Review

Probiotic Fermented Food Inhibits Viral Infection; a Concept of Modern Era

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Probiotic Fermented Food Inhibits Viral Infection; A Concept of Modern Era

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Abstract: The utilization of fermented foods has been a longstanding practice in human civilization worldwide for example sauerkraut from the Roman Empire, Jiangshui, and PaoCai, which are popular traditional foods in China. In Korea, Russia, and Mongolia, Kimchi and Kefir are widely used. Similarly, Japan, Indonesia, and Pakistan have their traditional fermented foods such as Miso, Natto, Tempeh, and sourdough, respectively. In America and Europe, fermented alcoholic beverages made from sorghum and maize are among the most common. Nevertheless, the full potential of fermented foods to enhance the bioavailability of bioactive compounds and restore probiotic communities has yet to be thoroughly explored. In this review, we focus on the bioactive compounds and probiotic stability in food fermented with probiotic bacterial strains. Probiotic fermented food improves the bioactive compound contents and has been gaining interest in basic and clinical research. Bioactive compounds, including phenolic, alkaloids, terpenoids, flavonoids, stilbenes, coumarins, tannins, anthocyanidins, flavones, isoflavonoids, and polyphenols, along with beneficial bacteria such as *Lactobacilli, Bifidobacteria, Pediococcus,* and *Weissella* demonstrate increased levels and restoration in probiotic fermented foods. These bioactive compounds, combined with a thriving microbiota, play a role in preventing viral infections by targeting influenza, noroviruses (NoVs), Murine norovirus-1 (MNV-1), and COVID-19, while also stimulating the host's immune function. Clinical and pre-clinical investigations are warranted to explore the dose-response and duration efficacy of probiotic fermented foods against viral infections.

Keywords: fermented food; probiotics; bioactive compounds and antiviral potential

1. Introduction

Fermented foods have been prepared and utilized as a diet since the development of human civilizations [1,2]. It is valuable for human health by relieving the blood cholesterol levels, providing protection against pathogens, and hazardous and carcinogenic substances, and also improving the indicators of lactose intolerance [3,4]. With the confidence of health assistance, fermented foods have bioactive compounds and useful native microbiota [5], which can promote nutritional values and degradation of proteins and long-chain polymers into small peptides [6,7]. For example, angiotensin-1-converting enzyme [8], valyl-prolyl proline, and isoleucyl-prolyl-proline inhibitors observed in fermented food [9], which could treat hypertension and other health disorders. Similarly, the bioactive compounds and probiotic bacterial strains were found in the fermented food with antioxidant, and antiviral potential and various mechanisms of action [10]. The bioactive compounds and probiotic bacterial strains in the fermented food towards wide-range viral infections were employed within the in vitro and vivo reports [11], which boosted the host's immune function directly or indirectly. Microbial fermentation of food is an economical method of generating the metabolites as compared to the other techniques because food fermentation does not need any hydrolysis before purification [12]. The amino acids comprised might be acidic, basic, or hydrophobic and provide fragrance to the bioactive compound in food fermentation [13]. These bioactive compounds are accountable for the suppression of viral activity by inhibiting their adhesin and boosting consumers' immunity [14]. Moreover, whey [15], and yogurt [16,17] fermented with Lactobacillus produce ACE inhibitory bioactive which modulates the toll-like receptor-4. The bioactive peptide (P18) generated by Bacillus subtilis [18], within the legume-based fermented foods, comprises the major microbiota [19].

Microflora of the Bifidobacteria and Lactobacilli might have the capability as anti-viral. For example, cell-free supernatants of Lactobacillus spp., Streptococcus thermophilus, and Bifidobacterium bifidum cultures in yogurt produce metabolites that can prevent influenza virus infection [20]. Moreover, Lactobacillus delbrueckii formed the bacteriocin and was also found as an anti-influenza [21]. Clinical trials showed that the mucosal cells (IL-6 and IL-10) increase were observed in the clinical trials by using fermented food rich in bioactive and probiotics [22]. It was also reported that during the COVID-19 outbreak, low death rats in Asia, Africa, and Europe were because of the use of the fermented diet on a large scale. In this review, we summarized the bioavailability of the bioactive compounds and probiotic bacterial communities in the fermented food along with the health function. Probiotic-fermented food advances the ability against different viral infections including respiratory, alimentary, herpes, and simplex viruses, and COVID-19 was also investigated. Furthermore, fermented food safety from contamination and decaying have been summarized.

