

# The Role of Traditional Fermented Foods Containing Probiotics in Combating Covid-19

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## Abstract

Since, 2019 Coronavirus disease (Covid-19) is the cause of global concern, affecting millions. Dysbiosis of the intestinal microbiome, immune dysregulation, hyper-inflammation, and cytokine-storm are the major molecular symptoms of the disease. The administration of conventional antiviral, anti-inflammatory, and immunomodulatory medications have not been clinically proven and not beneficial for the relief of disease. They produce undesirable, lethal side effects and may lose efficacy on the mutant viruses. Since, dysbiosis is the one of the major symptoms of the disease therefore scientists are trying to incorporate the specific beneficial microbes that are antiviral. Gut bacteria may play a significant role in fighting against viruses as they are known to be omnipresent, they appear to communicate with vital parts of the body, and are known to produce neurotransmitters to initiate the immune system. The development of advanced technologies such as Fecal Microbiota Transplantation (FMT), manipulating, engineering the beneficial microbes that block COVID interaction, entry, and further making it less desirable for the virus survival and proliferation *in-vivo* is the vision research. This approach may give an arsenal to help the body fight against viruses. In this regard, probiotics are a promising choice, as they regulate the immune system and several studies have reported the prophylactic and therapeutic role of probiotics in managing Covid-19. In light of these reports, this review strives to focus on traditional Indian fermented foods rich in probiotics and their potential role in treating and/or controlling respiratory diseases like Covid-19.

**Keywords:** Covid-19; Vaccines; Drugs; Probiotics; Fermented Foods; Respiratory Diseases

## Introduction

### Covid-19: An overview

#### Symptoms and molecular interaction

Emergent respiratory illness is the cause of the severe acute respiratory syndrome coronavirus (SARS-CoV-2). All Covid-19 patients exhibit mild to moderate symptoms, out of which about 15 % progress to the severe pneumonia, 5.0 % eventually develop acute respiratory distress syndrome (ARDS), septic shock, and/or finally leads to multiple organ failure [1]. The mechanistic understanding, and pathology of Covid-19 begins with the virus and host cell interaction followed by binding of the transient glycoprotein present on the viral surface to the host ACE2 (angiotensin-conversion-enzyme 2) cellular receptor for intracellular invasion. Zhang et al. 2020 showed ACE2 is not only observed in alveolar epithelial cells, but also present in intestinal epithelial cells [2]. Therefore, these studies suggest that intestine perhaps be another route for Covid-19 infection [3, 4]. The microbiome dysbiosis in intestinal cells results in cytokine storm causing inflammation, a favorable environment for SARS to adhere and proliferate [5]. Recent reports state that the TMPRSS2 antigen (Transmembrane Serine Protease-2), and the cellular serum protease, are primary proteins exploited by Covid-19 that supports replication in the host organism [6, 7].

#### Covid-19 and host immune response

The infection of SARS-CoV-2 activates innate and adaptive immune responses, leading to uncontrolled inflammatory responses causing systemic tissue damage. In severe Covid-19 patients, lymphopenia is a common symptom, with significantly fewer CD<sup>4+</sup> T-cells, CD<sup>8+</sup> T-cells, B- cells, and natural killer cells (NK). The significant reduction in the percentage of monocytes, eosinophil, and basophil also occurs very often [8]. An increase in the number of neutrophils and in the ratio of neutrophils to lymphocytes generally indicates a higher severity of the disease and a poor clinical outcome. Deregulation of the Covid-19 primary marker proteins such as NKG2A (natural killer cell receptor 2A localized on cytotoxic lymphocytes), NK cells (natural killer cell), and CD<sup>8+</sup> T-cells was a common phenomenon. Even the other major markers de-regulated

such as CD<sup>4+</sup> T-cells, B-cells, and the markers of exhaustion on cytotoxic lymphocytes normalize in patients who have recovered or are on the road to recovery. Later, it was observed that the presence of antibodies specific to SARS-CoV-2 in the bloodstream of recovered patients. Often, patients with severe Covid-19 exhibit significantly elevated pro-inflammatory cytokines such as IL-6 (interleukin), IL-1 $\beta$ , IL-2, IL-8, IL-17, G-CSF (granulocyte colony-stimulating factor), IP-10 (Interferon-gamma induced protein-10), MCP-1 (Monocyte chemoattractant protein-1), MIP-1 $\alpha$  (Macrophage inflammatory protein-1) (also known as CCL-3) and TNF- $\alpha$  (tumor necrosis factor- $\alpha$ ) and the surge is characterized as “cytokine storm” [9].

