observed a core set of intestinal microbiota that could precisely foretell proteomic biomarkers among subjects highly correlated with proinflammatory cytokines. According to them, the genera *Bacteroides* and *Streptococcus* and the order *Clostridiales* correlated negatively with most of the tested inflammatory cytokines, whereas the genera *Lactobacillus, Blautia and Ruminococcus* presented positive associations. Next generation sequencing searching for potential taxonomic biomarkers (microbiome signatures) capable of predicting the evolution and prognosis of COVID-19 (Allali et al., 2021) can be a useful strategy. Furthermore, the intestinal microbiome might be associated to the incidence of biomarkers forecasting COVID-19 course through its structure and metabolic activity (Gou et al., 2021; Zołkiewicz, Marzec, Ruszczynski, & Feleszko, 2020).

Some authors suggest the use of intranasal specific probiotics to combat pathogens in the airways and lungs, associated with modulation of immune activity, as a promising area of research in the prevention and treatment of COVID-19 (Conte & Toraldo, 2020; Olaimat et al., 2020).

5. Clinical evidence of probiotics to prevent or treat COVID-19

Several clinical studies on influenza, rhinovirus, and respiratory syncytial virus have highlighted the potential of probiotics to decrease the risk and seriousness of viral diseases in the respiratory tract (Karl, 2021).

Recently some clinical trials with probiotics in patients with COVID-19 have been initiated. Table 2 shows briefly all studies (until December 2021) registered at ClinicalTrials.gov. Observing Table 2, it appears that most of the registered studies are in the recruitment phase. Of the 29 studies registered, only 9 have been completed. Regarding intervention,

Table 2
Studies registered in ClinicalTrials.gov database related to the effects of probiotics and synbiotics in the prevention and therapy of COVID-19.

Identifier	Investigators	Country	Recruitment status	Age	Supplement	Study design	Number enrolled	Intervention	Primary outcome measures	Access link
NCT04366089	Francesco Pugliese	Italy	Recruiting	≥18 y	• Probiotic	Parallel Assignment	152	• SivoMixx (2×10^{11} of *Streptococcus thermophilus* DSM322245, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lacticaseibacillus paracasei* DSM 32243, *Lactiplantibacillus plantarum* DSM 32244, *Levilactobacillus brevis* DSM 27961) + Oxygen-ozone therapy + Standard of care or Control with Oxygen-ozone therapy + Standard of care • Six sachets (SivoMixx) twice a day	• Number of patients, in treatment, needing orotracheal intubation	https://clinicaltrials.gov/ct2/show/NCT04366089
NCT04366180	Not informed	Spain	Recruiting	≥20 y	• Probiotic	Parallel Assignment	314	• *Loigolactobacillus* K8 (3×10^9 CFU) or Placebo (maltodextrin) • One capsule/day for 2 months	• Occurrence of healthcare workers infected with SARS-CoV-2	https://clinicaltrials.gov/ct2/show/NCT04366180
NCT04390477	Vicente Navarro	Spain	Completed	≥18 y	• Probiotic	Parallel Assignment	40	• Probiotic (1×10^9 CFU) or Placebo • One oral capsule/day for 30 days	• Patients with discharge to ICU	https://clinicaltrials.gov/ct2/show/NCT04390477
NCT04399252	Anthony Sung and Paul Wischmeyer	United States	Completed	≥1 y	• Probiotic	Parallel Assignment	182	• *Lacticaseibacillus rhamnosus* GG or Placebo • Two capsules/day for 28 days	• Occurrence of one or more COVID-19 symptoms along the study interval	https://clinicaltrials.gov/ct2/show/NCT04399252
NCT04420676	Not informed	Austria	Recruiting	≥18 y	• Synbiotic	Parallel Assignment	120	• Omni-Biotic® 10 AAD (*Bifidobacterium bifidum* W23, *Bifidobacterium lactis* W51, *Enterococcus faecium* W54, *Lactobacillus acidophilus* W37, *Lactobacillus acidophilus* W55, *Lacticaseibacillus paracasei* W20, *Lactiplantibacillus plantarum* W1, *Lactiplantibacillus plantarum* W62, *Lacticaseibacillus rhamnosus* W71 and *Ligilactobacillus salivarius* W24) + a matrix containing maize starch, maltodextrin, inulin, potassium chloride, hydrolyzed rice protein, magnesium sulphate, fructooligosaccharides (FOS), enzymes (amylases), vanilla flavor and manganese sulphate or Placebo (matrix containing maize starch, maltodextrin, inulin, potassium chloride, hydrolyzed rice protein, magnesium sulphate, fructooligosaccharides (FOS), enzymes (amylases), vanilla flavor and manganese sulphate) • Administrated twice a day	• Calprotectin present in stool	https://clinicaltrials.gov/ct2/show/NCT04420676
NCT04458519	Martin Y Desrosiers	Canada	Completed	18-59 y	• Probiotic	Parallel Assignment	23	• Nasal probiotic irrigations with Probiorinse (2.4×10^9 CFU of *Lactococcus lactis* W136, (NPN: 80085895)) or Nasal placebo irrigations with saline (NeilMed Sinus Rinse, (NPN: 80027142)) • Nasal irrigations twice-daily for 14 days	• Alteration in severity of infection by COVID-19	https://clinicaltrials.gov/ct2/show/NCT04458519
NCT04462627	Hanane El Kenz	Belgium	Recruiting	≥18 y	• Probiotic	Parallel Assignment	500	Not detailed	• Levels of anti-A and -B antibody • Blood group	https://clinicaltrials.gov/ct2/show/NCT04462627