2. Fermented food microbial profile, function and bioactive compounds

Food fermentation processing and preservation methods are responsible for different flavors, shelf-life, and texture of food which occur due to the chemical variations in foods [23]. Plants, dairy, alcohol, and marine products based on fermented foods are available worldwide. Among vegetables and fruits, fermented food has a long history in human civilization [24]. For example, sauerkraut (sour cabbage), was used by people of the Roman Empire [25]. PaoCai and Jiangshui a famous traditional food in China and Kimchi in Korea have been used for a long time [26]. The fermented soybeans called "Miso" and "Natto are used in Japan while" Indonesian "Tempeh" [27] has different impacts on human health. Similarly, fermented alcoholic beverages from fruits, cereals, and milk were prepared under culture-dependent and independent techniques [28]. For example, the fermentation of sake [29], flavor liquor [30] grape wine [31], and alcoholic [32], under different cultures and parameters. Fermented food is a hotspot of metagenomics, metaproteomics, metabolomics, and diverse meta-analyses [33]. The following are the different analyses to explore fermented food.

2.1. Microbial profile and function

Dairy-fermented products have increased attention [34], and are part of the diet worldwide [35], according to the International Dairy Federation (IDF). It could improve insulin sensitivity reduce cholesterol levels and control blood pressure in the body [36]. Airag, a famous fermented beverage of Mongolia has been prepared from unpasteurized mare's milk which cures various health diseases [37]. Thermophilus and Delbrueckii from yogurt improve food digestion and reestablish the gut microbiota [25]. Fermented foods are rich in probiotic bacterial strains and used for different health functions as shown in Table 1. The microbial diversity in the fermented foods investigated such as Firmicutes and Proteobacteria in the cheese, jueke, and koumiss was the pre-dominant phyla [38]. Similarly, Lactobacillus, Leuconostoc, Weissella, Enterococcus, and Pediococcus were observed in the fermented vegetables and fruits [39]. In the cheese and Kefir samples collectively Lactococcus, Lactobacillus, Streptococcus, Acetobacter, and Leuconostoc bacterial strains were found dominant [40]. Wu et al. investigated that L. casei, L. helveticus, and L. plantarum were higher microbiota in the koumiss [41]. Furthermore, Enterococcus faecalis, Lactococcus lactis, Leuconostoc mesenteroides, L. plantarum, L. casei, and L. zeae were reported in the Chinese sauerkraut (PaoCai) [42]. It is suggested that the isolated probiotic strains from fermented food could be employed for basic and clinical research. Additionally, the increasing admiration and use of bacterial probiotics are a theme of lucrative financial attention [43] which could be studied for different disorders and physiological

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functions [44]. The yogurt, nutrition bars, snacks, infant foods, and many more have been fermented with the probiotic bacterial strain to increase the nutritional values. Therefore, physicians (gastroenterologists) use commercial lyophilized pills [45]. However, scientific verification of probiotics in fermented food to improve human health function has still not been explored.

2.2. Detection of bioactive compounds in fermented food

Analytical instruments including gas chromatography with mass spectroscopy (GC-MS), High-performance liquid chromatography (HPLC) [85], High-Resolution Nuclear Magnetic Resonance (H-NMR) [10], and ultra-high performance liquid chromatography quadrupole time-of-flight mass spectrometry (UHPLC Q-TOF MS/MS [86] has been used mainly used for the analysis food metabolites (Table 2). The bioactive compounds isothiocyanates and hexanoic acid in the higher concentrations were found in the nozawana zuke while acetic acid, acetoin, and 2,3- butanedion were observed in the low levels [87]. Barley fermented with L. plantarum dy-1 increased the indole- 3-lactic acid, phenyl lactic acid, homovanillic acid, and cafestol while in contrast amino acids, nucleotides, saccharides, and other organic acids declined [88]. 2,4-di-tert-butylphenol, fatty acid esters and sugar derivatives were reported by using the GC-MS analysis in the fermented whole grain [89]. Similarly, in the potherb mustard pickle the volatiles compound allyl, butenyl, isobutanyl, and phenyl ethyl group in the side chain as substituents, for the side-chain (R groups) were detected [90]. Additionally, gamma-aminobutyric acid (GABA), acetoin, acetoacetate, cellobiose, and alanine were identified using H-NMR in the fermented cantaloupe [91]. The integrated lipomics and metabonomic method was employed and 108 metabolites and 174 lipids were reported in the fermented milk [92]. A total of 35 bioactive compounds were observed in the L. plantarum P9 additive fermented milk among which the high levels of detected compounds were fatty acids, peptides, and celluloses [93]. The efficient and sustainable fermented foods were screened with multiple meta-omics tools and by using statistical analysis as shown in the Table 2.

