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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^{4+} T-cells, CD^{8+} 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^{8+} T-cells was a common phenomenon. Even the other major markers de-regulated such as CD^{4+} 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-1β, 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-1α (Macrophage inflammatory protein-1) (also known as CCL-3) and TNF-α (tumor necrosis factor-α) 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 Coronovirus [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-α 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-β), 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 dynsentry	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.acidophillus	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	*Lactobacillus fermentum, L. Plantarum, l.Casei,*	Tamang et al, 2005
2.	Sinki	Radish tap roots	*Lactobacillus fermentum, L. Brevis and L.Plantarum*	Tamang, 1993
3.	NgariPuntius sophore (Phoubu)	Fish	*E. Faecium, L. Fructosus, L.amylophilus, L. Plantarum*	Thapa et al. (2004), Jeyaram et al. (2009)
4.	HentakEsomus danricus (Fish)	Fish	*L. Lactis subsp. Cremoris, L. Plantarum, E. Faecium, L. Fructosus, L. Amylophilus*	Thapa et al. (2004), Jeyaram et al. (2009)
5.	Kinema	Soybeans	*E. Faecium*	Sarkar et al. (2002), Tamang (2003),
6.	Tungrymbai	Tungrymbai	*E. Faecium*	Tamang et al. (2009), Sohliya et al. (2009)
7.	Soibum	Bamboo shoots	*Enterococcusdurans, streptococcus lactis, B. Subtilis, B. Licheniformis, B. Coagulans,*	Tamang and Tamang B, 2009;Tamang et al, 2008
8.	Mesu	Bamboo shoots	*Lactobacillus plantarum, L. brevis and L. Pentosaceus*	Tamang and sarkar, 1996

9.	Churpa	Milk	*Lactobacillus plantarum, L. Curvatus, L. Fermentum,*	Tamang et al, 2009

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. aeroginosa* [54]. LAB isolates from Kimchi, produce antimicrobial compounds against *E. coli, S. typhimurium, S. aureus* and *L. monocytogenes* [55]. *Weisella 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 $^{L}452^{R}$ and $^{E}484^{Q}$ in the receptor-binding domain (RBD) of the spike protein [62]. The other mutations $^{G}142^{D}$ and $^{P}681^{R}$ located outside the RBD. The secondary mutations are $^{H}1101^{D}$ and $^{T}95^{I}$. 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 $^{D}111^{D}$ occurred along with the RBD mutations $^{L}452^{R}$ and $^{E}484^{Q}$, but not seen in the cluster without the $^{E}484^{Q}$ mutation [67]. These mutations known to reduce inter and intramolecular interactions compared to the wild-type virus. The mutant $^{E}484^{Q}$ involved in the disruption of an electrostatic bond in the RBD. The mutation $^{P}681^{R}$ causes increased transmissibility, as the furin cleavage site could help increased membrane fusion. Both the mutations $^{L}452^{R}$ and $^{E}484^{Q}$ 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]. Bacteriods 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 Coxsackei 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 Barbiere 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-γ. 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-α 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-γ, 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-γ, 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-γ, TNF-α) 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-α, IL-β, NF-κB 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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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.

References

1. Xu K, Cai H, Shen Y, Ni Q, Chen Y, et al. (2020) Management of COVID-19: the Zhejiang experience. Journal of Zhejiang University (medical science) 49: 147-57.

2. Zhang H, Kang Z, Gong H, Xu D, Wang J, et al. (2020) The digestive system is a potential route of 2019-nCov infection: a bioinformatics analysis based on single-cell transcriptomes. BioRxiv.

3. Infusino F, Marazzato M, Mancone M, Fedele F, Mastroianni CM, et al. (2020) Diet supplementation, probiotics, and nutraceuticals in SARS-CoV-2 infection: a scoping review. Nutrients 12: 1718.

4. Li Q, Guan X, Wu P, Wang X, Zhou L, et al. (2020) Early transmission dynamics in Wuhan, China, of novel coronavirus–infected pneumonia. New England journal of medicine 382: 1199-207.

5. Yang Y, Shen C, Li J, Yuan J, Yang M, et al. (2020) Exuberant elevation of IP-10, MCP-3 and IL-1ra during SARS-CoV-2 infection is associated with disease severity and fatal outcome. MedRxiv 02-20029975.

6. Gurwitz D (2020) Angiotensin receptor blockers as tentative SARS‐CoV‐2 therapeutics. Drug development research 81: 537-40.

7. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181: 271-80.

8. Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. (2020) Dysregulation of immune response in patients with coronavirus 2019 (COVID-19) in Wuhan, China. Clinical infectious diseases 71: 762-8.