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Table 2 (*continued*)

Identifier	Investigators	Country	Recruitment status	Age	Supplement	Study design	Number enrolled	Intervention	Primary outcome measures	Access link
NCT04507867	Fernado Leal Martínez	Not informed	Completed	30-75 y	• Synbiotic	Sequential Assignment	240	• Nutritional Support System (NSS) + 2 sachets of NSS-1: Spirulina Maxima 2.5 g, folic acid 5 mg, Glutamine 5g, Cyanomax Ultra (10 g of powder), ascorbic acid 1 g, zinc 20 mg, selenium 100 mcg, cholecalciferol 2000 IU, resveratrol 200 mg, concentrated omega 3 fatty acids (10 g of powder), L-Arginine 1.5 g, and magnesium 400 mg + 500 mg of *Saccharomyces bourllardii* or Control with only NSS • Probiotic: 2 capsule/day during the first 6 days	• Several parameters associated to biochemical, hematological, anthropometric, and nutritional parameters; dietary information; body composition; COVID-19 symptoms; oxygen therapy; and mood.	https://clinicaltrials.gov/ct2/show/NCT04507867
NCT04517422	Not informed	Mexico	Completed	18-60 y	• Probiotic	Parallel Assignment	300	• Probiotics (*Lactiplantibacillus plantarum* CECT30292, *Lactiplantibacillus plantarum* CECT 7484, *Lactiplantibacillus plantarum* CECT 7485, and *Pediococcus acidilactici* CECT 7483) or Placebo (maltodextrin)	• Severity of COVID-19 progression; stay of patients at ICU; and death rate	https://clinicaltrials.gov/ct2/show/NCT04517422
NCT04581018	Siew Chien Ng	Hong Kong	Recruiting	≥18 y	• Synbiotic	Parallel Assignment	50	• Health supplements (synbiotic, 4g/day) + standard care or Control with only standard care • Twenty-eight days of health supplements (synbiotic)	• Combined score of symptoms	https://clinicaltrials.gov/ct2/show/NCT04581018
NCT04621071	Jean-Charles Pasquier	Canada	Completed	≥18 y	• Probiotic	Parallel Assignment	84	• Probiotics (2 strains 10^{10} CFU) or Placebo (potato starch and magnesium stearate) • Two capsules/day for a maximum of 25 days • The participants will stop the treatment if they are admitted to the hospital	• Duration of COVID-19 symptoms	https://clinicaltrials.gov/ct2/show/NCT04621071
NCT04666116	Not informed	Spain	Recruiting	18-99 y	• Probiotic	Parallel Assignment	96	Not detailed	• Viral load along the admission phase to the nasopharyngeal smear	https://clinicaltrials.gov/ct2/show/NCT04666116
NCT04730284	Siew Ng	Hong Kong	Recruiting	≥18 y	• Synbiotic	Single Group Assignment	20	• Health supplements (synbiotic, 4g/day) • Twenty-eight days of health supplements (synbiotic)/day	• Shifts in intestinal microbiome	https://clinicaltrials.gov/ct2/show/NCT04730284
NCT04734886	Robert J Brummer	Sweden	Completed	18-60 y	• Probiotic	Parallel Assignment	400	• *Limosilactobacillus reuteri* DSM 17938 (10^8 CFU) + vitamin D3 (10 μg) or Placebo + vitamin D (10 μg) • Two capsules/day for 6 months	• Specific antibodies for SARS-CoV-2	https://clinicaltrials.gov/ct2/show/NCT04734886
NCT04756466	Anxo Fernandez-Ferreiro	Spain	Active, not recruiting	≥60 y	• Probiotic	Parallel Assignment	201	• *Lactobacillus* probiotic strain (3×10^9 CFU/day) or Placebo (maltodextrin) • One capsule/day for 3 months	• Occurrence of infection by SARS-CoV-2	https://clinicaltrials.gov/ct2/show/NCT04756466
NCT04793997	Not informed	Belgium	Suspended	18-65 y	• Probiotic	Parallel Assignment	150	• Throat spray: Throat spray containing 3 beneficial *lactobacilli* strains or Placebo spray • Daily use for 2 weeks	• Change in gravity of infection symptoms by COVID-19 after the utilizing microbiome spray	https://clinicaltrials.gov/ct2/show/NCT04793997
NCT04798677	Julian A. Mateus Rodríguez	Spain	Recruiting	≥18 y	• Synbiotic	Parallel Assignment	90	• ABBC1 Immunoessential Powder (*Saccharomyces cerevisiae* + beta-glucan complex + selenium and zinc) or Placebo in participants who had taken COVID-19 vaccine • Dissolution in water for 30 days	• Shift in the acute and delayed immune response to the influenza vaccine and against COVID-19 after administration of supplement • Alteration in blood concentration of zinc and selenium	https://clinicaltrials.gov/ct2/show/NCT04798677
NCT04813718	Not informed	Austria	Recruiting	≥18 y	• Synbiotic	Parallel Assignment	20	• Omni-Biotic Pro Vi 5 or Placebo.	• Microbiome composition • Gut barrier	https://clinicaltrials.gov/c

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Table 2 (*continued*)

