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Basic study

COVID-19 and gut dysbiosis, understanding the role of probiotic supplements in reversing gut dysbiosis and immunity

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ABSTRACT

In December 2019, an outbreak of novel beta-coronavirus started in Wuhan, China, spread globally as coronavirus disease 2019 (COVID-19) pandemic and is still underway. The causative agent for COVID-19 identified as a novel strain of beta coronavirus named nSARS-CoV-2. The nSARS-CoV-2 primarily targets the respiratory tract and results in severe acute respiratory distress (ARDS), leading to the collapse of the respiratory tract. The virus internalizes primarily via ACEII receptor, and many tissues reported a significant level of expression of ACEII receptor including lungs, hearts, kidneys, and gastrointestinal tract. The clinical manifestations of COVID-19 are diverse, but growing evidence suggests that gut dysbiosis is one of them and poses a threat to native immunity. The human microbial ecology plays a vital role in human physiology, including building immunity. The gastrointestinal tract (GIT) habitats trillions of beneficial microbes' precisely bacterial species synchronize with human physiology and remain symbiotic. On the contrary, harmful microbiota seeks an opportunity to break the equilibrium failure of balance between beneficial and detrimental human gut microbiota results in impaired physiology and immunity. The grown research evidence demonstrated that infection caused by the nSARS-CoV-2 result in moderate to severe diarrheal outcomes. The diarrheal conditions in COVID-19 patients are due to alteration of gut microbial ecology. The management of COVID-19 requires specialized therapeutics along with a series of nutraceuticals. Probiotics remain vital nutrient supplements in COVID-19 management, offer relief in diarrhea and improve/restore immunity. This study uses available data/findings to emphasize an association between COVID-19 and gut dysbiosis. The study also provides a scientific basis of impaired immunity during gut dysbiosis in COVID-19 and how probiotics help restore and improve impaired immunity and diarrhea.

Mots clés :
Dysbiose intestinale
nSARS-CoV2
COVID19
Nutraceutiques
Probiotiques et immunité

RÉSUMÉ

En décembre 2019, une épidémie de nouveau bêta-coronavirus a commencé à Wuhan, en Chine, s'est propagée dans le monde entier comme la pandémie de maladie à coronavirus 2019 (COVID-19) et est toujours en cours. L'agent causal de la COVID-19 identifié comme une nouvelle souche de coronavirus bêta nommée nSARS-CoV-2. Le nSARS-CoV-2 cible principalement les voies respiratoires et entraîne un syndrome de détresse respiratoire aiguë (SDRA), entraînant l'effondrement des voies respiratoires. Le virus s'internalise principalement via le récepteur ACEII, et de nombreux tissus ont signalé un niveau d'expression significatif du récepteur ACEII, y compris les poumons, les cœurs, les reins et le tractus gastro-intestinal. Les manifestations cliniques de la COVID-19 sont diverses, mais de plus en plus de preuves suggèrent que la dysbiose intestinale est l'une d'entre elles et constitue une menace pour l'immunité native. L'écologie microbienne humaine joue un rôle vital dans la physiologie humaine, y compris le renforcement de l'immunité. Le tractus gastro-intestinal (GIT) abrite des trillions d'espèces bactériennes de microbes bénéfiques qui se synchronisent précisément avec la physiologie humaine et restent

Abbreviations: ARDS, Acute Severe Respiratory Syndrome; nSARS-CoV-2, Novel Severe Acute Respiratory Syndrome Coronavirus 2; COVID-19, Coronavirus Disease 2019; GIT, Gastrointestinal Tract; GALT, Gut associated Lymphoid Tissues; ORF, Open Reading Frame; CDC, Centre for Disease Control; FAQ, Food and Agriculture Organization; TNF α, Ttumor necrosis factor-α; GM-CSF, Granulocyte-macrophage colony-stimulating factor; IL, Interleukin; IFN, Interferon; ACEII, Angiotensin Converting Enzyme II; *ROS, Reactive Oxygen Species.*

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symbiotiques. Au contraire, le microbiote nocif cherche une occasion de rompre de l'équilibre entre le microbiote intestinal humain bénéfique et préjudiciable entraîne une altération de la physiologie et de l'immunité. Les preuves de recherche croissantes ont démontré que l'infection causée par le nSARS-CoV-2 entraîne des résultats diarrhéiques modérés à sévères. Les conditions diarrhéiques chez les patients atteints de COVID-19 sont dues à une altération de l'écologie microbienne intestinale. La prise en charge de la COVID-19 nécessite des traitements spécialisés ainsi qu'une série de nutraceutiques. Les probiotiques restent des suppléments nutritifs essentiels dans la prise en charge de la COVID-19, offrent un soulagement de la diarrhée et améliorent / restaurent l'immunité. Cette étude utilise les données et les résultats disponibles pour souligner une association entre la COVID-19 et la dysbiose intestinale. L'étude fournit également une base scientifique de l'immunité altérée pendant la dysbiose intestinale dans COVID-19 et comment les probiotiques aident à restaurer et à améliorer l'immunité altérée et la diarrhée.

