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Review

SARS-CoV-2 microbiome dysbiosis linked disorders and possible probiotics role



Ahmad Ud Din ^{a,1}, Maryam Mazhar ^{b,1}, Muhammed Waseem ^c, Waqar Ahmad ^{d,a}, Asma Bibi ^e, Adil Hassan ^f, Niaz Ali ^g, Wang Gang ^a, Gao Qian ^a, Razi Ullah ^f, Tariq Shah ^h, Mehraj Ullah ⁱ, Israr Khan ^j, Muhammad Farrukh Nisar ^k, Jianbo Wu ^{a,*}

^a Drug Discovery Research Center, Southwest Medical University, Luzhou, 646000, Sichuan, China

^b Research Center of Integrated Traditional Chinese and Western Medicine, Affiliated Traditional Medicine Hospital, Southwest Medical University, Luzhou, China

^c State Key Laboratory for Conservation and Utilization of Subtropical Agro-Bioresources, College of Horticulture, South China Agricultural University, Guangzhou, 510642, China

^d College of Marine Life Sciences and Institute of Evolution and Marine Biodiversity, Ocean University of China, Qingdao, 266003, China

^e Institute of Zoonosis Anhui Medical University, Hefei Anhui, 230032, China

^f Key Laboratory for Bio-rheological Science and Technology of Ministry of Education, State and Local Joint Engineering Laboratory for Vascular Implants Bioengineering College of Chongqing University, Chongqing, 400030, China

^g State Key Laboratory for Conservation and Utilization of Subtropical Agro-bio-resources, College of Life Science and Technology, Guangxi University, 100 Daxue Road, Nanning, 530004, Guangxi, China

^h State Key Laboratory of Grassland Agro-Ecosystem, School of Life Sciences, Lanzhou University, Lanzhou, 730000, China

ⁱ Department of Biotechnology School of Fermentation Engineering Tianjin University of Science and Technology China, China

^j School of Life Sciences, Lanzhou University, China

^k Department of Physiology and Biochemistry, Cholistan University of Veterinary and Animal Sciences (CUVAS), Bahawalpur, 63100, Pakistan

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ABSTRACT

In December 2019, a pneumonia outbreak of unknown etiology was reported which caused panic in Wuhan city of central China, which was later identified as Coronavirus disease (COVID-19) caused by a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) by the Chinese Centre for Disease Control and Prevention (CDC) and WHO. To date, the SARS-CoV-2 spread has already become a global pandemic with a considerable death toll. The associated symptoms of the COVID-19 infection varied with increased inflammation as an everyday pathological basis. Among various other symptoms such as fever, cough, lethargy, gastrointestinal (GI) symptoms included diarrhea and IBD with colitis, have been reported. Currently, there is no sole cure for COVID-19, and researchers are actively engaged to search out appropriate treatment and develop a vaccine for its prevention. Antiviral for controlling viral load and corticosteroid therapy for reducing inflammation seems to be inadequate to control the fatality rate. Based on the available related literature, which documented GI symptoms with diarrhea, inflammatory bowel diseases (IBD) with colitis, and increased deaths in the intensive care unit (ICU), conclude that dysbiosis occurs during SARS-COV-2 infection as the gut-lung axis cannot be ignored. As probiotics play a therapeutic role for GI, IBD, colitis, and even in viral infection. So, we assume that the inclusion of studies to investigate gut microbiome and subsequent therapies such as probiotics might help decrease the inflammatory response of viral pathogenesis and respiratory symptoms by strengthening the host immune system, amelioration of gut microbiome, and improvement of gut barrier function.

1. COVID-19 prelude

The recent ongoing global pandemic, COVID-19, caused by novel SARS-CoV-2, first appeared in Wuhan, Hubei province of China. In

December 2019, the seafood and wet animal wholesale market were considered a hot zone of the epidemic eruption. It was soon identified as a highly contagious and infectious disease with an exponential increase in daily cases. COVID-19 mainly affects the respiratory system causing

* Corresponding author at: Drug Discovery Research Center, Southwest Medical University, Luzhou, 646000, China.

E-mail address: jbwucn1996@yahoo.com (J. Wu).

¹ These two authors equally contributed.