Identifier	Investigators	Country	Recruitment status	Age	Supplement	Study design	Number enrolled	Intervention	Primary outcome measures	Access link
									• Immunological and inflammatory parameters • Lung volume • Gas diffusion	t2/show/NCT04813718
NCT04847349	Daniel B Horton	United States	Recruiting	18-60 y	• Probiotic	Parallel Assignment	45	• Probiotic OL-1, standard dose or Placebo (maltodextrin) • One capsule/day for 21 days	• Alteration in the levels of serum IgG with property *anti*-SARS-CoV-2	https://clinicaltrials.gov/ct2/show/NCT04847349
NCT04854941	Not informed	Russia	Completed	18-75 y	• Probiotic	Parallel Assignment	200	• Probiotics (10^9 CFU of each strain: *Lacticaseibacillus rhamnosus* PDV 1705, *Bifidobacterium bifidum* PDV 0903, *Bifidobacterium longum* subsp. *infantis* PDV 1911 and *Bifidobacterium longum* PDV 2301) or standard treatment for COVID-19 • 3 times/day for 2 weeks	• Mortality among hospitalized patients	https://clinicaltrials.gov/ct2/show/NCT04854941
NCT04877704	Not informed	United Kingdom	Not yet recruiting	18-85 y	• Probiotic	Single Group Assignment	60	• *Symprove* probiotic (a water-based formula containing live, active bacteria) or a matched Placebo to *Symprove* probiotic	• Length of stay in the hospital bed	https://clinicaltrials.gov/ct2/show/NCT04877704
NCT04884776	Joyce WY Mak	Hong Kong	Recruiting	≥18 y	• Probiotic	Parallel Assignment	484	• Microbiome immunity formula (10^{10} of probiotics blend of 3 Bifidobacteria/sachet) or Placebo • 2 sachets/day for 12 weeks.	• Renovation of intestinal dysbiosis	https://clinicaltrials.gov/ct2/show/NCT04884776
NCT04907877	Zoriana Hoda	Not informed	Not yet recruiting	18-65 y	• Probiotic	Parallel Assignment	300	• Probiotic NordBiotic ImmunoVir (5×10^9 of a mixture of *Bifido-* and *Lactobacilli*) or Placebo (maltodextrin) • Once a day for 28 days	• Overall score of symptoms	https://clinicaltrials.gov/ct2/show/NCT04907877
NCT04922918	Not informed	Spain	Recruiting	74-98 y	• Probiotic	Single Group Assignment	25	• Fermented milk containing *Ligilactobacillus salivarius* MP101 ($>10^9$ CFU) • Daily for 4 months	• Barthel index • MNA score • Nasal and fecal immune profile	https://clinicaltrials.gov/ct2/show/NCT04922918
NCT04937556	Not informed	Spain	Recruiting	18-65 y	• Probiotic	Parallel Assignment	60	• Capsule containing *Ligilactobacillus salivarius* (10^9 CFU), vitamin D and zinc citrate • One capsules/day for 28 days	• IgM and IgG (Immunoglobulin M and G) levels of specific antibody for the SARS-CoV-2 virus	https://clinicaltrials.gov/ct2/show/NCT04937556