9. Shi Y, Wang G, Cai XP, Deng JW, Zheng L, et al. (2020) An overview of COVID-19. Journal of Zhejiang University-SCIENCE B 21: 343-60.

10. Akour A (2020) Probiotics and COVID‐19: is there any link?. Letters in applied microbiology 71: 229-34.

11. Angurana SK, Bansal A (2020) Probiotics and Coronavirus disease 2019: think about the link. British Journal of Nutrition 126: 564-1570.

12. Antwi-Amoabeng D, Kanji Z, Ford B, Beutler BD, Riddle MS, et al. (2020) Clinical outcomes in COVID‐19 patients treated with tocilizumab: An individual patient data systematic review. Journal of medical virology 92: 2516-22.

13. Atal S, Fatima Z (2020) IL-6 inhibitors in the treatment of serious COVID-19: a promising therapy?. Pharmaceutical medicine 34: 223-31.

14. Boulware DR, Pullen MF, Bangdiwala AS, Pastick KA, Lofgren SM, et al. (2020) A randomized trial of hydroxychloroquine as post-exposure prophylaxis for Covid-19. New England Journal of Medicine 383: 517-25.

15. Geleris J, Sun Y, Platt J, Zucker J, Baldwin M, et al. (2020) Observational study of hydroxyl-chloroquine in hospitalized patients with Covid-19. New England Journal of Medicine 382: 2411-8.

16. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, et al. (2020) Remdesivir for the Treatment of Covid-19 -Final Report. New England Journal of Medicine 383: 1813-26.

17. Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, et al. (2020) Remdesivir for 5 or 10 days in patients with severe Covid-19. New England Journal of Medicine 383: 1827-37.

18. Wang LY, Cui JJ, Ouyang QY, Zhan Y, Guo CX, et al. (2020) Remdesivir and COVID-19. The Lancet 396: 953-4.

19. Cao B, Wang Y, Wen D, Liu W, Wang J, et al. (2020) A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine 382: 1787-99.

20. Mohtadi N, Ghaysouri A, Shirazi S, Shafiee E, Bastani E, et al. (2020) Recovery of severely ill COVID-19 patients by intravenous immunoglobulin (IVIG) treatment: A case series. Virology 548:1-5.

21. Joyner MJ, Wright RS, Fairweather D, Senefeld JW,

Bruno KA, et al. (2020) Early safety indicators of COVID-19 convalescent plasma in 5000 patients. The Journal of clinical investigation 130.

22. Singh AK, Phatak S, Singh NK, Gupta A, Sharma A, et al. (2021) Antibody Response after First-dose of ChAdOx1-nCOV (Covishield) and BBV-152 (Covaxin) amongst Health Care Workers in India: Preliminary Results of Cross-sectional Coronavirus Vaccine-induced Antibody Titre (COVAT) study. medRxiv.

23. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, et al. (2021) Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomised controlled phase 3 trial in Russia. The Lancet 397: 671-81.

24. Havervall S, Marking U, Greilert-Norin N, Ng H, Gordon M, et al. (2021) Antibody responses after a single dose of ChAdOx1 nCoV-19 vaccine in healthcare workers previously infected with SARS-CoV-2. EBioMedicine 70:103523.

25. Meo SA, Bukhari IA, Akram J, Meo AS, Klonoff DC (2021) COVID-19 vaccines: comparison of biological, pharmacological characteristics and adverse effects of Pfizer/BioNTech and Moderna Vaccines. Eur Rev Med Pharmacol Sci 1663-9.

26. Hill C, Guarner F, Reid G, Gibson GR, Merenstein DJ, et al. (2014) Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11: 506-14.

27. Khaneghah AM, Abhari K, Eş I, Soares MB, Oliveira RB, et al. (2020) Interactions between probiotics and pathogenic microorganisms in hosts and foods: A review. Trends in Food Science & Technology 95: 205-18.

28. Prasad J, Gill H, Smart J, Gopal PK (1998) Selection and characterization of Lactobacillus and Bifidobacterium strains for use as probiotics. International Dairy Journal 8: 993-1002.

29. Gill H, Prasad J (2008) Probiotics, immunomodulation, and health benefits. Adv Exp Med Biol 606: 423-54.

30. Ray M, Ghosh K, Singh S, Mondal KC (2016) Folk to functional: an explorative overview of rice-based fermented foods and beverages in India. Journal of Ethnic Foods 3: 5-18.

31. Platel K (2020) Functional foods in Indian tradition and their significance for health. In Nutritional and Health Aspects of Food in South Asian Countries. Academic Press 87-98.