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acute and severe respiratory infection manifesting pneumonia as a classic clinical characteristic [1]. SARS-CoV-2 infection's pathogenesis is based on the increased production of inflammatory cytokines, leading to lung injury, organ failure, and subsequent death [2]. In general, corticosteroid therapy is employed to control inflammatory diseases [3] and acute respiratory distress syndrome (ARDS) in clinical settings. However, it is either ineffective or avoided due to side effects in COVID-19. Therefore, it was not recommended by WHO [3,4]. Vaccine development takes a long way to be practically available for use in clinical settings [5–9]. Despite respiratory distress as a significant symptom of COVID-19, this viral disease is associated with some non-classical symptoms affecting other organs such as gastrointestinal infection (GIT) [10,11] and diarrhea [12] along with ulcerative colitis [13]. Fascinatingly, patients with GIT symptoms had more severe respiratory disorders [14,15], which might be associated with microbial dysbiosis, where a decline in beneficial microbes *Lactobacillus* and *Bifidobacterium* was found [16].

On the other hand, the richness of *Clostridium hathewayi*, *Clostridium ramosum*, and *Coprobacillus* were positively correlated while that of *Faecalibacterium prausnitzii* was inversely correlated with the severity of the disease [17]. Furthermore, gut dysbiosis and strains such as *Clostridium hathewayi*, *Clostridium ramosum*, and *Coprobacillus* directly link with diarrhea, colitis, IBD, inflammation, etc [18–20]. Also, the increased death prevalence in the COVID-19 ICU patients seems correlated with the increased, antibiotics use and ICU. associated gut microbial dysbiosis [21,22]. Therefore, the current scenario demands a detailed investigation of novel therapeutic approaches toward gut microbiome dysbiosis, boosting the gut microbiome associated immune system, decreasing related symptoms, and viral infection progression would be vital. Manipulating gut microbiota with probiotics as a supplementary therapy to enhance the immune system presents a brighter option with reduced side effects and promising effectiveness by revitalizing the own defence mechanism. However, probiotics' mechanism is scarce and requires extensive research for future acceptance and approval in the case of COVID-19 [5,23]. In this review, we are highlighting the possible mechanisms of actions to expand our understanding and knowledge of gut microbiome link with various symptoms of COVID-19 comorbidities for future research and possible use of probiotics as a supplementary therapeutic in COVID-19 prevention strategies.

2. Role of probiotics in different diseases

Probiotics are live microorganisms or components of dead bacteria that are safe and free of vectors, which, when administered in specific doses, can confer health benefits by inducing resistance against antibiotics, xenobiotics, and pathogenicity or toxicity factors by strengthening immunity through the route of the gut. Strains of diverse microbiota likewise, *Bifidobacterium*, *Enterococcus*, *Lactobacillus*, *Saccharomyces boulardii*, and *Escherichia coli* Nissle 1917, *Lactococcus*, *Leuconostoc*, *Pediococcus*, and *Streptococcus* are widely used as probiotics [24,25] for the amelioration of GIT associated disorders including acute, nosocomial and antibiotic-associated diarrhea, *Clostridium difficile*-associated diarrhea, inflammatory bowel disorders in adults, and allergic disorders like atopic dermatitis and allergic rhinitis in infants [26,27]. Interestingly, probiotics' role is not limited to the disorders mentioned above; instead, its functional importance is emerging. The researchers show more great interest in identifying the vast therapeutic benefits that probiotics can achieve for treating different diseases. There is a growing field of research towards the possible use of probiotics as co-adjuvants in treating metabolic disorders such as type 2 diabetes, obesity, metabolic syndrome, and non-alcoholic fatty liver disease. However, probiotics' mechanisms of action have not been studied well in different disease conditions and are still in infancy but hold great promise as probiotics' actions are diverse and heterogeneous [28].

Respiratory tract infections (RTI) are the most prevalent diseases

globally, in children, elderly, and immunocompromised individuals. Various studies have revealed the use of probiotics in the treatment of RTI by decreasing the incidence and severity of the diseases [29]. Respiratory conditions including chronic lung disorder; asthma [30], bacterial infections; tuberculosis [31], chronic obstructive pulmonary disease (COPD), cystic fibrosis, and viral infection such as influenza are all associated with intestinal manifestations and alterations in the composition of gut microbiota, suggesting the correlation between lungs and gut [32]. The use of probiotics has been studied preclinically and is found to be beneficial in asthma models [33]. The administration of *Lactobacillus casei* or *L. rhamnosus* and *Bifidobacterium Bifidum* were found to decrease the viral titers and alleviate the symptoms in respiratory influenza virus infection [32,34]. Similarly, nasal administration of *Lactobacillus rhamnosus* provided protection against respiratory syncytial virus infection in mice models [30]. Hence, probiotic treatment might have beneficial effects by reducing disease-induced inflammation and fortifying mucosal immunity, thereby controlling the spread of viral infections [32].