NCT04941703	Not informed	United States	Recruiting	≥18 y	• Probiotic	Parallel Assignment	30	• Capsule containing probiotics and 296 ml magnesium citrate • Two capsules/day for 6 days	• Reduction in the incidence of COVID-19 cases on the ordinal outcome scale	https://clinicaltrials.gov/ct2/show/NCT04941703
NCT04950803	Siew Ng	Hong Kong	Recruiting	≥18 y	• Probiotic	Parallel Assignment	280	• Sachet containing 3 Bifidobacteria (10^{10} CFU) • One sachet/day for 3 months	• Any comorbidities, including clinical manifestations related to COVID-19.	https://clinicaltrials.gov/ct2/show/NCT04950803
NCT05043376	Not informed	Pakistan	Completed	≥18 y	• Probiotic	Parallel Assignment	50	• Tablet containing *Streptococcus salivarius* K12 • Two tablets/day for 2 weeks	• Improvement of parameters associated to COVID-19 (clinical improvement)	https://clinicaltrials.gov/ct2/show/NCT05043376
NCT05080244	Jean-Charles Pasquier	Canada	Recruiting	≥18 y	• Probiotic	Parallel Assignment	618	• Capsule containing 2 strains (10^{10} CFU) • Two capsules/day for 10 days	• Number of patients with COVID-19 after of 90 days of diagnosis	https://clinicaltrials.gov/ct2/show/NCT05080244

ICU: intensive care unit; IgG: immunoglobulin G; MNA: Mini nutritional assessment; No studies results were posted at moment.

most studies are using oral supplementation.

However, two studies opted for intervention using nasal spray with probiotic strains. In this sense, Endam et al. (2020) showed that *Lactococcus lactis* W136 could safely be administered via nasal irrigation in subjects with chronic rhinosinusitis and this intervention was correlated with enhancement in sinus symptoms, and mucosal scores. In addition, it is interesting that microbiome change was associated with a relative abundance increase of *Dolosigranulum pigrum*, which is a pathobiont bacteria that has potentially beneficial effects in the upper airways. The same research group evaluated the intranasal administration of *L. lactis* W136 in twenty-three individuals within 96 h of diagnosis of COVID-19. They showed that fourteen-day intranasal therapy was associated with a reduction in symptom severity, fatigue, olfactory dysfunction, and shortness of breath. (Endam, Tremblay, Filali, & Desrosiers, 2021). Even though it is the result of a pilot study, the findings are promising.