1. The nSARS-CoV-2 and COVID-19 pandemic

In December 2019, the first-ever case of COVID-19 outbreak was reported at Wuhan, China, spread a global pandemic within four months. The causative agent for viral pneumonia was described as a new member of beta coronavirus, i.e., novel SARS-CoV-2 [1,2]. The nSARS-CoV-2 is RNA based capsulated virus that primarily targets the respiratory tract, which causes the severe acute respiratory syndrome. In 2020, precisely March 11, the World Health Organization declared a global pandemic [3]. There have been speculations that nSARS-CoV-2 has crossed jumped to humans from wild species; however, the scientific basis is limited. Earlier cases based on the previous history of beta coronavirus outbreak, i.e., SARS in 2002 and MERS in 2014, possess a significant similarity with the virus, i.e., nSARS-CoV-2 responsible for the pandemic [4,5]. The prime route for human-to-human transmission is aerosol-based respiratory droplets. However, other routes of viral spreads cannot be denied entirely, such as fecal matter, surfaces, and water. The transmissibility (R0) of nSARS-CoV-2 remains significantly high (1.5–2.5) compared to previous coronavirus outbreaks and influenza. The most recent data from the World Health Organization (WHO) and the Centre for Disease Control (CDC) show four major strains of nSARS-CoV-2 remain in circulation across the globe. The B.1.1.7 alpha variant was first reported in the United Kingdom in late 2020, while B.1.351 was first reported in South Africa in December 2020. In 2020, B.1.617.2, a delta variant, was reported in India, while in Brazil, P.1, a gamma variant, was reported in 2021 [6,7]. Recently, the world has been facing new challenges to cope with highly infectious variants of nSARS-CoV-2, i.e., Omicron, rapidly spreading across the globe. Omicron, a variant, was first reported in South Africa in November 2021 associated with a very high R0 value but less pathogenic [8,9]. These variants were associated with frequent mutations leading to higher transmissibility and pathogenecity. Considering epidemiology data, high transmissibility and pathogenecity are also associated with host risk factors such as age, sex, co-morbidity, etc. [10,11].

Among the coronaviruses (CoVs) which infect humans, nSARS-CoV-2 is the seventh member of the Coronaviridae family. It is interesting to note here other three members from Coronaviridae family Alphacoronavirus (α-CoV), Gamma-coronavirus (γ-CoV) and Delta-coronavirus (δ-CoV) do not infect human while Beta-coronavirus (β-CoV) only cause respiratory distress disorder to human [12,13]. The genome of nSRAS-CoV-2 has comprised of 30 kb encodes non-structural polyprotein, i.e., Open reading Frame 1a/b (ORF 1a/b). The ORF 1a/b under sequential cleave results in 15/16 proteins with four structural and five accessory proteins (ORF3a, ORF6, ORF7, ORF8, and ORF9) [14]. The structural proteins are crucial to understanding the infection biology of nSARS-CoV-2 and are comprised of Spike Protein (S), i.e., a surface glycoprotein, the membrane protein (M), the envelope protein (E), and nucleocapsid protein (N) [7]. The viral attachment to host cell and internalization involve S protein via enzyme-based S protein cleave into S1 and S2 subunits. Here, the S1 subunit finds affinity to ACEII receptor, and the S1 subunit further goes for a conformational change to interact with receptor-binding domain (RBD) of ACEII receptor [15]. The alveolar epithelial cells of the respiratory tract are the prime location for nSARS-CoV-2, where the virus rapidly replicates. The higher viral load of virus in the alveolar epithelial cell triggers an immune response and drives several inflammatory mediators, pro-inflammatory cytokines resulting in a cytokine storm [16]. The clinical manifestation of cytokine storm is acute respiratory distress syndrome (ARDS).