3. Probiotics-novel approach to boost immunity in viral infections

Considering the ineffectiveness or side effects of the available therapies in treating COVID-19, additional supplements with a proven record of amelioration of inflammation may be considered. One such therapy includes the supplementation of probiotics might be helpful as of its effectiveness in previous viral diseases such as in influenza through boosting immunity [35,36]. In addition, probiotic ameliorate pathogenicity by modulating monocyte chemoattractant protein-1 (MCP-1), which is SARS-2 virus linked mediator and subsequent amelioration of inflammation [35,37]. Similarly, probiotics may act as a modulator of dysbiosis caused by viral infection [38,39], which seems to have promising effects in COVID-19 as well, especially in the attenuation of GIT symptoms. Probiotics may lessen the extent of disease severity by balancing the gut microbiome, which might have valuable outcomes due to its role in the gut–lung axis communication [40–42], and vitamin A regulation [43], which is directly linked with the immune system [44]. More recently, Barcik and his co-worker associated gut microbiota dysbiosis with dysregulation of microbiota-related immunological processes and subsequent onset of various respiratory disease [45].

Consequently, microbiome analysis must be included in clinics as a diagnostic test as previous viral infections have caused dysbiosis [46]. Probiotic use might be helpful in SARS-CoV-2 specifically as its effect on GIT, lungs [47], and kidneys have been documented, which has a strong association with microbiome [40,48]. Gut microbiome analysis and evaluation in COVID-19 individuals, as well as the addition of probiotics in various food items in patients' daily diets, might be useful because of its proven record of anti-inflammatory and antiviral properties in multiple trials and studies [49,50], which some are listed (Sup Table 1).

4. Recent evidence of probiotics in COVID-19 - preclinical and clinical studies

Among various therapeutic options against COVID-19, probiotics were also proposed by the National Health Commission of China and the National Administration of Traditional Chinese Medicine [51,52]. Interestingly, many clinical studies using Traditional Chinese Medicine have been listed in China's clinical studies registry, but few with focusing the gut microbiome. Although the reinforcement of gut microbiota might not directly affect severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the gut-lung cross-talk has been implicated in the pathogenesis of some respiratory diseases [53]. Around 58–71 % of patients suffering from COVID-19 were treated with antibiotics [52], of which 2–36 % of patients suffered from diarrhea, which might be associated with administered antibiotics and subsequent dysbiosis [54]. This led to the suggestion that strengthening the

colonic flora might ameliorate vulnerability to secondary infections, and antibiotics induced diarrhea can be managed using probiotics [55,56]. During the COVID-19 pandemic in China, studies showed that 2–47 % of critically ill patients require mechanical ventilation [57,58].

In contrast, a clinical trial concluded that the supplementary of probiotics treatment containing *Lactobacillus rhamnosus* GG, live *Bacillus subtilis*, and *Enterococcus faecalis*, developed significantly less ventilator-associated pneumonia compared with those without probiotic supplementation [59]. There is currently only very limited data available on the COVID-19 induced disturbance in gut microbiota and the possible probiotics role (Table 1). A small case study from a Chinese researcher reported that some COVID-19 patients suffered from microbial dysbiosis with decreased *Lactobacillus* and *Bifidobacterium* - the non-pathogenic bacteria yet, preliminary animal studies did not show any correlation between the presence of *Lactobacillus acidophilus* and *Bacillus clausii* with the reduction of expression of coronavirus receptor in the murine small intestine as compared with control and post-Salmonella infection models [16,60]. Therefore, irrational use of conventional probiotics should be disregarded in COVID-19 unless we further expand our understanding of SARS-CoV-2 pathogenesis and its effect on gut microbiota and then explore various probiotics' roles in combating COVID-19 with valid evidence. It is hoped that manipulating the gut microbiota might play fruitful roles as a therapeutic strategy of COVID-19 and its comorbidities [53]. However, the therapeutic strength of probiotics in

Table 1
Studies which focus on gut microbiome and probiotics in COVID-19.