The most commonly species used in clinical trials are *Bifidobacterium longum, Bifidobacterium animalis* subsp. *Lactis, Bifidobacterium bifidum, Lacticaseibacillus rhamnosus, Lactobacillus acidophilus, Lactiplantibacillus plantarum, Limosilactobacillus reuteri, Loigolactobacillus coryniformis, Ligilactobacillus salivarius*, *Enterococcus faecium,* and *Saccharomyces cerevisiae*. In addition, most species/strains are known as probiotic microorganisms with proven benefits in improving the immune system (West et al., 2021) or modulating the intestinal microbiota (Zhang et al., 2021).

Even in small numbers, some clinical studies with probiotics and patients with COVID-19 have already published their results, as shown in Table 3. In this way, d'Ettorre et al. (2020) showed that 70 patients with COVID-19, hospitalized, supplemented with *Streptococcus thermophilus* DSM 32345, *L. acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lacticaseibacillus paracasei* DSM 32243, *L. plantarum* DSM 32244, *Levilactobacillus brevis* DSM 27961, *B. lactis* DSM 32246, and *B. lactis* DSM 32247 for seven days. All patients treated with probiotics showed a reduction of diarrhea and other symptoms compared to the placebo group. Oral bacteriotherapy reduced the risk of developing respiratory diseases by eight times.

An interesting retrospective study carried out on 800 COVID-positive patients with diarrhea supplemented with probiotics showed that the disease duration time in the patients that were supplemented with probiotics, was significantly shorter compared to the control group and the probiotics contributed to relieving patients' abdominal distension, nausea, vomiting, and other gastrointestinal symptoms (Huaren & Zazhi, 2021).

Gutierrez-Castrellon et al. (2021) performed a randomized controlled trial with 150 symptomatic COVID-19 outpatients. The volunteers were supplemented with *L. plantarum* KABP022, KABP023 and KAPB033, and *Pediococcus acidilactici* KABP021 for 30 days. Remission was achieved by 53% in the probiotic group compared to 28% in placebo.

Tang et al. (2021) performed a first double-blind, randomized, placebo-controlled trial of 1132 individuals who ingested *L. rhamnosus* GG for 28 days that had household contact with individuals who have recently ($\leq$7 days) tested positive for COVID-19. Unfortunately, the researchers reported that the results of the of the primary and secondary outcomes have yet to be published, but this study has already revealed that probiotics are inexpensive and safe (Tang et al., 2021).

Finally, at present, there is good clinical evidence to ensure the role of probiotics to improve human immunity, thus inhibiting colonization by pathogens and decreasing the incidence and gravity of infections (Olaimat et al., 2020). Clinical studies associated with administration of probiotics to treat COVID-19 have demonstrated relevant data on the benefits of these strains for treating this disease. However, more studies should be carried out to evaluate the capacity of probiotics to fight COVID-19. Nevertheless, we believe that soon more clinical studies will be available, supporting the use of probiotics in the form of supplements or nasal spray as additional tools to mitigate the effects of COVID-19.

6. Advantages and prospects of using postbiotics and microbial metabolites in preventing and alleviating SARS-CoV-2 infection

The definition of postbiotics is recent in the scientific literature. According to Salminen et al. (2021), a postbiotic is defined as "a preparation of inanimate microorganisms and/or their components that confers a health benefit on the target host." One way to produce postbiotics is through fermentation, an ordinary and cheap process that has been around for thousands of years; in this sense, the preparation must include inanimate microorganisms in the presence, or absence of cell components such as lipids, vitamins, complex molecules, peptides or fragments of these microorganisms.