The growing number of research evidence has demonstrated that nSARS-CoV-2 infections leading to COVID-19 are primarily associated with the respiratory tract. However, extrapulmonary clinical manifestations were also reported after nSARS-CoV-2 infections. The respiratory illness is mainly due to the activation and release of pro-inflammatory cytokines to the alveolus [17]. The alveolus after an effective nSARS-CoV-2 cellular load triggers release/recruitment of tumor necrosis factor-α (TNF α), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukin-1 (IL-1), interleukin-6 (IL-6),), IL-1β, IL-8, IL-12, and interferon (IFN)-γ. The research evidence also demonstrated that the chronic infection of nSARS-CoV-2 is associated with massive/several-fold higher release of cytokines as IL6 and TNF-α result in a cytokine storm in COVID-19 patients (symptomatic cases) [1,18]. Even though nSARS-CoV-2 primarily targets the respiratory system, extrapulmonary system effects have been reported. The growing understanding of nSARS-CoV-2 provides a scientific basis for the impact of virus infection on cardiovascular, renal, neuronal, and gastrointestinal systems. There are significantly fewer clinical investigations towards the effects of nSARS-CoV-2 on extrapulmonary systems [19]. However, diarrhea, nausea and vomiting, anorexia, and abdominal pain are common symptoms reported in many clinical studies. Studies based on GIT endoscopy demonstrated nSARS-CoV-2 Nucleocapsid protein in epithelia of the small and large intestine [20]. Further, a close association of nSARS-CoV-2 with GIT was reported with many immune cells, i.e., plasma and lymphocytes in the lamina propria of the small and large intestine. The gut microbiota plays a vital role in establishing gut immunology, and during nSARS-CoV-2 infections, impaired immunity may result in gut dysbiosis [21]. The critical question here arises: does viral particles and or components trigger system inflammation? If so, these viruses and or particles might influence gut immunology first.

2. Human microbial ecology

The human gut is the natural habitat of more than trillions of microbes, including bacteria, fungi, archaebacteria and viruses. The number of microbe's habitat in the human gut, which is nearly

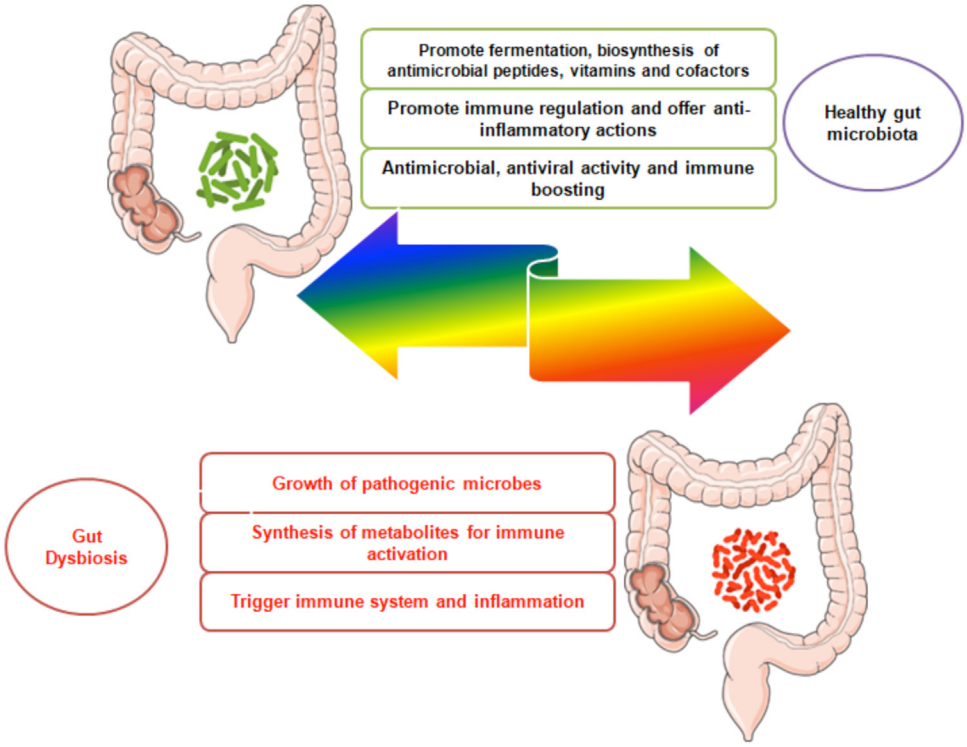

Fig. 1. Figure demonstrates the relationship between healthy microbiota and gut dysbiosis.