#### Ways of control and mitigation of Covid-19

As of now, there is no defined approach for the prevention and treatment of novel Coronavirus [10]. The available treatment options focus on symptom mitigation of patients with serious respiratory infections. However, on symptoms alleviation, common antiviral therapeutic drugs like remdesivir, lopinavir/ritonavir and favipiravir are prescribed / and used to inhibit viral entry. Small chemical antiviral molecules such as hydroxychloroquine, chloroquine, corticosteroids, IVIG, colchicine, azithromycin, IL-1 inhibitors, IL-6 inhibitors, anti-TNF- $\alpha$  agents and plasma therapy are explored in multiple clinical trials globally against Covid-19 infection. The common therapeutics and inflammatory suppressors for Covid-19 mitigation are Interferon-beta (IFN- $\beta$ ), and tocilizumab [11,12,13,14,15,16,17,18,19,20,21] are prescribed. The recent vaccines such as Covishield, Covaxin, Sputnik V, Oxford AstraZeneca, Pfizer-BioNTech, and Moderna are a few among many vaccines across the world to prevent further transmission of Coronavirus disease [22, 23, 24, 25].

#### Probiotics

WHO defines probiotics as "live micro-organisms that, render health benefits when administered in sufficient quantities" [26]. Probiotics modulate the gut microbiome by inhibiting harmful / opportunistic bacterial growth [27]. Various bacteria such as Lactobacillus, a few Enterococcus, and Bifidobacteria are very common probiotic bacteria [28]. Probiotics render health benefits such as immune modulation, controls rotavirus infection, proliferation, and

antibiotic-assisted diarrhoea. They are involved in the prevention, management of gastroenteritis, in controlling intestinal inflammatory disorders like Crohn's disease, paediatric atopic disorders, and Pouchitis [29]. Although the exact mechanisms of probiotics modulating the immune system to combat Covid-19 are yet to be proven. Their efficacy largely depends on the dose, duration of the treatment, frequency, environment, and the strain itself. It is thus important to study the mechanisms and pathways of probiotics and to optimize their use for clinical purposes. The microbiome of a few traditional fermented foods does contain probiotics such as LAB, and *Bifidobacterium* [30]. Probiotics, obtained from these fermented foods may have a role in mitigating the Covid-19 [11]. Hence, it is essential to understand the various Indian traditional fermented foods enriched with beneficial microbes/probiotics.

### Indian traditional fermented foods

The variety of Indian traditional fermented foods have been widely appreciated, accepted globally for its use of herbs and spices, providing appetizing dishes with numerous medicinal properties [31, 32]. In India, traditional knowledge about food production, preservation methods, and therapeutic effects have passed through generations. Every ethnic and traditional group has a unique dietary culture representing their heritage and socio-cultural relations. Each food prepared and processed by various ethnic and traditional groups is unique, and distinct to each other. This is mainly due to large variations in their geographical locations, environmental conditions, and their food preparations/preferences [33].

Tribal traditional and ethnic foods can't be viewed in isolation; rather, they are part of a complex system where various factors such as nutrition, food security, health, culture, ethics, economy, and environmental sustainability are most important. The processing and preparation of traditional foods message us about food and traditional cultures of tribal populations and most importantly their incremental ways of learning, adjusting to sustain the life and ecosystem [34]. Traditional Indian fermented foods are acceptable as functional foods because they contain antioxidants, dietary fibre, probiotics, and palliative compounds [35,30]. These functionally proven bioactive molecules known to reduce body weight, control blood sugar levels and initiate the immune system [36, 37]. Processing methods like germination, malting, and fermentation improve the functional properties of foods [38]. Based on the geographical arrangements, India has four different regions such as Northern, Southern, Eastern, and Western. The culture, history, language, climatic conditions, and food of each region are different. Therefore, their preparation of traditional foods, ingredients, and spices differ. Table 1, 2, and 3 shows a detailed list of fermented foods developed, and produced in each region. Each fermented food has its own microbiota that improves the quantity, quality of proteins, minerals, vitamins, fatty acids and essential amino acids in the food [39]. Traditional foods like Dahi, gundruk, sinki, iniziangsang, iromba, rai fermenté, kanjika and handua possess medicinal properties [40]. Currently, there are hundreds of fermented foods with a variety of basic materials and preparation methods [40]. As of today, various fermented foods have been developed and even marketed, that contain different source material and preparation methodology (Table 1, 2, 3).