32. Joshi VK, editor (2019) Indigenous fermented foods of South Asia. CRC press.

33. Kwon DY (2015) What is ethnic food?. Journal of ethnic foods 2: 1.

34. Sharma I, Kapale R, Kango N (2020) Ethnic Fermented Foods and Beverages of Madhya Pradesh. In Ethnic Fermented Foods and Beverages of India: Science History and Culture. Springer 287-303.

35. Chaudhary A, Sharma DK, Arora A (2018) Prospects of Indian traditional fermented foods as functional foods. Indian J Agric Sci 88: 1496-501.

36. Garcia-Gonzalez N, Battista N, Prete R, Corsetti A (2021) Health-promoting role of Lactiplantibacillus plantarum isolated from fermented foods. Microorganisms 9: 349.

37. Martinez-Villaluenga C, Penas E, Frias J (2017) Bioactive peptides in fermented foods: Production and evidence for health effects. In Fermented foods in health and disease prevention. Academic Press 23-47.

38. Sarkar P, DH LK, Dhumal C, Panigrahi SS, Choudhary R (2015) Traditional and ayurvedic foods of Indian origin. Journal of Ethnic Foods 2(3):97-109.

39. Jeyaram K, Singh A, Romi W, Devi AR, Singh WM, et al. (2009) Traditional fermented foods of Manipur. Indian J Tradit Knowl 8: 115-21.

40. Satish Kumar R, Kanmani P, Yuvaraj N, Paari KA, Pattukumar V, et al. (2013) Traditional Indian fermented

foods: a rich source of lactic acid bacteria. International journal of food sciences and nutrition 64: 415-28.

41. Tamang JP, Sarkar PK, Hesseltine CW (1988) Traditional fermented foods and beverages of Darjeeling and Sikkim–a review. Journal of the Science of Food and Agriculture 44: 375-85.

42. Tamang JP, Tamang B, Schillinger U, Franz CM, Gores M, et al. (2005) Identification of predominant lactic acid bacteria isolated from traditionally fermented vegetable products of the Eastern Himalayas. International journal of food microbiology 105: 347-56.

43. Tamang B, Tamang JP, Schillinger U, Franz CM, Gores M, et al. (2008) Phenotypic and genotypic identification of lactic acid bacteria isolated from ethnic fermented bamboo tender shoots of North East India. International Journal of Food Microbiology 121: 35-40.

44. Pal V, Jamuna M, Jeevaratnam K (2005) Isolation and characterization of bacteriocin producing lactic acid bacteria from a south Indian special Dosa (appam) batter. J Cult Collect 4: 53-60.

45. Iyer BK, Singhal RS, Ananthanarayan L (2013) Characterization and in vitro probiotic evaluation of lactic acid bacteria isolated from idli batter. Journal of food science and technology 50: 1114-21.

46. Marco ML, Heeney D, Binda S, Cifelli CJ, Cotter PD, et al. (2017) Health benefits of fermented foods: microbiota and beyond. Current opinion in biotechnology 44: 94-102.

47. Zmora N, Suez J, Elinav E (2019) You are what you eat: diet, health and the gut microbiota. Nature reviews Gastroenterology & hepatology 16: 35-56.

48. Thapa N, Pal J, Tamang JP (2006) Phenotypic identification and technological properties of lactic acid bacteria isolated from traditionally processed fish products of the Eastern Himalayas. International journal of food microbiology 107: 33-8.

49. Dewan S, Tamang JP (2007) Dominant lactic acid bacteria and their technological properties isolated from the Himalayan ethnic fermented milk products. Antonie van Leeuwenhoek 92: 343-52.

50. Thapa N, Pal J, Tamang JP (2004) Microbial diversity in ngari, hentak and tungtap, fermented fish products of North-East India. World Journal of Microbiology and Biotechnology 20: 599-607.

51. Holzapfel WH, Haberer P, Snel J, Schillinger U, in't Veld JH (1998) Overview of gut flora and probiotics. International journal of food microbiology 41: 85-101.

52. Hummel S, Veltman K, Cichon C, Sonnenborn U, Schmidt MA (2012) Differential targeting of the E-cadherin/β-catenin complex by Gram-positive probiotic lactobacilli improves epithelial barrier function. Applied and environmental microbiology 78: 1140-7.

53. Tamang JP, Dewan S, Tamang B, Rai A, Schillinger U, et al. (2007) Lactic acid bacteria in hamei and marcha of North East India. Indian Journal of Microbiology 47(2):119-25.

54. Tamang JP, Tamang B, Schillinger U, Guigas C, Holzapfel WH (2009) Functional properties of lactic acid bacteria isolated from ethnic fermented vegetables of the Himalayas. International journal of food microbiology 135(1):28-33.