S. No	Study Title	Article Type	Refs.
1	Targeting the gut–lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection	Review	[157]
2	Microbiota Modulating Nutritional Approaches to Countering the Effects of Viral Respiratory Infections Including SARS-CoV-2 through Promoting Metabolic and Immune Fitness with Probiotics and Plant Bioactives	Review	[158]
3	Traditional Chinese medicine for COVID-19 treatment	Review	[159]
4	Gut microbiota and Covid-19- possible link and implications	Review	[160]
5	Probiotics and COVID-19 : one size does not fit all	Review	[161]
6	Potential Effects Immunomodulators on Probiotics in COVID-19 Preventing Infection in the Future. A Narrative Review	Review	[162]
7	The small intestine, an underestimated site of SARS-CoV-2 infection: from Red Queen effect to probiotics	Review	[60]
8	Considering the Effects of Microbiome and Diet on SARS-CoV-2 Infection: Nanotechnology Roles	Review	[163]
9	Antiviral effects of probiotic metabolites on COVID-19	Express Communication	[164]
10	Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic	Review	[165]
11	Nutrition Therapy in Critically Ill Patients With Coronavirus Disease 2019	Review	[166]
12	Approach to Nutrition in Cancer Patients in the Context of the Coronavirus Disease 2019 (COVID-19) Pandemic: Perspectives	Review	[167]
13	Diet Supplementation, Probiotics, and Nutraceuticals in SARS-CoV-2 Infection: A Scoping Review	Review	[168]
14	Dietary recommendations during the COVID-19 pandemic	Review	[169]
15	Can Probiotics and Diet Promote Beneficial Immune Modulation and Purine Control in Coronavirus Infection?	Review	[170]
16	Should Probiotics, honey, and escin be used in the prevention or treatment of COVID-19?	Review	[171]

lowering the risk of mortality in COVID-19 patients is uncertain due to limitation of available clinical data, and so there is a need of prompt studies for probiotic validation (Table 2).

5. COVID-19 associated diarrhea and probiotic use

A recent study of H1N1 influenza A virus patient was found with GIT signs and symptoms such as diarrhea and abdominal pain, which demonstrated that they should be followed for GIT symptoms even though the disease is respiratory [61]. Similarly, 30 % of patients with the Middle East Respiratory Syndrome (MERS) and 10.6 % of SARS-Cov-1 patients have been found to suffer from diarrhea [62]. Likewise, SARS-CoV-2 has also been found to cause diarrhea [47,63,64]. In another study, 43.8 % of COVID-19 individuals were found with diarrhea like symptoms [65]. Current therapies such as corticosteroids; antivirals such as chloroquine and hydroxychloroquine, Lopinavir/Ritonavir, Remdesivir, Nelfinavir, Ribavirin nucleoside analog, plasma therapy, Tocilizumab antibody, Baricitinib, Nitazoxanide; immunomodulator such as interferons along with other drugs such as Arbidol, Favipiravir have been reviewed in detail in COVID-19 which in some way or the other have either side effects or ineffective or need further validation [66]. Therefore, to date, there is no sole treatment for COVID-19. Studies have indicated gut microbial dysbiosis in viral diseases and antiviral therapies [67,68] that might also be the case in COVID-19.

In most cases, precisely the GIT symptoms of diarrhea are closely associated with altering gut microbial diversity and alleviated with probiotics use as described previously [69,70]. However, the gut microbiome's role during COVID-19 infection and its improvement through probiotics and prebiotics have not been much focused [71]. Therefore, improving the gut microbial diversity with already available probiotics as an additive and supplementary treatment [72] might help combat SARS-CoV-2 associated diarrhea.

6. IBD in COVID-19 and possible probiotic role

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD), and ulcerative colitis (UC), is a condition in which the gastrointestinal immune system responds inappropriately due to various triggering factors, including gut microbial dysbiosis [73,74]. IBD is commonly managed with immunosuppressing medications to alleviate inflammation. It is known that over 1 million residents in the USA and 2.5 million in Europe are estimated to have IBD [75]. Only 44 % of them have been to a clinic in the past three years. During the current coronavirus pandemic, an increased incidence of IBD has been documented [76]. As anxiety in IBD patients is more common because of social distancing and isolation in COVID-19 as described previously [77], it may worsen patients' condition, which might not be underestimated. Conventionally, the immunosuppressant is used to control inflammation in COVID-19, might not be helpful in IBD individuals as well but the therapeutic in use still not reliable completely as well comorbid individual with IBD might be at more high risk in COVID-19 case; as corticosteroids have been found to worsen the condition of IBD patients suffering from COVID-19 infection [78]. As discussed previously, gut microbiome dysbiosis may occur during viral disease, increasing the incidence of IBD and ulcerative colitis [79]. Probiotics have a proven record of alleviating IBD and colitis by modulating gut microbiome and inflammation; therefore, it might help supplementary therapy in COVID-19 [80–82]. Probiotics may work through its metabolites such as organic acids, bacteriocins, peptides, and multiple critical targets in various metabolic pathways, including inflammation, and may alleviate IBD [83].