**Table 1:**

S.NO	FOOD	INGREDIENTS	MICROORGANISMS	REFERENCE
1.	Idli	Rice and Black gram	Lactobacillus delbrueckii, L. fermenti, L. lactis, Streptococcus faecalis	M Ray et al. (2016)
2.	Dosa	Rice and Black gram	L. mesenteroides, L. fermentum, Bacillus amyloliquefaciens, L. lactis, L. delbrueckii, and L. plantarum, S. cerevisiae	M Ray et al. (2016)
3.	Uttapam	Rice and Urad dahl	L. pentosus and L. plantarum	M Ray et al. (2016)
4.	Vada	Rice, chana dal, moong dal, tur dal, and urad dal.	Pediococcus sp., Streptococcus sp., and Leuconostoc sp.	M Ray et al. (2016)

5.	Appam	Rice	Bacillus spp., Pediococcus pentosaceus, and L. plantarum.	M Ray et al. (2016)
6.	Koozhu	Ragi	W. paramesenteroides, L. fermentum	Satish et al. (2010)

Table 2:

S.NO	FOOD	SUBSTRATE	MICROORGANISMS PRESENT	REFERENCE
1.	Peja	Rice	Not reported. Taken as supplement for people taking antibiotics	I.Sharma et al
2.	Rabdi	Maize	Pediococcus acidilactici, Micrococcus sp. and Bacillus	Steinkraus 1996
3.	Mahua	Madhuca indica (flower)	Not reported. Liquid transquilizer. Used to treat fever and dysentery	Kumar and Rao 2007
4.	Haria	Rice beverage	LAB, Bifidobacteria, Sacchromyces cerevisiae	Sha et al, 2012
5.	Shrikhand	Milk	Lactobacillus acidophilus, L.sporogenes and L.rhamnosus	Swapna and chavannavar 2013
6.	Matha	Curd	Lactobacillus acidophilus, L.sporogenes and L.rhamnosus	Swapna and chavannavar 2013
7.	Ambil	Rice/sorghum/ragi	LAB viz Lactobacillus bulgaricus, L.acidophilus	Shinde 2011
8.	Kurdai	Wheat	Pediococcus.pentosaceus, P.acidolactici, Lactobacillus sp.	Surve et al. 2014
9.	Kharodya	Pearl millet	L.mesenteroides, L.fermentum, S.faecalis	Steinkraus 1983

Table 3:

S.NO	FOOD	SUBSTRATE	MICROORGANISMS PRESENT	REFERENCE
1.	Gundruk	Radish and Cauliflower	<i>Lactobacillus fermentum, L. Plantarum, L.Casei,</i>	Tamang et al, 2005
2.	Sinki	Radish tap roots	<i>Lactobacillus fermentum, L. Brevis and L.Plantarum</i>	Tamang, 1993
3.	NgariPuntius sophore (Phoubu)	Fish	<i>E. Faecium, L. Fructosus, L.amylophilus, L. Plantarum</i>	Thapa et al. (2004), Jeyaram et al. (2009)
4.	HentakEsomus danricus (Fish)	Fish	<i>L. Lactis subsp. Cremoris, L. Plantarum, E. Faecium, L. Fructosus, L. Amylophilus</i>	Thapa et al. (2004), Jeyaram et al. (2009)
5.	Kinema	Soybeans	<i>E. Faecium</i>	Sarkar et al. (2002), Tamang (2003),
6.	Tungrymbai	Tungrymbai	<i>E. Faecium</i>	Tamang et al. (2009), Sohliya et al. (2009)
7.	Soibum	Bamboo shoots	<i>Enterococcusdurans, streptococcus lactis, B. Subtilis, B. Licheniformis, B. Coagulans,</i>	Tamang and Tamang B, 2009; Tamang et al, 2008
8.	Mesu	Bamboo shoots	<i>Lactobacillus plantarum, L. brevis and L. Pentosaceus</i>	Tamang and sarkar, 1996

9.	Churpa	Milk	<i>Lactobacillus plantarum</i> , <i>L. Curvatus</i> , <i>L. Fermentum</i> ,	Tamang et al, 2009
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It has been reported that the North-Eastern Himalayan (NEH) region has developed various vegetable-based fermented foods for bioprocessing, storage, and consumption (Table 3). Further, it is understood that Lactic acid bacteria (LAB) play a significant role in the fermentation, preservation, and processing of ethnic, traditional fermented foods. A few vegetable-based, fermented foods of Nepal, Sikkim, and Bhutan are Gundruk, sinki, and khalpi are rich in LAB [41]. These foods contain various beneficial microbes of the LAB family among which *L. plantarum*, *L. brevis*, *P. pentosaceus*, *P. acidilactici*, and *Leuconostoc fallax* are the dominant [42]. The Himalayan tender-bamboo shoot is also a source of few traditional fermented foods such as mesu, soidon, soibum, and soijim. These fermented foods mostly contain functional LAB strains viz. *L. brevis*, *L. plantarum*, *L. curvatus*, *P. pentosaceus*, *L. mesenteroides subsp. mesenteroides*, *L. fallax*, *L. lactis*, *L. citreum*, and *Enterococcus durans* [43]. A few of the LAB strains are known as starter cultures because of their protective and functional properties. They are used to controlled and optimized fermentation of vegetable products (Tamang and Tamang, 2009; 2010). Major South Indian fermented tasty, healthy breakfasts such as Idli, Uthappam, Appam, and Dosa reported to contain various beneficial microbes such as LAB [30, 44, 45]. Subsequent, inhibition studies of these LAB's prove that they are antagonistic to common pathogens and food spoilage bacteria like *B. cereus*, *S. aureus*, *L. monocytogenes*, *P. aeruginosa*, *V. para haemolyticus*, and *A. hydrophila* [44].