55. Tamang JP, Shin DH, Jung SJ, Chae SW (2016) Functional properties of microorganisms in fermented foods. Frontiers in microbiology 7:578

56. Patel A, Prajapati JB, Holst O, Ljungh A (2014) Determining probiotic potential of exopolysaccharide producing lactic acid bacteria isolated from vegetables and traditional Indian fermented food products. Food Bioscience 5:27-33.

57. Grosu-Tudor SS, Zamfir M (2013) Functional properties of lactic acid bacteria isolated from Romanian fermented vegetables. Food Biotechnology 27: 235-48.

58. Jeyaram K, Singh WM, Premarani T, Devi AR, Chanu KS, et al. (2008) Molecular identification of dominant microflora associated with 'Hawaijar'—a traditional fermented soybean (Glycine max (L.)) food of Manipur, India. International journal of food microbiology 122:

259-68.

59. Yamamoto S, Saito M, Tamura A, Prawisuda D, Mizutani T, et al. (2021) The human microbiome and COVID-19: A systematic review. PloS one 16(6): e0253293.

60. Harvey WT, Carabelli AM, Jackson B, Gupta RK, Thomson EC, et al. (2021) SARS-CoV-2 variants, spike mutations and immune escape. Nat Rev Microbiol 19: 409-24.

61. Riemersma KK, Grogan BE, Kita-Yarbro A, Jeppson GE, O'Connor DH, et al. (2021) Vaccinated and unvaccinated individuals have similar viral loads in communities with a high prevalence of the SARS-CoV-2 delta variant. medRxiv.

62. Li G, Zhou Z, Du P, Yu M, Li N, et al. (2021) The SARS-CoV-2 spike L452R-E484Q variant in the Indian B. 1.617 strain showed significant reduction in the neutralization activity of immune sera. Precision Clinical Medicine 4: 149-54.

63. Wu K, Werner AP, Moliva JI, Koch M, Choi A, et al. (2021) mRNA-1273 vaccine induces neutralizing antibodies against spike mutants from global SARS-CoV-2 variants. bioRxiv.

64. Xie X, Zou J, Fontes-Garfias CR, Xia H, Swanson KA, et al. (2021) Neutralization of N501Y mutant SARS-CoV-2 by BNT162b2 vaccine-elicited sera. BioRxiv.

65. Greaney AJ, Loes AN, Crawford KH, Starr TN, Malone KD, et al. (2021) Comprehensive mapping of mutations in the SARS-CoV-2 receptor-binding domain that affect recognition by polyclonal human plasma antibodies. Cell host & microbe 29: 463-76.

66. Weisblum Y, Schmidt F, Zhang F, DaSilva J, Poston D, et al. (2020) Escape from neutralizing antibodies by SARS-CoV-2 spike protein variants. Elife 9: e61312.

67. Resende PC, Bezerra JF, Vasconcelos R, Arantes I, Appolinario L, et al. (2021) Spike E484K mutation in the first SARS-CoV-2 reinfection case confirmed in Brazil, 2020.Virological 10.

68. Cherian S, Potdar V, Jadhav S, Yadav P, Gupta N, et al. (2021) SARS-CoV-2 spike mutations, L452R, T478K, E484Q and P681R, in the second wave of COVID-19 in Maharashtra, India. Microorganisms 9: 1542.

69. Castro Dopico X, Ols S, Loré K, Karlsson Hedestam GB (2021) Immunity to SARS‐CoV‐2 induced by infection or vaccination. Journal of Internal Medicine 291: 32-50.

70. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, et al. (2020) Factors associated with COVID-19-related death using OpenSAFELY. Nature 584: 430-6.

71. Chen J, Vitetta L (2021) Modulation of Gut Microbiota for the Prevention and Treatment of COVID-19. Journal of Clinical Medicine 10: 2903.

72. Wang JW, Kuo CH, Kuo FC, Wang YK, Hsu WH, et al. (2019) Fecal microbiota transplantation: review and update. Journal of the Formosan Medical Association 118: S23-31.

73. Fuller R (1989) Probiotics in man and animals. J Appl Bacteriol 66: 365-78.

74. HUIS IN'T VELD JJ, Havenaar R, Marteau P (1994) Establishing a scientific basis for probiotic R&D. Trends in biotechnology 12: 6-8.

75. GJ GF (1998) Probiotics. International Journal of Food Microbiology 39: 237-8.

76. Sonnenburg JL, Chen CT, Gordon JI (2006) Genomic and metabolic studies of the impact of probiotics on a model gut symbiont and host. PLoS biology 4: e413.

77. Lee SM, Donaldson GP, Mikulski Z, Boyajian S, Ley K, et al. (2013) Bacterial colonization factors control specificity and stability of the gut microbiota. Nature 501: 426-9.