1014, represents a mere number and diversity [22,23]. The studies have also demonstrated that different gut sections allow colonization of various microbes, primarily from Bacteroidetes and Firmicutes [24]. These natural bacterial habitats provide several beneficial roles to human physiology including, immunity. The grown research evidence offers a scientific basis for the diverse habitat of microbes in the human gut, i.e., these microbes play a crucial role in the fermentation process of non-digestible substances like dietary fibers and endogenous mucus. Gut microbiota remains associated with three significant aspects of human health one; beneficial role such as the production of antibiotics, reducing toxins, improving lipid metabolism, low gut inflammation, controlling insulin sensitivity, and minimizing the risk of infections [25]. Secondly, pH and water/mineral control are associated with gut microbiota and homeostatic balance. The studies also demonstrated that gut microbiota, especially harmful microbes and or altered colonization of gut microbiota, results in the onset of various diseases [26]. As per recent findings, systemic/metabolic inflammation, insulin intolerance, cardiovascular disorders, diabetes, neurological disorders, and cancer may result from altered gut microbiota. The genome sequencing enabled to characterize gut microbial ecology where Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, Verrucomicrobia, Firmicutes, and Bacteroidetes genus represents more than 90% of human gut microbial/bacterial diversity and population under healthy conditions [27,28]. Further, Firmicutes phylum represents nearly 250 different genera Lactobacillus, Bacillus, Clostridium, Enterococcus, and Ruminicoccus [29].

3. Gut dysbiosis

The research investigation demonstrated more than 1000 different microbial species habitats in the human gut with an increasingly large number of populations, i.e., 1014. There are helpful and harmful microbes; bacteria, fungi, and viruses. Both valuable and harmful microbial species remain in a close cross talk and create a homeostatic balance between colonized microbes and the host gastrointestinal tract [30]. The healthy homeostatic balance between microbial ecology restricts the growth of potentially pathogenic microbes. Hence, the human gut remains a reservoir of beneficial microbes and maintains a healthy host-microbial interaction. Studies have demonstrated that host health positively correlates with the homeostatic balance of gut microbial ecology [31]. Gut dysbiosis is when intestinal microbiota fails to restore homeostatic balance in colonized microbial species. Several risk factors such as infection, food, daily lifestyle, age, gender, and environmental factors trigger the breakdown of the homeostatic balance of gut microbial ecology [32]. As a result, the gut environment allows harmful/potentially pathogenic microbes to grow and colonize. The altered microbial ecology results in negative cross-talk with the host and triggers several diseases. Gut microbial ecology remains a highly dynamic state in humans, and any change leads to altered functional composition, metabolic activities, and local distribution [33]. Gut dysbiosis results in the loss of beneficial microbial species, overall microbial biodiversity, and excessive growth of harmful microbes. The studies also investigated that gut dysbiosis affects gut immunology and provides an opportunity for various microbes and microbial products to elicit an immune response.

4. Gut dysbiosis and immunity

Gut microbiota plays a vital role in gut immunology and immunity, both humoral and cellular. The gut-associated lymphoid tissues (GALT) are predominantly present in the small intestine, and a healthy gut microbiota helps in the functions of gut lymphoid tissues [34]. The physiological changes are related to stimuli from gut microbiota (signaling molecules and gut microbiota-driven metabolites) via hematopoietic cells of the innate immune system [35]. As a result, a healthy gut microbiota establishes a balance (immune homeostasis) between signaling molecules and gut immunology. There is a significant change in microbial

Table 1
The table summarize major studies associated with altered gut microbial profile after nSARS-CoV-2.

S. No.	Study	Reference
	In this pilot study, 15 patients were profiled for gut microbiota and reported significant change in the bacteria over control. The change in gut microbial ecology also depends on severity of disease	[58]
	The study demonstrates COVID-19 remain associated with not only change in the gut microbial ecology but also specific bacteria such *Faecalibacterium prausnitzii*, *Clostridium butyricum*, *Clostridium leptum*, and *Eubacterium rectal*	[59]
	Respiratory infection remain associated with altered gut microbial ecology but the study demonstrated specific viral infection leads to change in particular gut microbes. Here, in the study, gut microbiome signature was entirely different in nSARS-CoV-2 infection compare to influenza	[60]
	The study demonstrates the change in gut microbial ecology after nSARS-CoV-2 infection leads to altered immune response. This is primarily due to change in gut microbial immunology where colonizing microbes play a vital role	[61]
	In a follow up study, after six month from discharge the gut microbial ecology was not stored and consequently the gut immunology/immune response reported poor	[62]
	The study demonstrates, altered gut microbial ecology remains associated with altered Metabolome. Here, in this study, non human primates' shows changes in short chain fatty acids after infection with nSARS-CoV-2. The SCFAs are key metabolites from gut microbes	[63]

population and diversity during gut dysbiosis, resulting in a difference in the whole signaling cascade [36]. Disturbed gut homeostasis due to altered gut microbiota causes leaky gut triggers inflammation. The bacterial species Bacteroides fragilis contribute complex immunogenic substances such as lipopolysaccharide essential for gut immune homeostasis. During gut dysbiosis, there is a significant loss of Bacteroides fragilis population break reversal mechanism of gut immunology [37]. The immunity may comprise based on new and or pathogenic microbial diversity due to gut dysbiosis. In the long-term, gut dysbiosis triggers GALT and results in recurrent inflammation (Fig. 1). The chronic and recurrent inflammation further decreases the population and diversity of beneficial microbes in the gut. The studies have also demonstrated that gut dysbiosis restricts the growth and colonization of useful microbes and diversity and promotes microbial translocation [38]. It is evident that GIT expresses varying pH and other physiological changes in different segments and massive microbial translation (even useful) serves as a stimulatory signal to the immune system's GALT and hematopoietic cells [39,40].