### Fermented foods against opportunistic pathogen

Consumption of fermented foods rich in probiotics help strengthening the immune system, modulate the gut microbiome and keeps away the opportunistic infectious pathogens from invasion [46,47]. *L. lactis* subsp. *cremoris*, from Sukako maacha (fermented dried fish of India and Nepal) exhibited antimicrobial activity against *S. aureus* and *Listeria innocua* [48]. The residents of Himalayan region are the major consumers of fermented milk products like dahi, chhurpi, somar, shyow, philu, and mohi. *Lactococcus* and *Lactobacillus* isolates from fermented milk products exhibits

antagonistic activity against Gram-negative bacteria like *E. agglomerans*, *Enterobacter cloacae*, and *K. pneumonia* subsp. *pneumonia* [49]. Lactic acid bacterial (LAB) isolates and *B. subtilis* from tungtap, (a fermented fish dish of Northeast) showed inhibition against *E. faecium* and *S. mutans* [50]. LAB are the major residents of gastrointestinal tract [51]. The high degree of hydrophobicity and adhesion to intestinal epithelial cells by LAB isolates from fermented fish products indicates its probiotic potential. This implies to prevent pathogenic adherence or colonization in intestinal epithelial cell [50]. Hummel et al., 2012 proposed that probiotics prevent the entry of pathogenic bacteria by modulating epithelial cell barrier function and maintaining tight junctions [52].

### LAB's and their antagonistic activity against food spoilage bacteria

It has been reported that Hamei the fermented food contains LAB and *Pediococcus pentosaceus* that produce bacteriocin a postbiotic observed to be antagonistic to *Listeria* spp. [53]. *L. plantarum* from inziangsang, a fermented leafy vegetable shows antagonistic properties against *Listeria* spp., *S. aureus*, *B. cereus*, *S. mutans*, *E. cloacae*, *E. agglomerans*, and *P. aeruginosa* [54]. LAB isolates from Kimchi, produce antimicrobial compounds against *E. coli*, *S. typhimurium*, *S. aureus* and *L. monocytogenes* [55]. *Weissella cibaria* from fermented cabbage exhibits antimicrobial activity against both Gram-positive and Gram-negative bacteria [56]. Dahi, predominant with *L. lactis* produces nisin Z inhibiting *L. monocytogenes*, *E. coli*, and *Salmonella* spp. [57]. The famous Hawaijar, a fermented soybean is rich in *B. subtilis*, proven to provide health benefits [58]. All the above reports have proven that consumption of fermented foods given at most importance to control and mitigate the bacterial infections. This is feasible strategically, culturally, and economically.

### Why Probiotics for Covid-19 mitigation?

Recent studies have indicated that there is a significant communication between SARS-CoV-2 and

individual gut microbiome [59]. Specifically, in the second wave of Covid-19 infections, the virus does not produce symptoms in a few, but life-threatening ones in others. This means the same organism behaves differently in various hosts and is a major mystery of Covid-19 infections. There are two major reasons for the cause one being the state / variations of the patient's GUT microbiome and the other the generation of various Covid-19 mutants. The virulence of each mutant may differ a few may be highly virulent, and a few may not be. Few mutants studied and reported to date are D614G, variant 501Y.V2, and N501Y mutation [60]. As per the Center for Disease Control and Prevention, (CDC) USA, the Delta variant is highly contagious, more than 2x as contagious as previous variants. CDC also states that variant may cause serious illness in unvaccinated populations specifically [61]. This may be due to the mutations and evolution / resistance developed and variant is the most cause of global concern as on today.