78. Caballero S, Carter R, Ke X, Sušac B, Leiner IM, et al. (2015) Distinct but spatially overlapping intestinal niches for vancomycin-resistant Enterococcus faecium and carbapenem-resistant Klebsiella pneumoniae. PLoS pathogens 11: e1005132.

79. Derrien M, van Hylckama Vlieg JE (2015) Fate,

activity, and impact of ingested bacteria within the human gut microbiota. Trends in microbiology 23: 354-66.

80. Zhang C, Derrien M, Levenez F, Brazeilles R, Ballal SA, et al. (2016) Ecological robustness of the gut microbiota in response to ingestion of transient food-borne microbes. The ISME journal 10: 2235-45.

81. Larsen N, Vogensen FK, Gøbel R, Michaelsen KF, Abu Al-Soud W, et al. (2011) Predominant genera of fecal microbiota in children with atopic dermatitis are not altered by intake of probiotic bacteria Lactobacillus acidophilus NCFM and Bifidobacterium animalis subsp. lactis Bi-07. FEMS Microbiol Ecol 75: 482-96.

82. Dotterud CK, Avershina E, Sekelja M, Simpson MR, Rudi K, et al. (2015) Does maternal perinatal probiotic supplementation alter the intestinal microbiota of mother and child?. Journal of pediatric gastroenterology and nutrition 61: 200-7.

83. Rutten NB, Gorissen DM, Eck A, Niers LE, Vlieger AM, et al. (2015) Long term development of gut microbiota composition in atopic children: impact of probiotics. PloS one 10: e0137681.

84. Avershina E, Lundgård K, Sekelja M, Dotterud C, Storrø O, et al. (2016) Transition from infant- to adult-like gut microbiota. Environ Microbiol 18: 2226-36.

85. Laursen MF, Laursen RP, Larnkjær A, Michaelsen KF, Bahl MI, et al. (2017) Administration of two probiotic strains during early childhood does not affect the endogenous gut microbiota composition despite probiotic proliferation. BMC microbiology 17: 1-9.

86. Alander M, Korpela R, Saxelin M, Vilpponen-Salmela T, Mattila-Sandholm T, et al. (1997) Recovery of Lactobacillus rhamnosus GG from human colonic biopsies. Letters in Applied Microbiology 24: 361-4.

87. Zhang L, Han H, Li X, Chen C, Xie X, et al. (2021) Probiotics use is associated with improved clinical outcomes among hospitalized patients with COVID-19. Therapeutic advances in gastroenterology 14:17562848211035670.

88. Rishi P, Thakur K, Vij S, Rishi L, Singh A, et al. (2020) Diet, Gut Microbiota and COVID-19. Indian J Microbiol 60: 1-10.

89. Dhar D, Mohanty A (2020) Gut microbiota and Covid-19-possible link and implications. Virus research 285: 198018.

90. Gu S, Chen Y, Wu Z, Chen Y, Gao H, et al. (2020) Alterations of the Gut Microbiota in Patients with Coronavirus Disease 2019 or H1N1 Influenza. Clin Infect Dis 71: 2669-78.

91. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, et al. (2020) Alterations in Gut Microbiota of Patients With COVID-19 During Time of Hospitalization. Gastroenterology 159: 944-55.e8.

92. Hung YP, Lee CC, Lee JC, Tsai PJ, Ko WC (2021) Gut Dysbiosis during COVID-19 and Potential Effect of Probiotics. Microorganisms 9: 1605.

93. Patel NA (2020) Pediatric COVID-19: Systematic review of the literature. American journal of otolaryngology 41: 102573.

94. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, et al. (2020) Clinical characteristics of coronavirus disease 2019 in China. New England journal of medicine 382: 1708-20.

95. Tsay TB, Yang MC, Chen PH, Hsu CM, Chen LW (2011) Gut flora enhance bacterial clearance in lung through toll-like receptors 4. Journal of biomedical science 18: 1-8.

96. Lu W, Fang Z, Liu X, Li L, Zhang P, et al. (2021) The Potential Role of Probiotics in Protection against Influenza a Virus Infection in Mice. Foods 10: 902.

97. Su S, Shen J, Zhu L, Qiu Y, He JS, et al. (2020) Involvement of digestive system in COVID-19: manifestations, pathology, management and challenges. Therap Adv Gastroenterol 13: 1756284820934626.

98. Tapiovaara L, Lehtoranta L, Poussa T, Mäkivuokko H, Korpela R, et al. (2016) Absence of adverse events in healthy individuals using probiotics--analysis of six randomised studies by one study group. Beneficial Microbes 7: 161-9.