7. An integrated mucosal immunity - gut-lung cross talk and probiotic role

An essential concept of an integrated mucosal immunological system

Table 2Registered Clinical Trials (<https://clinicaltrials.gov/>; https://clinicaltrials.gov/ct2/who_table) focusing on probiotics role in COVID-19.

S. No	Clinical Trial Title	Clinical Trial No	Country	Trial Completion Status (Y/N)
1	Study to Evaluate the Effect of a Probiotic in COVID-19	NCT04390477	Spain	N
2	Evaluation of the Probiotic Lactobacillus Coryniformis K8 on COVID-19 Prevention in Healthcare Workers	NCT04366180	Spain	N
3	Efficacy of Intranasal Probiotic Treatment to Reduce Severity of Symptoms in COVID-19 Infection	NCT04458519	Canada	N
4	Oxygen-Ozone as Adjuvant Treatment in Early Control of COVID-19 Progression and Modulation of the Gut Microbial Flora (PROBIOZOVID)	NCT04366089	Italy	N
5	Reduction of COVID 19 Transmission to Health Care Professionals	NCT04462627	Belgium	N
6	Synbiotic Therapy of Gastrointestinal Symptoms During Covid-19 Infection (SynCov)	NCT04420676	Austria	N
7	Effect of Lactobacillus on the Microbiome of Household Contacts Exposed to COVID-19	NCT04399252	United States	N
8	Evaluating the Safety, Tolerability and Immunogenicity of bacTRL-Spike Vaccine for Prevention of COVID-19	NCT04334980	United States	N
9	A prospective, multicenter, open-label, randomized, parallel-controlled trial for probiotics to evaluate efficacy and safety in patients infected with 2019 novel coronavirus pneumonia (COVID-19)	ChiCTR2000029974	China	N
10		ChiCTR2000029999	China	N

Table 2 (continued)

S. No	Clinical Trial Title	Clinical Trial No	Country	Trial Completion Status (Y/N)
	A clinical study for probiotics in the regulation of intestinal function and microflora structure of novel coronavirus pneumonia (COVID-19)			
11	Stress-reduction Using Probiotics to Promote Ongoing Resilience Throughout COVID-19 for Healthcare Workers (SUPPORT COVID-19 Healthcare Workers)	ACTRN12620000480987p	New Zealand	N
12	Application of Regulating Intestinal Flora in the Treatment of Severe Novel Coronavirus Pneumonia (COVID-19)	ChiCTR2000029849	China	N
13	Bacteriotherapy in the Treatment of COVID-19 (BACT-ovid)	NCT04368351	Italy	N
14	Clinical Trial to Evaluate the Efficacy of Food Supplement Manremyc® Against SARS-COV-2 Infection (COVID-19) in Healthcare Workers	NCT04452773	Spain	N
15	A pilot, multiple dose study to evaluate the efficacy and safety of MRx-4DP0004 in hospitalised patients with symptoms of COVID-19 (SARS-CoV-2 infection)	eudract_number:2020-001597-30	United Kingdom	N
16	Immunological efficacy of lactic acid bacteria for COVID-19	R000046202	Japan	N
17	Evaluation of the effect of taking Newgen beta-gluten probiotic composite powder to nutrition intervention of patients with novel coronavirus pneumonia (COVID-19)	ChiCTR2000030897	China	N
18	Clinical trial for the washed	ChiCTR2000032737	China	N

(continued on next page)

Table 2 (continued)

S. No	Clinical Trial Title	Clinical Trial No	Country	Trial Completion Status (Y/N)
	microbiota transplantation in the treatment of novel coronavirus pneumonia (COVID-19) patients suspected with gut microbiota dysbiosis			

was developed in 1978, which suggested that our body's mucosal sites, including oral, respiratory, intestinal, and cervical, functioned as a unit and a system-wide organ to protect against pathogens. The idea of an integrated mucosal immunological system such as the lung-gut axis is supported by the fact that these two mucosal sites share the same embryonic origin and are similar structurally and functionally [84,85]. Still, the field is in its infancy, and it is required to understand the complexity and interactions of the mucosal immune system as an integrated global organ for future advances in understanding mucosal immunology and for future treatment of various chronic and inflammatory diseases alongside its association with gut [84,85]. As it is well known that a leaky gut due to dysbiosis may worsen the disease condition including lung disorder [86] as well as there might have more chances of infiltration of SARCoV-2 into the gut lumen and subsequently into the lymphatic system, which might cause infection in a secondary site and may increase the severity in COVID-19 [87]. Dysbiosis of the gut and lung microbiota occurs in various acute pulmonary diseases [88–91]. Additionally, corticosteroids may induce dysbiosis as well [92], which are commonly used in COVID-19. More recently, Fanos and co-workers hypothesized that gut microbiota influences angiotensin-converting enzyme 2 (ACE2) at the intestinal and pulmonary level so that probiotics may overcome tackle the disease severity [92]. The addition of probiotics to improve gut microbiome and lung microbiome [85,92], seems promising to overcome disease severity in COVID-19 in terms of modulation of lung and gut microbiome. Furthermore, microbial metabolites, such as short-chain fatty acids (SCFAs) concentration, influence airways disease, have been previously documented. Higher fibers containing diet were found to enhance SCFA and subsequent protection from allergic inflammation [93]. The addition of dietary supplements might be helpful in lung inflammation in COVID-19.