### Covid-19 mutant recent developments

The second wave mutants found in India are the B.1.617, single amino acid that changes <sup>L</sup>452<sup>R</sup> and <sup>E</sup>484<sup>Q</sup> in the receptor-binding domain (RBD) of the spike protein [62]. The other mutations <sup>G</sup>142<sup>D</sup> and <sup>P</sup>681<sup>R</sup> located outside the RBD. The secondary mutations are <sup>H</sup>1101<sup>D</sup> and <sup>T</sup>95<sup>I</sup>. The B.1.1.7 variant does not show any impact on the severity of the disease and, vaccine efficacy [63, 64, 65, 66]. The spike protein cluster of mutations did not include E484Q and had T19R and D950N mutations. There are various antiviral molecules produced by probiotics, as per the WGS data. Each one shows the specificity therefore, there is a possibility that a few might be active even on mutants.

### Mutations affecting Inter and Intramolecular interactions

The mutation <sup>D</sup>111<sup>D</sup> occurred along with the RBD mutations <sup>L</sup>452<sup>R</sup> and <sup>E</sup>484<sup>Q</sup>, but not seen in the cluster without the <sup>E</sup>484<sup>Q</sup> mutation [67]. These mutations known to reduce inter and intramolecular interactions compared to the wild-type virus. The mutant <sup>E</sup>484<sup>Q</sup> involved in the disruption of an electrostatic bond in the RBD. The mutation <sup>P</sup>681<sup>R</sup> causes increased transmissibility, as the furin cleavage site could help increased membrane fusion. Both the mutations <sup>L</sup>452<sup>R</sup> and <sup>E</sup>484<sup>Q</sup> involved in the disruption of the interaction of the

REGN10933 and P2B-2F6 neutralizing antibodies with the spike protein, thus reducing their neutralizing effect [68]. The rapid generation of various mutants raises a question on the efficacy and functional capabilities of new Covid-19 vaccines. It has been reported that, most of the substitution mutants have the capability to evade immune response at the initial phase of infection. Subsequently, causing devastating and rapid lethality [69].

It was documented that the Covid-19 infection and symptoms are rapid and worse in elderly people and people with co-morbidities such as diabetes, heart disease, obesity, and cancer [70]. These comorbidities represent a gut dysbiosis a number of preliminary studies have demonstrated un-usual microbiomes in hospitalized Covid-19 patients. This instigates that there is a strong link / relationship among gut microbes and Covid-19 severity. Hence, it may be possible to alter and engineer the gut microbiome to fight SARS-CoV-2 [71].

### How Probiotics Affect the Microbiota

It has been hypothesized that voluntary modification of the gut microbiota is possible with the use of human feces to treat viral infections. Similar to the past, the present-day fecal microbiota transplantation (FMT) technology has been followed to mitigate intestinal disorders in a few developed countries, and still it is in infantile and is not yet universally prescribed for therapeutic use [72]. In FMT the microbiota of healthy humans are isolated, processed and introduced into the patients. FMT failed to explain the specific bacterial strains for this cause and their action, mechanism. Therefore, the present researchers intend to identify, isolate and use specific strains of bacteria to obtain a specific clinical impact.

Fuller, 1989; Huis et al. in 1994 stated that the definition of probiotics has linked to nutritional health [73, 74]. Later, probiotics were defined as living microorganisms that must be ingested in sufficient quantities to have a positive effect on health, and this is not limited to the nutritional effects [75, 26]. Therefore, all definitions only provide insight into how probiotics influence health: one-way by influencing the resident microbiota (a general means), intestinal epithelial cells, and, globally the immune system (a specific means).

Based on their localization there are two different microbiotas, they are parietal microbiota that lives in mucus or attached to the intestinal wall and the luminal microbiota that lives in food transit and stools [76, 77, 78]. The microbiota composition of an individual depends on the diet, exposition to ingested probiotics, environmental conditions of the intestine, and the other factors of the host such as transient exposure to strains in the ecosystem [79, 80].

The luminal and parietal microbiota compositions altered upon probiotic treatment. The probiotics such as *Lactobacillus* and *Bifidobacteria* were naturally retrieved in 2–31 % of the untreated subjects [81, 82, 83, 84, 85]. Also observed the presence of these microbes along with the microbiota upon probiotic therapy. This implies that the probiotics can live with microbiota without negatively affecting the gut microbiota. Finally, concluded that probiotic bacteria remain in the minority when compared to the resident microbiota [86], therefore, certainly, there is a cross talk among the microbiome and probiotics *in-vivo*.