99. Li J, Zhao J, Wang X, Qayum A, Hussain MA, et al. (2019) Novel Angiotensin-Converting Enzyme-Inhibitory Peptides From Fermented Bovine Milk Started by Lactobacillus helveticus KLDS.31 and Lactobacillus casei KLDS.105: Purification, Identification, and Interaction Mechanisms. Front Microbiol 10: 2643.

100. Minato T, Nirasawa S, Sato T, Yamaguchi T, Hoshizaki M, et al. (2020) B38-CAP is a bacteria-derived ACE2-like enzyme that suppresses hypertension and cardiac dysfunction. Nature communications 11: 1-2.

101. Kanauchi O, Andoh A, AbuBakar S, Yamamoto N (2018) Probiotics and para-probiotics in viral infection: clinical application and effects on the innate and acquired immune systems. Current pharmaceutical design 24: 710-17.

102. Starosila D, Rybalko S, Varbanetz L, Ivanskaya N, Sorokulova I (2017) Anti-influenza activity of a Bacillus subtilis probiotic strain. Antimicrobial agents and chemotherapy 61: e00539-17.

103. Maeda N, Nakamura R, Hirose Y, Murosaki S, Yamamoto Y, et al. (2009) Oral administration of heat-killed Lactobacillus plantarum L-137 enhances protection against influenza virus infection by stimulation of type I interferon production in mice. International immune-pharmacology 9: 1122-5.

104. Iwabuchi N, Xiao JZ, Yaeshima T, Iwatsuki K (2011) Oral administration of Bifidobacterium longum ameliorates influenza virus infection in mice. Biological and Pharmaceutical Bulletin 34: 1352-5.

105. Kumova OK, Fike AJ, Thayer JL, Nguyen LT, Mell JC, et al. (2019) Lung transcriptional unresponsiveness and loss of early influenza virus control in infected neonates is prevented by intranasal Lactobacillus rhamnosus GG. PLoS pathogens 15: e1008072.

106. Bottari B, Castellone V, Neviani E (2021) Probiotics and covid-19. International Journal of Food Sciences and Nutrition 72: 293-9.

107. Rautava S, Salminen S, Isolauri E (2008) Specific probiotics in reducing the risk of acute infections in infancy–a randomised, double-blind, placebo-controlled study. British Journal of Nutrition 101: 1722-6.

108. Eguchi K, Fujitani N, Nakagawa H, Miyazaki T (2019) Prevention of respiratory syncytial virus infection with probiotic lactic acid bacterium Lactobacillus gasseri SBT2055. Sci Rep 9: 4812.

109. Ang LY, Too HK, Tan EL, Chow TK, Shek LP, et al. (2016) Antiviral activity of Lactobacillus reuteri Protectis against Coxsackievirus A and Enterovirus 71 infection in human skeletal muscle and colon cell lines. Virol J 13:111.

110. Lee DK, Park JE, Kim MJ, Seo JG, Lee JH, et al. (2015) Probiotic bacteria, B. longum and L. acidophilus inhibit infection by rotavirus in vitro and decrease the duration of diarrhea in pediatric patients. Clinics and research in hepatology and gastroenterology 39: 237-44.

111. Anwar F, Altayb HN, Al-Abbasi FA, Al-Malki AL, Kamal MA, et al. (2021) Antiviral effects of probiotic metabolites on COVID-19. Journal of Bio-molecular Structure and Dynamics 39: 4175-84.

112. Al Kassaa I, Hamze M, Hober D, Chihib NE, Drider D (2014) Identification of vaginal lactobacilli with potential probiotic properties isolated from women in North Lebanon. Microbial ecology 67: 722-34.

113. Barbieri N, Herrera M, Salva S, Villena J, Alvarez S (2017) Lactobacillus rhamnosus CRL1505 nasal administration improves recovery of T-cell mediated immunity against pneumococcal infection in malnourished mice. Beneficial microbes 8: 393-405.

114. Salva S, Nuñez M, Villena J, Ramón A, Font G, et al. (2011) Development of a fermented goats' milk containing Lactobacillus rhamnosus: in vivo study of health benefits. Journal of the Science of Food and Agriculture 91: 2355-62.

115. Chiba E, Tomosada Y, Vizoso-Pinto MG, Salva S, Takahashi T, et al. (2013) Immunobiotic Lactobacillus rhamnosus improves resistance of infant mice against respiratory syncytial virus infection. International immunopharmacology 17: 373-82.

116. Baud D, Dimopoulou Agri V, Gibson GR, Reid G, Giannoni E (2020) Using probiotics to flatten the curve of

coronavirus disease COVID-2019 pandemic. Frontiers in public health 8: 186.