Supplementation of postbiotics is attractive considering that the administration of inactivated/dead cells will reduce the risks related to intake of live bacteria, mainly for immunocompromised subjects (Barros et al., 2020; Yesilyurt, Yılmaz, Agagündüz, & Capasso, 2021). In the context of COVID-19, the use of postbiotics also seems to be an interesting strategy due to the critical state that is established among some patients.

Regarding COVID-19, few studies regarding postbiotics and microbial metabolites are available, however the findings are interesting and demonstrate a potential of using them in this approach. Overall, microbial metabolites can be transported by the bloodstream to the lungs and act by inhibiting viral replication; in addition, they can improve the immune response against viruses. Some examples of soluble compounds able to be transported via the circulation and reach the lungs are: secondary bile acids, desaminotyrosine and short-chain fatty acids (butyrate) (Gautier et al., 2021).

The exact mechanism of postbiotics is not fully understood, but they might promote a cross-talk between the intestinal microbiota and the host's immune system through interactions with cell-surface molecules, such as peptidoglycans (Akatsu, 2021) and may play a beneficial role in minimizing COVID-19 infection.

Few clinical trials and experimental studies are available in the literature regarding postbiotics. A recent study reports that the metabolic product of *L. plantarum*, plantaricin BN, plantaricin D, plantaricin W, plantaricin JLA-9, presented antiviral activity by blocking the protein S, which is essential in the life cycle of SARS-CoV-2 (Anwar et al., 2021). At the same line, it was shown that the lactococcine G from *L. plantarum* presented high affinity to bind to SARS-CoV-2 proteins S, and this bio-antimicrobial peptide presents minimal side effects (Balmeh, Mahmoudi, & Fard, 2021).

More research is need regarding postbiotics and SARS-CoV-2 infection, in particular with the development of well-planned clinical trials considering animal and human population and the establishment of adequate parameters which allow safe scientific conclusion, as well as the optimal dosage.

7. Conclusion

The COVID-19 pandemic has changed the world panorama and brought countless economic, political, social and, above all, human health consequences, due to its degree of lethality and sequelae. In this regard, with the aim of indicating new evidences and perspectives, the findings presented by this review emphasize that the modulation of the gut/lung microbiome is promising for the prevention/treatment of patients with COVID-19, due to the immunomodulatory properties associated to probiotics. To date, few clinical trials involving the administration of these supplements to combat COVID-19 have been concluded. Reduction in the duration of the disease and the severity of symptoms as fatigue, olfactory dysfunction and breathlessness, nausea and vomiting and other gastrointestinal symptoms were some of the main findings. On the other hand, probiotics should not be recommended to immunocompromised patients in corticosteroid therapy.

Given this current scenario, this review presents a very promising prospect regarding the use of probiotics, prebiotics, synbiotics, and