### Modulation of gut microbiota by Probiotics

The gut microbiome plays a crucial role in maintaining gut health [87]. Bacteriodes such as bacteriodes, *Prevotella*, and firmicutes like *Eubacterium*, *Lactobacillus* spp. make about 90 % of the human gut microbiome, with minor proportions of Actinobacteria, Fusobacteria, Proteobacteria, and *Verrucomicrobium* spp. [88]. It has been observed that Covid-19 patients possess a significant reduction of beneficial symbionts like *Lactobacillus* and *Bifidobacteria* in the gut, and increased count of opportunistic pathogenic bacteria like *Streptococcus*, *Rothia*, and *Actinomyces* [1, 89, 90, 91, 92]. Subsequently, leading to gut dysbiosis, further leads to bacterial translocation, followed by secondary bacterial infections, and multiple organ damage [91]. This could be a reason of disease severity among Covid-19 patients with extreme ages [93, 94]. Toll-like receptor- 4 signaling helps gut microbiome to increase lung defense [95]. This suggests dysbiosis in the gut affect immune responses in lung, thus alleviating pulmonary inflammatory response [96]. Therefore, modulating the gut microflora perhaps help in prevention and treatment of Covid-19 [87]. Developing new therapies for treatment of Covid-19 is time-consuming [87], and cost effective. Therefore, in February 2020, to maintain intestinal micro-

ecology China's National Health Commission and National Administration (version 5) recommended use of probiotics for Covid-19 patients. Probiotics regulate innate immunity, and helps in alleviating inflammatory conditions [97]. Therefore, we hypothesize that probiotics can modulate gut microbiome and help treat respiratory illness in Covid-19 patients.

### Anti-viral activity of Probiotics

Viruses are major causative agents of Upper respiratory tract infections (UTI) [11]. Probiotics administration is safe reduce duration and severity of UTI [98]. Probiotics exert anti-viral immunity eliminating viruses thereby facilitate Covid-19 [71]. *Lactobacilli* and *Paenibacillus* synthesize peptides bind ACE2 there by blocking SARS-COV-2 binding to target cells [99,100]. Lactic acid bacteria prevent viral infections by reducing titers of cytomegalovirus and Ebola [101]. The anti-influenza activity of *L. lactis* JCM 5805 control viral replication and spread. P18, a peptide from probiotic strain *B. subtilis* exhibits complete inhibition of influenza virus infections *in-vitro* [102]. Researchers used influenza virus A/F/M/1/47 (H1N1) to produce respiratory infection in Mice [96]. Heat-killed *L. plantarum* exhibit decreased viral counts in lung and thereby increasing Mice survival time [103]. *B. longum* BB536 upon treatment on Mice reduces the viral count, and loss of body weight were observed [104]. *L. rhamnosus* GG has shown to increase TLR-4 signaling, boosting antiviral response in influenza animal models [105]. It also helps to improve intestinal and lung homeostasis by increasing regulatory T-cells, subsequently improving antiviral defense finally decreasing pro-inflammatory cytokines in systemic and respiratory infections [106]. Another study found a combination of *L. rhamnosus* GG and *B. animalis* subsp. *Lactis* BB12 shown to inhibit the incidence of respiratory viral diseases [107]. *L. gasseri* reduced viral respiratory infection by increasing IFN type I and II secretion [108]. *L. reuteri* *Protectis* exhibit significant antiviral activity against Cocksackei virus type A strains 6 and 16 and enterovirus 71 [109]. Probiotics like *B. longum* and *L. acidophilus* are effective against Rotavirus [110]. In a computational docking study, Anwar et al., reported protein metabolites like Plantaracin W, Plantaracin D and Plantaracin JLA-9 synthesized by *L. plantarum* blocked the binding of SARS-

COV-2 to ACE receptor [111]. Al Kassaa et al. and Barbieri et al. their human and animal experiments reported that LABs are generally, used as antiviral agents to prevent respiratory infections [112,113]. This leads to reduced SARS-COV-2 infection in upper respiratory tract [11].

Daily administration of LAB's active pro-inflammatory strain and oral immunization of Plantarum L-137 showed a decrease in *H1N1 influenza* virus titer in the lungs of infected Mice. Further, proven that *L. rhamnosus* CRL 1505 has the ability to boost the immune system by secretion of IFN- $\gamma$ . This helped in reducing viral load in lung tissue after the challenge with a respiratory syncytial virus, without antibiotics [114,115]. This attribute may be exploited in reducing Covid-19 infections as it infects, and amplifies in the lungs. Administering fermented beverages (containing probiotics) and probiotics like *L. casei* Shirota showed to increase antibody immune responses to influenza virus vaccination in the elderly in general. The administration of probiotics maintains the microbiome of gut-lung axis and thus Covid-19 infection be altered [116]. These findings demonstrate that probiotic therapy is a good, cost-efficient, and effective treatment for respiratory infections such as Covid-19 [10].