117. Chen J, Hall S, Vitetta L (2021) Altered gut microbial metabolites could mediate the effects of risk factors in Covid‐19. Reviews in Medical Virology 31: 1-13.

118. Marasco G, Lenti MV, Cremon C, Barbaro MR, Stanghellini V, et al. (2021) Implications of SARS‐CoV‐2 infection for neuro-gastroenterology. Neurogastroenterology & Motility 33: e14104.

119. Kawashima T, Hayashi K, Kosaka A, Kawashima M, Igarashi T, et al. (2011) Lactobacillus plantarum strain YU from fermented foods activates Th1 and protective immune responses. Int Immunopharmacol 11: 2017-24.

120. Molina-Tijeras JA, Diez-Echave P, Vezza T, Hidalgo-García L, Ruiz-Malagón AJ, et al. (2021) Lactobacillus fermentum CECT5716 ameliorates high fat diet-induced obesity in mice through modulation of gut microbiota dysbiosis. Pharmacol Res 167: 105471.

121. Monteros MJ, Galdeano CM, Balcells MF, Weill R, De Paula JA, et al. (2021) Probiotic lactobacilli as a promising strategy to ameliorate disorders associated with intestinal inflammation induced by a non-steroidal anti-inflammatory drug. Scientific Reports 11: 1-5.

122. Hong N, Ku S, Yuk K, Johnston TV, Ji GE, et al. (2021) Production of biologically active human interleukin-10 by Bifidobacterium bifidum BGN4. Microbial Cell Factories 20: 1-4.

123. Groeger D, Schiavi E, Grant R, Kurnik-Łucka M, Michalovich D, et al. (2020) Intranasal Bifidobacterium longum protects against viral-induced lung inflammation and injury in a murine model of lethal influenza infection. EBioMedicine 60: 102981.

124. Timmerman HM, Niers LE, Ridwan BU, Koning CJ, Mulder L, et al. (2007) Design of a multispecies probiotic mixture to prevent infectious complications in critically ill patients. Clinical nutrition 26: 450-9.

125. Wang G, Wen J, Xu L, Zhou S, Gong M, et al. (2013) Effect of enteral nutrition and ecoimmunonutrition on bacterial translocation and cytokine production in patients with severe acute pancreatitis. Journal of surgical research 183: 592-7.

126. Bousquet J, Anto JM, Iaccarino G, Czarlewski W, Haahtela T, et al. (2020) Is diet partly responsible for differences in COVID-19 death rates between and within countries? Clin Transl Allergy 10:16.

127. Bousquet J, Czarlewski W, Blain H, Zuberbier T, Anto J (2020) Rapid response: why Germany's case fatality rate seems so low: is nutrition another pos‐sibility. Bmj 369: m1395.

128. Zabetakis I, Lordan R, Norton C, Tsoupras A (2020) COVID-19: the inflammation link and the role of nutrition in potential mitigation. Nutrients 12: 1466.

129. Bousquet J, Anto JM, Czarlewski W, Haahtela T, Fonseca SC, et al. (2021) Cabbage and fermented vegetables: From death rate heterogeneity in countries to candidates for mitigation strategies of severe COVID-19. Allergy 76: 735-50.

130. Jung JY, Lee SH, Jeon CO (2014) Kimchi microflora: history, current status, and perspectives for industrial kimchi production. Applied Microbiology and Biotechnology 98: 2385-93.

131. Tian S, Liu X, Lei P, Zhang X, Shan Y (2018) Microbiota: a mediator to transform glucosinolate precursors in cruciferous vegetables to the active isothiocyanates. Journal of the Science of Food and Agriculture 98: 1255-60.

132. Şanlier N, Gökcen BB, Sezgin AC (2019) Health benefits of fermented foods. Critical reviews in food science and nutrition 59: 506-27.

133. Vanduchova A, Anzenbacher P, Anzenbacherova E (2019) Isothiocyanate from broccoli, sulforaphane, and its properties. Journal of medicinal food 22: 121-6.

134. Quirante-Moya S, García-Ibañez P, Quirante-Moya F, Villaño D, Moreno DA (2020) The role of brassica bioactives on human health: are we studying it the right way?. Molecules 25: 1591.

135. Liu Q, Gao Y, Ci X (2019) Role of Nrf2 and its

activators in respiratory diseases. Oxidative medicine and cellular longevity 7090534.

136. Zhao H, Eguchi S, Alam A, Ma D (2017) The role of nuclear factor-erythroid 2 related factor 2 (Nrf-2) in the protection against lung injury. American Journal of Physiology-Lung Cellular and Molecular Physiology 312: L155-62.