8. Possible mechanism of action of Probiotics in COVID-19

Probiotics play their role in combating various diseases in terms of enhancing epithelial barrier function [94], as anti-inflammatory [95] improving gut microbial diversity [96], as the antagonist, for various harmful bacterial strains in the gut [97], blocking or enhancing multiple signalling pathways such as NF- κ B [98,99] and production of metabolites such as SCFAs which can work in lessening various diseases severity [100]. As evidenced, the COVID-19 pathogenesis includes disruption of the epithelial barrier, inflammation, and dysbiosis, which can be alleviated using probiotics supplementation. Moreover, there is an increased production of inflammatory mediators such as IL-6, TNF- α , C-reactive protein, IL-1b, IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and LDH observed in COVID-19 which were found responsible for acute respiratory distress syndrome (ARDS), arrhythmia, and shock [2]. A range of available probiotics works to decrease inflammation by alleviating these inflammatory mediators [101–103], which seems to be effective in COVID-19. Besides, the role of macrophages in hyper inflammation during COVID-19 pathogenesis cannot be ignored [101],

which can also be lessened through the use of probiotics to some extent [102,103]. It is expected that supplementation with appropriate probiotics may colonize the gut with the selected therapeutic bacterial strain, which can then spread to other parts of the body or extra-digestive sites and may enhance immunity against viral infections. It can be assumed that perhaps these probiotics microorganisms or their metabolites are engulfed directly by dendritic cells (DC) and macrophages through the intestinal lumen by penetrating into the intestinal epithelium, thereby transporting bacteria to other areas via blood stream; as in the case of COVID-19 may exhibit its affect in lungs [104, 105]. Furthermore, COVID-19 comorbidities can be ameliorated through probiotics miRNA's modulation, as well as regulation of signalling pathways such as NF- κ B and STAT1 [82,106,107].

9. COVID-19 ICU patients and probiotics

During the COVID-19 pandemic, most of the patients were kept in ICU. There have reports of increased use of antibiotics [108,109] during their stay. In contrast, the interplay between the gut and lung microbiome has been reported in a recent study during ARDS [110]. Studies have demonstrated an increased incidence of gut microbiome dysbiosis during ICU, leading to sepsis and death [111]. This dysbiosis may lead to various other dysfunctions such as IBD, disruption of the immune system, and, eventually, organ dysfunction [112]. In the case of COVID-19, it is speculated that the increased ratio of organ dysfunction might be associated with ICU induced gut microbial diversity [113] due to increased use of antibiotics in COVID-19 ICU individuals [114,115]. A recent review discourages the use of antibiotics in COVID-19 unless it is needed [116]. Studies show that probiotics strains *Lactobacillus rhamnosus* GG and *Bifidobacterium longum* were promising in reducing infection in ICU patients [117,118]. We assumed that the incidence of microbiome disturbance and subsequent organ failure in COVID-19 could be decreased with supplementation of probiotics as additional therapy as described previously [97,113]. Furthermore, minimizing the administration of corticosteroids and antibiotics [120] might be helpful as they are associated with dysbiosis.

10. Presence of ACE2 in probiotics strains and possible role in COVID-19

The SARCoV-2 entry comes upon its binding to human angiotensin-converting enzyme type 2 (ACE2) receptor on the surface of alveolar epithelial cells and subsequent inflammation, leading to high fever and lung injury. The main target organs of COVID-19 infection are primarily the lungs; however, the intestine is another viral target organ. It has been found that the receptors for SARS-CoV-2, angiotensin-converting enzyme 2 (ACE2) is highly expressed on differentiated enterocytes and cause infection in proliferative and mature enterocytes in the human small intestinal organoid (hSIO) model [119]. This role in viral pathogenesis has made ACE2 a potential target in COVID-19 prevention and control [120]. Recently, inhibitors such as angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II type-1 receptor blocker (ARB), have been proposed to effectively bind to the ACE2 receptor, neutralizing the virus and subsequent protection from lung injury [121, 122].