Another vital role of gut microbiota in energy homeostasis and during gut dysbiosis the energy homeostasis remains broken that trigger alternate mechanism for energy harvesting [41]. Such alternate mechanisms for energy harvesting synthesis a series of metabolites do have a stimulatory effect on immune system components such as dendritic cells, GALT, and T cells. The research findings also demonstrated that gut dysbiosis promotes oxidative stress and synthesizes a series of free radicals and reactive oxygen species (ROS) [42]. The oxidative stress damages bio-molecules and alters the expression of mitochondrial DNA that encodes several critical enzymes required for energy production. Gut dysbiosis remains associated with both hypo and hyperactivity of the immune system, which triggers several diseases such as diabetes, inflammation, insulin resistance, autoimmune diseases, inflammatory bowel disease, and several forms of cancer. It is interesting to note here that human microbiota is not entirely explored. Based on available research-based evidence, humoral and cellular immunity is closely associated with gut microbial population and diversity [43–45]. A loss of gut microbial population and diversity, i.e., gut dysbiosis, is a crucial trigger for various diseases and immunity remaining central. Additionally, during gut dysbiosis, microbial population and diversity pose a challenge to characterize them and difficult to establish a metabolic signature [46].

5. COVID-19 and gut dysbiosis

The overwhelming scientific findings suggest shedding of viral RNA in COVID-19 patients for a longer duration. The gastrointestinal epithelia may provide space nSARS-CoV-2 replications and release virus and virus components in the gut lumen. One of the recent areas in a current pandemic in the context of virus transmission, i.e., fecal-oral route, remains a thrust area for research. Similar to bacterial microbial ecology in the human gut, the viruses also find a natural habitat with an increasing diversity [47,48]. Gut virome defines the total number of prokaryotic and eukaryotic viruses present in the human gut. Under healthy conditions, i.e., host-virus relationship, the gut virus does not interfere significantly to host physiology; however, in the case of gut dysbiosis due to change in microbial population and diversity, the virus finds an opportunity to replicate significantly (Table 1). In the case of nSARS-CoV-2, there is a lack of clinical data, but based on preliminary research findings, coronavirus may infect/colonize gut epithelia and alter host physiology [49]. The clinical manifestations of COVID-19 patients demonstrated common symptoms like diarrhea, vomiting, nausea, and gastric discomfort. It is evident that ACEII receptors are highly expressed in gut epithelia provide an ideal opportunity nSARS-CoV-2 to infect and replicate. The 16S RNA and meta-genomics (NGS) studies in the hospitalized COVID-19 patients have shown an altered gut microbiota in humans [50]. The gut epithelia with the higher viral load nSARS-CoV-2 also influence gut immunology. Gut epithelia serve as a barrier between the gut and systemic circulation; the higher viral load breaks the gut epithelial barrier and triggers a robust immune response [51].

A healthy gut microbial ecology protects against harmful and pathogenic bacteria and viruses. The current understanding of viral gut immunology demonstrated that gut–blood barrier disruption

Table 2
Table summarizes bacterial species available as probiotics for dietary uses [70,71].

Genus	Probiotics species
Lactobacillus	*L. acidophilus*
	L. amylovorus
	L. casei
	L. gasseri
	L. helveticus
	L. johnsonii
	L. pentosus
	L. plantarum
	L. reuteri
	L. rhamnosus
Bifidobacterium	*B. adolescentis*
	B. animalis
	B. bifidum
	B. breve
	B. infantis
	B. longum
Lactic Acid Bacteria	*Enterococcus faecium*
	Lactococcus lactis
	Streptococcus thermophilus
Other microorganisms	*Bacillus clausii*
	Escherichia coli Nissle 1917
	Saccharomyces cerevisiae (boulardi)