137. Keleku-Lukwete N, Suzuki M, Yamamoto M (2018) An overview of the advantages of KEAP1-NRF2 system activation during inflammatory disease treatment. Antioxidants & redox signaling 29: 1746-55.

138. Chen B, Lu Y, Chen Y, Cheng J (2015) The role of Nrf2 in oxidative stress-induced endothelial injuries. The Journal of endocrinology 225: R83-99.

139. Horowitz RI, Freeman PR (2020) Three novel prevention, diagnostic, and treatment options for COVID-19 urgently necessitating controlled randomized trials. Medical hypotheses 143:109851.

140. Yan F, Polk DB (2011) Probiotics and immune health. Current opinion in gastroenterology 27: 496.

141. Miyauchi E, Morita H, Tanabe S (2009) Lactobacillus rhamnosus alleviates intestinal barrier dysfunction in part by increasing expression of zonula occludens-1 and myosin light-chain kinase in vivo. Journal of dairy science 92: 2400-8.

142. Karczewski J, Troost FJ, Konings I, Dekker J, Kleerebezem M, et al. (2010) Regulation of human epithelial tight junction proteins by Lactobacillus plantarum in vivo and protective effects on the epithelial barrier. American Journal of Physiology-Gastrointestinal and Liver Physiology 298: G851-9.

143. Laval L, Martin R, Natividad JN, Chain F, Miquel S, et al. (2015) Lactobacillus rhamnosus CNCM I-3690 and the commensal bacterium Faecalibacterium prausnitzii A2-165 exhibit similar protective effects to induced barrier hyper-permeability in mice. Gut microbes 6: 1-9.

144. Martín R, Chamignon C, Mhedbi-Hajri N, Chain F, Derrien M, et al. (2019) The potential probiotic Lactobacillus rhamnosus CNCM I-3690 strain protects the intestinal barrier by stimulating both mucus production and cytoprotective response. Scientific reports 9: 1-4.

145. Hijová E, Bertková I, Štofilová J, Strojný L, Chmelárová A, et al. (2018) Anti-inflammatory potential of Lactobacillus plantarum LS/07 in acute colitis in rats. Acta Vet-Beograd 68: 55-64.

146. Liu Z, Ma Y, Moyer MP, Zhang P, Shi C, et al. (2012) Involvement of the mannose receptor and p38 mitogen-activated protein kinase signaling pathway of the micro-domain of the integral membrane protein after enteropathogenic Escherichia coli infection. Infection and immunity 80: 1343-50.

147. Yin M, Yan X, Weng W, Yang Y, Gao R, et al. (2018) Micro Integral Membrane Protein (MIMP), a Newly Discovered Anti-Inflammatory Protein of Lactobacillus Plantarum, Enhances the Gut Barrier and Modulates Microbiota and Inflammatory Cytokines. Cell Physiol Biochem 45: 474-90.

148. Chong HX, Yusoff NAA, Hor YY, Lew LC, Jaafar MH, et al. (2019) Lactobacillus plantarum DR7 improved upper respiratory tract infections via enhancing immune and inflammatory parameters: A randomized, double-blind, placebo-controlled study. J Dairy Sci 102: 4783-97.

149. Shoaib A, Xin L, Xin Y (2019) Oral administration of Lactobacillus acidophilus alleviates exacerbations in Pseudomonas aeruginosa and Staphylococcus aureus pulmonary infections. Pak J Pharm Sci 32: 1621-30.

150. Chen J, Vitetta L (2020) Gut microbiota metabolites in NAFLD pathogenesis and therapeutic implications. International Journal of Molecular Sciences 21: 5214.

151. Chen J, Zhao KN, Vitetta L (2019) Effects of intestinal microbial–elaborated butyrate on oncogenic signaling pathways. Nutrients 11: 1026.

152. Imhann F, Vich Vila A, Bonder MJ, Lopez Manosalva AG, Koonen DPY, et al. (2017) The influence of proton pump inhibitors and other commonly used medication on the gut microbiota. Gut Microbes 8: 351-58.

153. Archer DL, Kramer DC (2020) The use of microbial accessible and fermentable carbohydrates and/or butyrate as supportive treatment for patients with coronavirus SARS-CoV-2 infection. Frontiers in Medicine 7: 292.

154. Anderson G, Reiter RJ (2020) Melatonin: roles in influenza, Covid-19, and other viral infections. Reviews in medical virology 30: e2109.

155. Sullivan, B (2021) Microbes in your gut may be new recruits in the fight against viruses. National Geographic Science Magazine.

156. Malka O, Kalson D, Yaniv K, Shafir R, Rajendran M, et al. (2021) Cross-kingdom inhibition of bacterial virulence and communication by probiotic yeast metabolites. Microbiome 9: 70.