Furthermore, the administration of the soluble form of ACE2 may also slow down the viral entry into cells and reduce the viral spread and protect the lungs from injury [123]. Studies demonstrate for oral delivery of human ACE2 using probiotic specie, *Lactobacillus paracasei* (LP), as a live vector for an effective treatment against Diabetes in the mouse model of diabetic nephropathy. It has been found that LP can efficiently express codon-optimized ACE2 and showed increased ACE2 activities in serum and tissues. These results suggest that engineered probiotic species can be employed as a live vector for human ACE2 with enhanced tissue bioavailability [124]. A similar approach can be tested for possible effective treatment and prevention of aggravation of

COVID-19 infection. The newly identified bacterial derived B38-CAP enzyme has been found similar to that of human ACE2-like enzyme. Its protective effects are suppressing hypertension and cardiac dysfunction and subsequent lung injury [125]. Use of this bacterial strain with B38-CAP enzyme or identification of other bacterial strains with similar properties might play a beneficial role in controlling/decreasing the severity and pathogenesis of COVID-19 while working as an alternative ACE2 receptor for SARS-CoV2 instead of human tissue.

11. Probiotics bacteriocins role in COVID-19

Some *Lactobacilli* and *Bifidobacteria* produce bacteriocins, peptides composed of 30–60 cationic amino acids with antimicrobial properties targeting energized membrane vesicles to disrupt the proton-motive force. These molecules are effective against a wide range of intestinal bacterial pathogens and viruses, such as rotavirus [26]. The bacteriocins' activity produced by various probiotic microorganisms [126] might help and assist in the treatment against COVID-19 infection. Additionally, there is an abundance of various harmful bacterial strains reported where various probiotics strains may work as an antagonist and decrease disease severity [127]. Furthermore, *Lactobacillus* and *Bifidobacterium* toxins are useful in multiple other viral infections [128,129]. A recent study reported a dysbiosis of fungal microbiome in COVID-19 disease [131], which might be lessened with probiotics that produce antifungal toxins [130,131].

12. Probiotics mucin production and COVID-19

The mucus is an extracellular secretion by mucous membranes lining the body cavities, including respiratory, digestive, and urogenital tracts; as a physical protective barrier, mucins-glycoproteins are the significant component. The latest research has shown a strong induction of COVID-19 viral replication via enterocytes [119]. However, goblet cells were found less infected in the human small intestinal organoid (hSIO) model [119]. This phenomenon can be related to mucus and mucin production, indicating that increased activity of goblet cells with induced mucin production may prevent virus invasion through the gut into the immune system [132]. Hence, mucin production might play a trapping and inhibiting role in viral replication in the intestine and prevent further aggravation and viral infection progression in the body [26]. Previously, It was shown that intestinal mucins from mice were effective in inhibiting some strains of rotavirus [104,133].

Moreover, mucin biopolymers have emerged to acts as broad-spectrum antiviral agents [134]. Suggesting that goblet cells and mucins production enhancement play a role in the host defence against rotavirus infection and seems promising in COVID-19. Probiotics promoting mucin and mucus production in the gut appear to, directly and indirectly, enhance gut immunity to the whole body's immunity [135]. *Lactobacillus* spp were reported to induce intestinal mucins and strengthening the mucus layer and glycocalyx over the intestinal epithelium thereby occupying the intestinal binding sites and inhibiting pathogenic adherence, preventing inflammation [136,137]. Moreover, probiotics are also known to alter qualitative properties of mucins preventing adherence of pathogens [138]. Strains with high adherence capacity have also shown to enhance the immunoglobulin A response to rotavirus [104]. Altogether this shows that enhancement of mucins production, primarily through supplementary probiotics therapy, might help SARS-CoV-2 infection.

13. Modulation of immune system through probiotics

The gut microbiota interacts with immune cells such as dendritic cells (DCs), monocytes/macrophages, and lymphocytes to release various immunomodulatory molecules to stimulate the innate and adaptive immune system. Viral infections are known to trigger innate

immune responses via interactions between intestinal epithelial cells (IECs) and immune cells and activation of pattern recognition receptors (PRRs) such as toll-like receptor 3 (TLR3), leading to secretion of proinflammatory mediators and increased local tissue damage and immunopathology [139]. Immunoregulatory probiotic or immunobiotic such as lactic acid bacteria (LAB), when administered, may interact with the intestinal epithelial cells (IECs) or immune cells associated with the lamina propria through toll-like receptors and induce the production of different cytokines or chemokines [140] which sends signals to other immune cells leading to the activation of the mucosal immune system, characterized by an increase in immunoglobulin A+ (IgA) cells of the intestine, bronchus and mammary glands, and the activation of T cells. Probiotics specifically activate regulatory T-cells that release IL-10 and favour IgG production instead of IgE [44]. An imbalance of effector T-helper (Th) and regulatory T-cells (T-regs) leads to impaired immune response [8].