leading to systemic endotoxemia is primarily driven by gut dysbiosis [41]. Several factors protect the integrity of gut epithelia, and healthy gut microbiota is critical [52]. The gut dysbiosis trigger rise in pathogenic bacteria and viruses trigger increased recruitment of immune cells such as T cell presenting antigen that further mobilizes inflammatory cytokines, i.e., IL10. These events result in a "leaky gut," opening a close interaction between the gut and systemic circulation [53]. In the chronic case of COVID-19, the T cells express a large number of antigens and diversity as well in gut lumen derived from bacterial and viral components cause a severe immune response by recruiting pro-inflammatory cytokines (IL-2, IL-6, IL-7, and IL-10), tumor necrosis factor-α (TNF-α), granulocyte colony-stimulating factor (GCSF), macrophage inflammatory protein 1-α (MIP-1α), monocyte chemo-attractant protein-1 (MCP-1), and 10 kD interferon gamma-induced protein (IP-10) [54–56]. In addition, the clinical interventions in COVID-19 often require external administration of pre and probiotics to restore/reverse gut immunology. It is important to note here, bacterial species available as probiotics do not restrict nSARS-CoV-2 directly but indirectly reduce the recruitment of inflammatory cytokines [57].

6. Probiotics

Probiotics represent a group of bacterial species capable of producing valuable bio-molecules, and immune stimulants help establish host immunity. The mechanism of probiotics differs from bacteria in the formulation [64]. As per FAO, live microorganism in prescribed quantity offers health benefits via colonizing beneficial bacteria to the human gut. Several commercially available probiotics for dietary use include Lactobacillus, Bifidobacteria, Escherichia coli, Enterococcus, etc. [65]. The research findings have demonstrated that probiotics help build the GIT barrier and establish the gut microbiome. Based on the types of bacteria present in probiotic formulations, these probiotics offer a series of metabolites such as antimicrobial peptides, beneficial organic acids, enhance fermentation, increase the activity of intestinal enzymes and trigger mucous secretion [23]. In addition, there is growing research showing that probiotics also provide a space in the gut lumen for intestinal repair and restrict the growth of microbes to alter pH. Additionally, probiotics such as Lactobacillus and Bifidobacterium species significantly eliminate harmful and pathogenic bacteria and restore immune responses [66,67] (Table 2). Probiotics have a wide range of physiological importance precisely in the case of the immune system via increasing Igs generation, enhancing macrophages and lymphocytes activity, and interferon (IFN)-ɤ stimulation. Several studies demonstrated that probiotics helped against viral infections [68]. Finally, the antiviral properties of probiotics are well established. Enterococcus faecium inhibits replication of enteropathogenic coronavirus transmissible gastroenteritis virus (TGEV) and Lactobacillus reuteri F275 protects from lethal infection of a pneumonia virus [69].

7. Probiotics and COVID-19 management

Since the outbreak of the COVID-19 pandemic, several treatment strategies were adopted either to reduce the inflammatory response or to shorten the duration of disease/inflammation. A series of antiviral, anti-inflammatory therapeutics, multivitamins, and probiotics were used in the clinical intervention [72,73]. The reports state a mixed response of probiotics combination with multivitamins and other therapeutics. The research evidence demonstrated that probiotics during COVID-19 treatment reduce viral load and inflammatory response. It is important to note that such interventions combined several multivitamins, antiviral and anti-inflammatory drugs. For example, in a study based on genomic sequence analysis of stool samples from COVID-19 patients, the population of Lactobacillus and Bifidobacterium were decreased, and these patients have reported a severe form of ARDS/respiratory distress [4,74]. The use of probiotics was also significant in minimizing the risk of multiple organ failure. For example, a study demonstrated that Paenibacillus sp.B38 suppressed Angiotensin-II-induced hypertension, cardiac hypertrophy, and fibrosis. Based on previous findings, L. rhamnosus CRL1505, L. gasseri SBT2055, L. casei DK128, B. bifidum, and B. subtilis showed improved immunity may serve as promising candidate for nSARS-CoV-2 [75–77]. Additionally, L. gasseri SBT2055, L. casei DK128, and B. subtilis 3 responses was significant in offering better survival in animal studies and L. rhamnosus CRL1505, L. gasseri SBT2055, and B. bifidum strains for anti-inflammatory properties (Table 3) [21,78,79].

Table 3
The table summarizes bacterial species as promising candidates for COVID-19 management and against nSARS-CoV-2 [80,81].