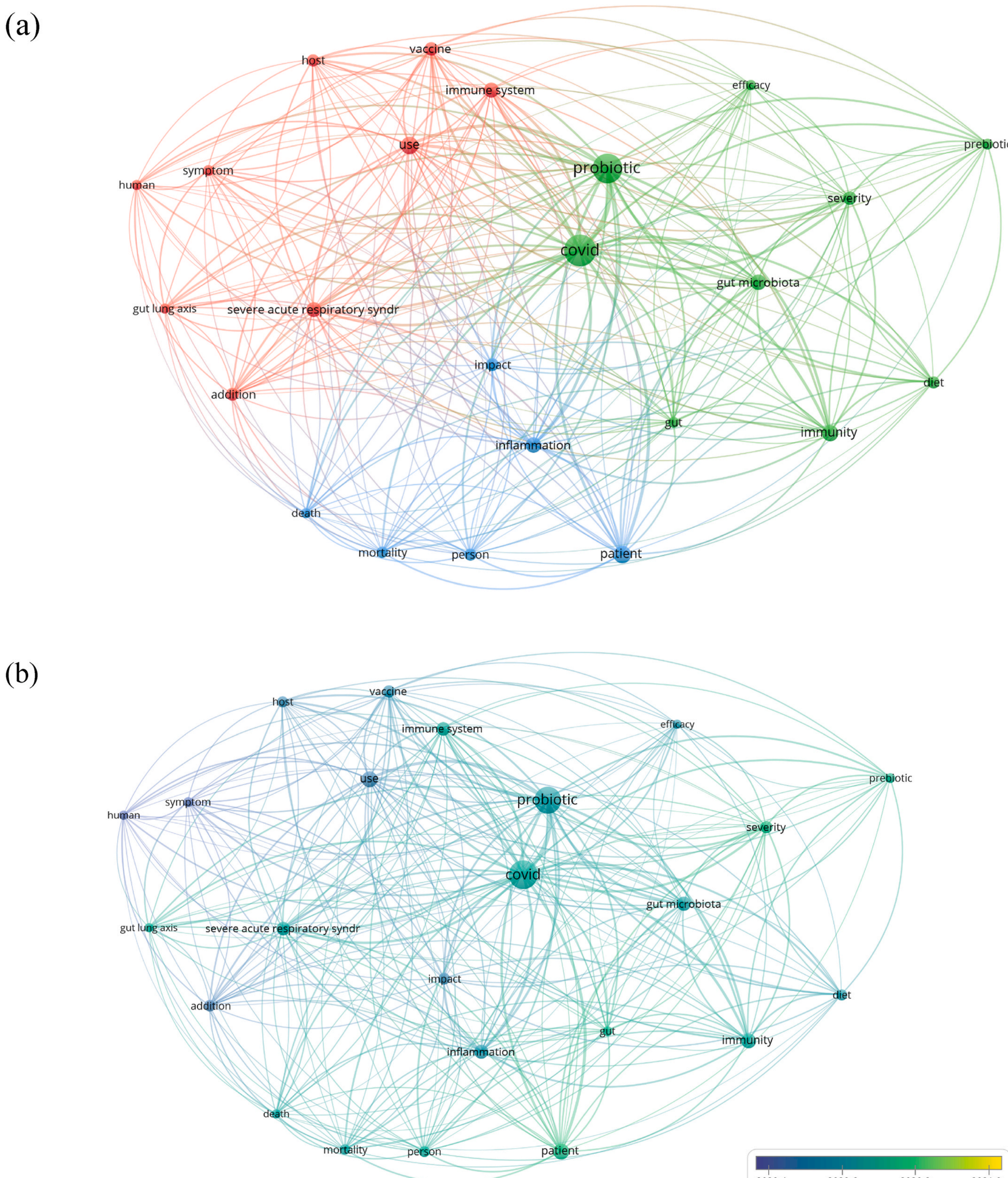

Fig. 3. Co-occurrence networks of terms in title/abstract of selected published papers available in Scopus database. The terms-networks are colored according to the three generated clusters (a) and a gradient color (b) which indicates the period of the terms occurrence from 2020 (blue) to 2021 (yellow). From the 2329 terms, 24 terms have occurred at least 9 times. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Table 3
Evidence of clinical trials with probiotic strain in coronavirus disease.