### Probiotics as Immuno-modulators

Probiotics regulate innate immunity and improve inflammatory conditions [87]. Gut dysbiosis results in chronic inflammation, and can cause hyper-inflammation as observed in SARS-COV-2 patients [117]. Covid-19 patients witness pro-inflammatory tone with cytokine storm due to intestinal dysbiosis [118]. Probiotics suppress the production of antigen-specific IgE via activation of Th-1 mediated immune response. This was subsequently, followed by NK cellular activity and *in-vitro* IgA production [119]. *L. fermentum* CECT5716 improve epithelial cell function and reduction in inflammation [120]. Also reported that *Lactobacilli* increase gut barrier, reduces TNF- $\alpha$  and increase IL-10 production [121]. *B. bifidum* specifically reduce IL-8 production in HT-29 cells [122]. Probiotics are well known for their anti-inflammatory effects and can reduce hyper-inflammation in Covid-19 patients [71]. *B. longum* 35624 reduces the viral load and improves mice survival by increasing (Interferon) IFN- $\gamma$ , surfactant Protein-D and reducing IL-6, IFN-type I and II [123]. Angurana et al.

demonstrated that administration of multi strain probiotic leads to reduction in pro-inflammatory cytokines and increased anti-inflammatory cytokines [11]. Other reports suggests that probiotics are useful in modulating inflammation in critically ill patients [124,125]. The anti-inflammatory properties of probiotics allow viral clearance and reduce immune-response damage in lungs and other organs. Thus, these immuno-modulatory effects of probiotics perhaps considered relevant in Covid-19 complications [116].

### Link between Fermented foods, Probiotics and Covid-19

The mortality ratio associated with Covid-19 pandemic is variable within and between countries [126]. Although many factors influence Covid-19 epidemic, diet, and ACE2 levels play an important role in controlling the mortality rates [126]. Some European countries are the prominent consumers of traditional fermented foods and have had witnessed lower mortality rates due to Covid-19. Therefore, nutrition and diet play an important role in defense against Covid-19 [127]. Mediterranean diet includes fermented foods proven to possess beneficial effects against allergic respiratory diseases and inflammatory responses [128]. Consumption of fermented foods like cabbage, and cucumber have significant impact on the mortality rates influenced by Covid-19 [129]. The making of fermented foods like Kimchi, Kefir, Sauerkraut containing live bacteria, popularly termed as probiotics is based on LAB fermentation [129]. LAB, including *Lactobacillus* spp. are the prominent species involved in the fermentation process [130]. Gut microbiome is responsible for cabbage fermentation [131]. LAB synthesize biologically active peptides possessing antioxidant activity [46,132]. Fermented vegetables are rich in Lactobacillus, the potent nuclear factor (erythroid-derived 2)-like -2 (Nrf2) activators [129]. Sulphoraphane present as glucoraphanin in stored form in Crucifer family of plants [133,134]. Upon fermentation glucoraphanin is converted to sulphoraphane, a potent Nrf2 activator [129]. The anti-fibrotic effects of Nrf2 prevents lung and endothelial damage further blocks IL-6 in inflammation models, thus they are helpful in mitigating severity of Covid-19 [135,136,137,138]. Hence, sulphoraphane suggested for Covid-19 treatment [139].



## Action and Mechanism of Probiotics in mitigating Covid-19

The viral infection begins with an attachment of the virus to a host cell surface and is an important step. It is known that probiotics have the ability to secrete mucins, and adhere to epithelial cells (Figure 1, Mechanism I). Therefore, this activity of probiotics directly binding to the viral surface and interrupting the infection process [3] is realistic in nature (Figure 1, Mechanism II). They also involved in the maintenance of tight junctions helping in the enhancement of barrier integrity restricting the viral entry into the cell (Figure 1, Mechanism III). At the physiological level, probiotics play a significant role in the maintenance of pH by secretion of various organics such as butyrate, and lactic acid. This in turn helps to target specific killing of pathogens, and competitive exclusion (Figure 1, Mechanism IV & V). The most important characters of probiotics are the synthesis and secretion of ocins / antimicrobials, the resulting product helps to fight against pathogens *in-vivo* (Figure 1, Mechanism V). The number and functions of antigen-presenting cells, NK cells, T-cells, as well as the levels of systemic and mucosal specific antibodies in the lungs are known to be enhanced by probiotics (Figure 1, Mechanism VI) [140]. They help to prevent acute respiratory distress syndrome (ARDS) by modifying the complex balance between pro-inflammatory and immune-regulatory cytokines that causes viral clearance. The presence of probiotic strains improves, and builds the integrity of tight junctions this may significantly reduce the invasion of SARS-CoV-2 [116] thus preventing infection (Figure 1). Probiotics involved in major functions of the body, they also involved in creating Eubiosis and knocking out Dysbiosis (removing infectious pathogenic bacteria from the system) (Figure.1, Mechanism VII).