Similarly, probiotics are known to modulate innate and adaptive antiviral immunity of the mucosal and systemic immune systems [143], maintain intestinal homeostasis during viral infections, and improve the resistance to viral infections, normalize gut permeability, and increase the production of virus-specific antibodies [141]. In one of the randomized controlled trial, children suffering from mucosal diseases such as diarrhea and bronchitis were administered with the probiotic *L. rhamnosus*' CRL1505 in a yogurt formulation, which was found to improve the mucosal immunity and reduced the incidence and severity of intestinal and respiratory infection in children [43]. Similarly, probiotics role in immune system stimulation, decreasing frequency of infection and increased production of antiviral antibodies have been demonstrated in various studies [42,142–145]. Considering the available evidence and facts, probiotic bacteria are emerging as a safe and natural strategy for various disease prevention and treatment and it may prove itself fruitful for COVID-19 as well [145].

14. Aging associated gut microbiome dysbiosis, Covid-19 and probiotic role

Aging is a combination of various processes disturbing various physiological processes such as genomic, metabolism, and immunological functions [146,147]. Aging is associated with an increased incidence of multiple diseases such as IBD, Diabetes, Alzheimer, cancer, cardiovascular diseases [147]. Studies demonstrated an increased incidence of dysbiosis in aged individuals compared to the youngsters [151]; which may lead to clinical issues including inflammation and gut-associated diseases by causing alterations in older people [148]. So, it seems wise to target the gut microbiome in age-linked comorbid COVID-19 patients through probiotics by stabilizing the gut microbiome [149]. Additionally, it is well-established that the extensive use of drugs/antibiotics is closely connected with a disturbance in the gut microbiome composition and functions [150]. It is speculated that extensive antibiotic use and age-associated gut microbiome disturbance might have synergistically contributed to the increased fatality rate in COVID-19 [151,152]. Studies in mice demonstrated the alleviation of age-linked dysbiosis through probiotics [153]. Furthermore, antibiotics and age-linked dysbiosis seem to have been lessened through probiotics treatments [154]. A recent study demonstrated that the ACE2 receptor is the critical factor in fewer outcomes in aged comorbid patients, where gut microbiome amelioration through probiotics seems to play its role in decreasing the fatality rate [155,156].

Conclusion

Most hospitalised individuals rely on corticosteroids, antibiotics, and antiviral for systematic inflammation and associated lung injury. These therapies' side effects cannot be ignored, including disruption of the gut microbiome and affecting individuals' well-being with related comorbidities such as GI symptoms. Besides, patients with severe disease

conditions in ICU associate with increased dysbiosis, leading to an increased death rate. Also, the link of gut dysbiosis with lungs microbiome cannot be ignored. On the other hand, gut microbial dysbiosis is also linked with an increased incidence of IBD, colitis, which might have increased the death toll and severity of the disease. Additional, disease management with the inclusion of microbial diversity screening as a routine test in infected individual and subsequent therapies with either probiotic, dietary fiber, prebiotics, or other supplements as food additives for microbiome improvement as well as alleviating GI symptoms might be useful in lessening inflammation, enhancing immune response, improving gut barrier function as well as probiotics antagonist effect against harmful bacterial strains which were found recently in COVID-19 Individuals. To date, there are ongoing clinical trials, but there are no or limited clinical trials with concluding outcomes to pave the way for specific probiotics strain use in SARS-CoV-2 infection. There is a need for prompt studies and trials for probiotics use in COVID-19, or the previously approved probiotic strains can be. There is enough evidence to consider probiotics and therapies such as dietary interventions, symbiotic, prebiotics, metabolome modulation, and fecal microbiota transplant as additional and supplement treatment along with other therapies in use.

Author contribution

Ahmad Ud Din and Maryam Mazhar contributed equally and wrote the first Draft of the Manuscript. Jianbo Wu supervised and critically revised. While all other authors contributed to revising, editing various sections, and helping in the final draft of the manuscript.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.biopha.2020.110947>.

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