Reference	Country	Study type	Subjects	Probiotic strain	Intervention	Main results
d'Ettorre et al. (2020)	Italy	Single group	Seventy patients with COVID-19 hospitalized	*Streptococcus thermophilus* DSM 32345, *Lactobacillus acidophilus* DSM 32241, *Lactobacillus helveticus* DSM 32242, *Lacticaseibacillus paracasei* DSM 32243, *Lactiplantibacillus plantarum* DSM 32244, *Levilactobacillus brevis* DSM 27961, *Bifidobacterium lactis* DSM 32246, *Bifidobacterium lactis* DSM 32247.	Daily oral 2.4 billion CFU bacteria for a period of 14 days	A probiotic intervention demonstrated a significant improving on the clinical conditions of patients with COVID-19
Tang et al. (2021)	United States	Double-blinded, randomized, placebo-controlled trial	One thousand one hundred and thirty-two individuals with household contact who tested positive for COVID-19	*Lacticaseibacillus rhamnosus* GG (ATCC 53103)	Daily oral *Lacticaseibacillus rhamnosus* GG or placebo for a period of 28 days	Probiotics are low-cost and safe. It can serve as a rapid intervention strategy in the prevention or reduction of symptoms against pandemic diseases
Endam et al. (2020)	Canada, Saudi Arabia, and United States	Prospective randomized clinical trial	Twenty-three individuals between aged 18–59 years having received lately PCR tested positive for SARS-CoV-2	*Lactococcus lactis* W136	Nasal irrigations through buffered isotonic solution containing 2.4×10^9 CFU of *Lactococcus lactis* W136 or buffered isotonic saline isolated for along the 2 weeks (twice daily)	Probiotic intranasal intervention was correlated with a reduced number of patients showing moderate/severe symptoms of fatigue, loss of perception of smell, and sensation of breathlessness, and by an improved proportion of individuals with moderate/severe facial pain or sore throat
Gutierrez-Castrellon et al. (2021)	Mexico and Spain	Single-center, quadruple-blinded randomized clinical trial	Three hundred outpatients with symptomatic COVID-19 (aged between 18 and 60 years) with positive nucleic acids test for SARS-CoV-2	*Lactiplantibacillus plantarum* KABP022, KABP023 and KAPB033, *Pediococcus acidilactici* KABP021	10^9 probiotic daily ingestion for a period of 30 days	Remission was achieved by 53% of probiotic group compared to 28% in placebo
Huaren and Zazhi (2021)	China	This retrospective single-center study	Eight hundred positive cases of COVID-19 (ordinary-type)	Multiple strains	Decrease or remission of diarrhea in COVID-19 patients	Duration of diarrhea in probiotic group was significantly shorter in relation to placebo group. The multiple strains had effect in reducing individuals' gastrointestinal symptoms as abdominal distension, nausea, vomiting, and among others
Mozota et al. (2021)	Spain	Single group	Twenty-nine residents of a nursing home who tested positive for COVID-19	*Ligilactobacillus salivarius* MP101	Daily consumption of 10^9 CFU of *Ligilactobacillus salivarius* MP101 per unit of product (125 g).	Certain immune factors can be utilized as possible nasal or fecal biomarkers of the benefits of supplementation of probiotic strain in the diet of elderly people infected with SARS-CoV-2.

postbiotics as an adjuvant due to safety, efficacy and low cost as a strategy in the prevention or treatment of COVID-19. In this sense, the use of probiotics, prebiotics, and postbiotics as well as next-generation probiotics may also represent a promising target of investigation in the fight against SARS-CoV-2 infection, as pointed out by Cho, Lee, Choi, and Lee (2021) and Cunningham et al. (2021). Therefore, the modulation of the intestinal microbiota through the use of these supplements represents a promising adjuvant approach for improving the health of patients with COVID-19.

CRediT authorship contribution statement

Douglas Xavier-Santos: Conceptualization, Methodology, Investigation, Writing-original draft. **Marina Padilha:** Conceptualization, Investigation, Writing-original draft. **Giovanna Alexandre Fabiano:** Conceptualization, Investigation, Writing-original draft. **Gabriel Vinderola:** Visualization, Conceptualization, Language editing, and proofing. **Adriano Gomes Cruz:** Conceptualization, Investigation, Writing-original draft. **Katia Sivieri:** Conceptualization, Investigation, Writing-original draft. **Adriane Elisabete Costa Antunes:** Conceptualization, Investigation, Writing - review & editing.

Declaration of competing interest

The authors declare to have no conflicts of interest.

Acknowledgments

The authors are grateful to UNICAMP, UNESP, UFRJ, IFRJ, UNL-CONICET (Argentina), Conselho Nacional de Desenvolvimento Científico e Tecnologico (CNPq), and Coordenaçao de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) financing code 001, in Brazil, for financial support. The authors thank Espaço da Escrita - Pro-Reitoria de Pesquisa - UNICAMP - for the language services provided.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tifs.2021.12.033.

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