Bacterial species	Mechanism
B. breve, L. rhamnosus, L. plantarum and L. casei	Inhibitory effects of TLR2, inhibits LPS-induced TNF production and reduces *TLR2*, *TLR4* and *TLR9* gene expression in THP-1 cells
Lactobacilli, L. casei DG	Modulate immune response by reducing mRNA levels of the pro-inflammatory cytokines IL-1α, IL-6, and IL-8 and TLR4
L. paracasei CNCM I-4034	Decreases the IL-12p40, IL-10, TGF-β1, and macrophage inflammatory protein (MIP)-1α
L. plantarum CCFM634, L. plantarum CCFM734, L. fermentum CCFM381,	Modulate immune response via TLR2/TLR6
L. salivarius CECT5713	Modulate cytokine production
E. faecium AL41	Down regulate IL-17 and activates IgA-producing cells
L. acidophilus CCFM137, S. thermophilus CCFM218	Modulate immune response via TLR2/TLR6

8. Molecular basis of probiotics use in COVID-19

The nSARS-CoV-2 infection primarily targets host respiratory epithelia and triggers a prompt and massive immune response. As a result, the lower respiratory tract, especially alveoli, receives a bulk of pro-inflammatory cytokines IL10, IL4, TNF-α, and CSF, etc., referred to as "cytokine storm". The response against the virus in alveoli triggers host-pathogen interaction and secretion of excessive mucous [82–84]. These events cause an ASRD collateral collapse of the respiratory system and death. The nSARS-CoV-2 also infects gut epithelia and promotes gut dysbiosis that further triggers the inflammatory cascade's immune system [85]. As live beneficial bacteria, the probiotics are capable of re-establishing gut microbial ecology and immune modulation. These valuable bacterial species as probiotics not only restore gut microbial ecology but also resolve inflammation by down-regulating pro-inflammatory mediators/cytokines (IL10, IL4, TNF-α, and CSF) (Fig. 2) [86]. Probiotics work in several antiviral, anti-inflammatory, antimicrobial, and immune modulation mechanisms. COVID 19 patients show significant gastric complications such as diarrhea, nausea, gastric discomfort, and loss of appetite [87]. These clinical manifestations are primarily due to gut dysbiosis driven by nSARS-CoV-2; the use of probiotics offers dual effects, one anti-inflammatory, and restoration of gut microbial ecology. There is growing research evidence showing the presence of the live virus, i.e., nSARS-CoV-2 and viral component in stool samples [88]. On the contrary, clinical investigations have also demonstrated that the use of probiotics significantly reduces virus and viral components in human

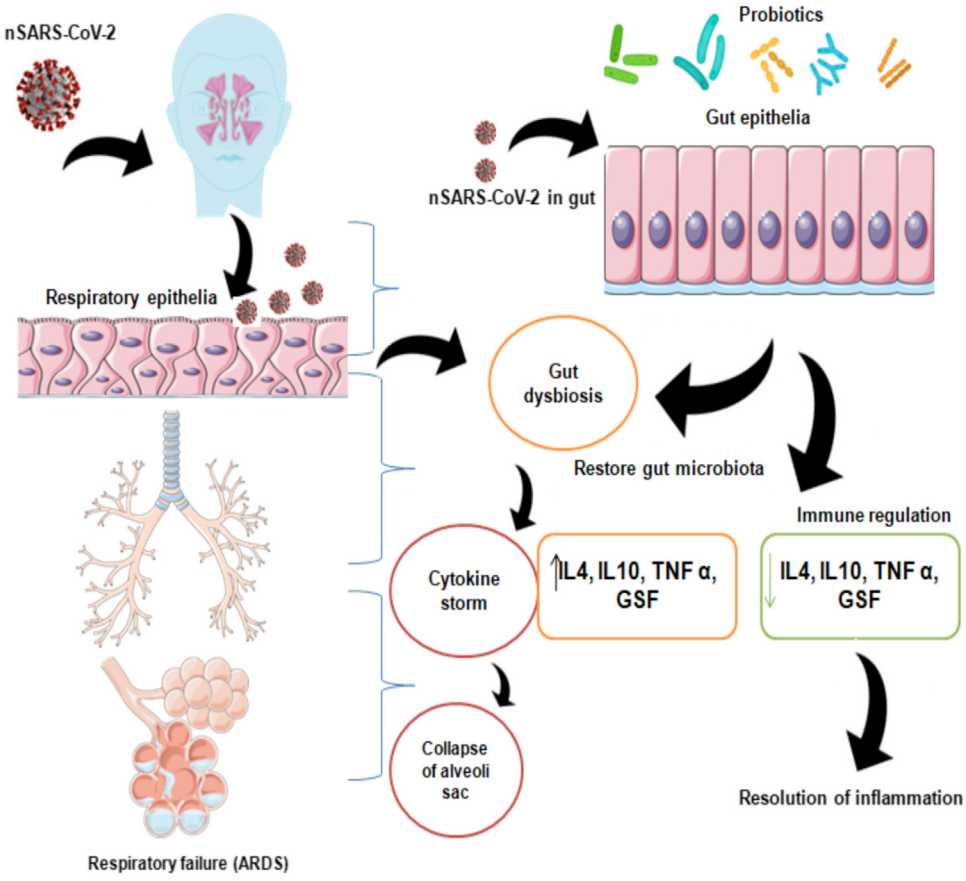

Fig. 2. The figure depicts the role of probiotics in COVID-19 management.

stool samples. List of probiotics used as part of antiviral treatment/management [89]:

- Bifidobacterium, Lactobacillus;
- Enterococcus and Bacillus;
- Bifidobacterium infantis;
- Lactobacillus acidophilus;
- Dung enterococcus;
- Bacillus cereus;
- Bifidobacterium longum;
- Lactobacillus bulgaricus;
- Streptococcus thermophiles;
- Bacillus Subtilis;
- Enterococcus Faecium.