The probiotic effector molecules such as ocins and organic effector molecules are known to protect gut barrier functions [141,142,143,144]. Emilia et al. reported that a domain of *L. plantarum* surface-layer protein induces anti-inflammatory activity in acute colitis Mice [145]. The inflammatory response initiates binding of surface layer proteins to mannose receptor of gut epithelial cells leading to the prevention of p38 MAPK by inhibiting (TLR-5) Toll-Like Receptor -5 pathway [146]. This phenomenon subsequently helps to suppress the expression of inflammatory cytokines

(IFN- $\gamma$ , IL-17, and IL-23) and to regulate IL-4 and IL-10 production [147].

Randomized placebo studies of *L. plantarum* conclude that there is a suppression of pro-inflammatory cytokine (IFN- $\gamma$ , TNF- $\alpha$ ) expression in middle-aged, enhanced expression of anti-inflammatory cytokines (IL-4, IL-10) in young adults, followed by higher levels of plasma peroxidation and oxidative stress [148]. The oral immunization of *Lactococcus* and pulmonary immunization of *P. aeruginosa*, *S. aureus* hypothesized that there was no lung damage, no systemic inflammation, and observed reduction in bacterial load [149]. Therefore, there is an intricate relation and effect of probiotics and lung function but, the exact mechanism(s) by which probiotics have antiviral activity is unknown.

## Microbiomes Fight with Viruses

Various reports have indicated the presence of different microbes in every organ, ranging from blood to the brain and even in the lungs. The recent studies envisage that gut microbes might influence the lung's health through chemical communication. Upon microbiome analysis of SARS-CoV-2 infected macaques, researchers found the altered gut microbiome by the tenth day of infection; the changes were persisting after 26 days. The hyper-inflammatory response in Covid-19 patients can be reduced by modulation of gut microbiota and commensal bacterial metabolites like SCFA (short chain fatty acids), amino acids and bile acid derivatives. SCFA, particularly butyrate exhibit anti-viral effects through secretion of mucins and antimicrobial peptide defensin [150]. Butyrate reduce cytokine storm by inhibiting pro-inflammatory molecules like TNF- $\alpha$ , IL- $\beta$ , NF- $\kappa$ B and increasing IL-10 production [151]. It also reduces gut inflammation by activating T-cells, enhances gut-barrier, and prevents endotoxins and bacterial translocation to extra-intestinal organs [152]. Several reports suggests that butyrate reduces Covid-19 infections [153,154]. Specifically, the microbial content that is involved in making SCFA (small chain fatty acids) reduced drastically and are important molecules involved in regulating the immune system. Subsequent studies of gut microbes and their products were mechanistically defined, and found that SCFAs of gut microbes travel via the bloodstream to the other parts of the body including the lungs to protect the

animals from respiratory viruses. The microbiome also fights with viruses in many other ways such as by the production of small molecular weight proteins known as bacteriocins, and chemical compounds such as butyrate, and lactate [155]. The recent developments of the effect of probiotics originated from kefir a milk fermented probiotic drink has revealed that it effectively healed Mice inflicted with a “cytokine storm” one of the major causes of death in Covid-19 patients. The effector molecules significantly eliminated cytokine storm, and helped in the maintenance of Eubiosis [156]. (Figure 1, Mechanism VII). This action further ensures the positive and commendable results of using/consuming fermented foods.

## Conclusions

Several studies have shown that probiotics are promising candidates for treating and preventing a number of bacterial and viral diseases. Ongoing research and *in-vitro/in-vivo* biochemical, biophysical and immunological testing of probiotics can lead to other options for controlling life-threatening diseases. It is, therefore, necessary to examine in depth all aspects of probiotics and host interactions. According to previous studies, it is essential to establish the precise mechanisms of probiotic pathways in host systems. Understanding probiotics can lead us to incorporate them as essential food supplements and/or as drugs, which is proving to be a good adjunctive therapeutic option. The above studies conclude that there is an intimate relation between fermented foods, probiotics, microbiome, and their ability to control viral infections. Therefore, Indian traditional fermented foods play a significant role at various intervals in inhibiting viral infections.

## Statements & Declarations

### Conflict of Interest

The authors declare no competing interests.

### Ethical Approval

The authors of this article did not conduct any human or animal experiments. Any data on these studies is gathered from the cited literature sources.

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Being a review article, No funding was received for conducting this study.

## Data Availability

The manuscript contains all of the supporting data and information and it adheres to research guidelines.

## Author contributions

LV, S and PMJ procured the data, KRG wrote the manuscript, edited and finalized for publication.

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