9. Challenges and future prospective

The significant challenge for interpreting the role of probiotics in COVID-19 management is the lack of clinical data. Probiotics used in COVID-19 management were combined with therapeutics and multivitamins; hence, the same efficacy remains debatable [90]. Further, stool sampling from COVID-19 provides precise data for gut dysbiosis and gut microbiota during nSARS-CoV-2 infections. Unfortunately, such studies are limited, and hence finding suitable probiotics that can offer both antiviral and immune-boosting activity remain unclear. The gut microbial ecology depends on several factors, including host and environmental hence probiotic formulation cannot be universal in COVID-19 [91]. The impact of nSARS-CoV-2 infection in COVID-19 has been reported in clinical samples (COVID-19 patients). In a pilot study, Zuo et al., 2020, have shown different in gut microbial ecology in COVID-19 patients compare to the control [92]. Additionally, Gu et al., 2020, had shown that varying gut microbial ecology in different respiratory infections including nSARS-CoV-2 and H1N1 compare to healthy control [93]. Thus, gut microbiota signature becomes crucial not only in diagnosis but also in the treatment of respiratory distress disorders. Additionally, the erratic behavior of individual COVID-19 patients during nSARS-CoV-2 infection shows entirely different clinical symptoms (symptomatic and asymptomatic); hence, defining the mechanism of a probiotic strain becomes difficult [94]. The analysis of stool samples at the genomic level is required to understand gut microbial ecology during nSARS-CoV-2 infection and COVID-19 in symptomatic and asymptomatic patients. The clinical trial studies are underway to investigate the role of probiotics in the COVID-19 disease management. As of now November 2021, five clinical studies have been completed with clinical trial registry number NCT04390477, NCT04458519, NCT04734886, NCT04854941 and NCT04517422 had shown preliminary response [95–100]. A large number of clinical studies, associated with nSARS-CoV-2 infection, for profiling of gut microbiota, along with supplement of probiotics, may provide molecular insights of probiotics uses in the COVID-19 disease management.

10. Conclusion

The nSARS-CoV-2 as a new member of beta-coronavirus is the causative agent for COVID-19 disease and global pandemic. The virus primarily targets the respiratory system precisely epithelia via ACEII receptor and triggers a severe immune response resulting in a cytokine storm. The cytokine storm causes excessive recruitment of pro-inflammatory mediators and results in respiratory distress leading to death in chronic cases. The gastrointestinal tract

also expresses the ACEII receptor, especially in gut epithelia, and stool samples demonstrated virus and viral component presence. The recent clinical investigations have shown that nSARS-CoV-2 infection can cause gut dysbiosis, and as a result, several gastric complications are acute symptoms in symptomatic COVID-19 patients. Several probiotics have been used in combination with therapeutics and multivitamins supplements to shorten the length of disease and tackle inflammation. The use of probiotics in COVID-19 disease management remains unclear as in the large number of clinical studies interventions were given with other therapeutics. However, based on previous findings, probiotics can offer an antiviral activity and help restore gut microbial ecology that indirectly boosts immunity. Several probiotics (bacterial species) were subjected to clinical trials and have shown promising results in the last year. However, as a pandemic is still underway and the virus possesses the capacity to change its genome, the use of probiotics, finding a suitable bacterial species as probiotics, and understanding the mechanism of probiotics in context with COVID-19 disease remain significant concerns worldwide. Indeed, selected bacterial species have shown anti-inflammatory and antiviral properties in previous studies against several pathogens, including viruses. Still, in the case of COVID-19 disease, our understanding of the nSARS-CoV-2 and COVID-19 illness is limited. In addition, the profiling stool samples from COVID-19 disease patients and complete genome characterization will help design probiotic formulations for COVID-19 disease management.

Human and animal rights

The authors declare that the work described has not involved experimentation on humans or animals.

Informed consent and patient details

The authors declare that the work described does not involve patients or volunteers.

Disclosure of interest

The author declares that he has no competing interest.

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Author contributions

All authors attest that they meet the current *International Committee of Medical Journal Editors* (ICMJE) criteria for Authorship.

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