Table 1. Fermented foods are used in different regions of the world and their health beneficial impact on human health and host spots for various probiotic strains. .

Fermented food	Isolated microorganisms	Properties	References
Koumiss	*Lactobacillus coryniformis, L. paracasei, L. kefiranofaciens L. curvatus L. fermentum, L. casei, L. helveticus, L. plantarum*	i. Resistance to low-acid ii. antimicrobial activities	[1]
Kimchi	*L. casei* DK128	i. IgG1 and IgG2 antibodies rapid initiation. ii. induction of innate immune cells and cytokines	[2]
Jiangshui	*Lactobacillus, Limosilactobacillus fermentum, and L. bacilli*	i. Effective in the treatment of hyperuricemia and gout. ii. Provides coldness to the body.	[3]
Yogurt	*Bifidobacterium animalis*	i. Suppressing the infection. Of *helicobacter pylori* ii. Lower the cholesterol levels in serum. iii. Stimulate the immune function. iv. Improve lactose metabolism. v. Antimicrobial, anticarcinogenic, antimutagenic, antidiarrheal properties	[4,5]
Kefir	*L. acidophilus, L. bulgaricus, S. thermophilus, L. crispatus, L. gasseri, L. jensenii, L. rhamnosus*	i. Act as lactose-tolerated and antibacterial. ii. Antidiabetic iii. -suppressing tumors, and acting as anti-hypertensive, -inflammatory, -oxidant, and -carcinogenic	[4]
Mango pickle, *Naan*	Indigenous microflora, yeast	i. Appetizer and meal purpose ii. Increase elasticity in blood vessels and produce new blood cells.	[6]
Sourdough (Khamir)	*Enterococcus mundtii,* and *Wickerhamomyces anomalus, Bacillus subtilis LZU-GM*	i. Gluten-degrading ii. Lower the risk of cancer, aging, and arthritis. iii. Relieve celiac disease	[7,8]
Fermented milk,	*Acinetobacter, Enterobacteriaceae, and Aeromonadaceae*	i. Immunomodulation and amelioration of colitis and diabetes. ii. Used for gastrointestinal disorders, cancer, high cholesterol and blood pressure	[9]

Shubat and Ayran	*Leuconostoc* and *Enterococcus*genera	Bile salt is tolerated and antibodies are susceptible	[10]
PaoCai	*Enterococcus faecalis, Lactococcus lactis, Leuconostoc mesenteroides, L. plantarum, L. casei* and *L. zeae*	i. Appetizers and vitamin absorption. ii. Anticancer	[11]
Fermented Portuguese olive	*L. plantarum and L. paraplantarum*	i. Acid and bile salt tolerant. ii. Simulated digestion. iii. Exopolysaccharide producing abilities	[12,13]
Koumiss	*L. helveticus* and *L. delbrueckii*	i. Treating ailment of urogenital tract and inflammatory disorders. ii. Source of the biogenic amines	[14]
Raw camel milk	*L. fermentum, L. plantarum, L. casei, Lactococcus lactis, Enterococcus faecium,* and *Streptococcus thermophiles*	i. Monitoring diabetes including cholesterol levels, liver and kidney ailment. ii. Oxidative stress decreases and heals the wound.	[15]
Pickle and cucumber		i. Prolonged the shelf life. ii. Anti-nutrients and reduced the toxic level.	[6]
Tarhana	*Streptococcus thermophilus, L. fermentum, Enterococcus faecium, Pediococcus pentosaceus, Leuconostoc pseudomesenteroides, Weissella cibaria, L. plantarum, L.delbrueckii, Leuconostoc citreum, L. paraplantarum* and *L. casei.*	i. Rich source of minerals and nutrients. ii. Effect pathogens and enhanced shelf life.	[16]
Meju, Doenjang, Jeotgal, and *Mekgeolli*	*Leuconostoc mesenteroides, L. plantarum, Aspergillus, Bacillus, Bacillussiamensis, Halomonas* s p., *Kocuria* sp., and *Saccharomyces cerevisiae*	i. Anticancer, anti-obesity, ii. Antioxidant, and anti-inflammatory, anti-diabetes	[17]
Dhokla	*L. plantarum* and *Weissella cibaria*	i. Antimicrobial activity ii. Bile tolerances iii. Antibiotic susceptible	[18]
Cheese	*L. lactis L. delbrueckiiL. helveticus, L. casei, L. plantarum, L. salivarius, Leuconostoc* spp., *Strep. thermophilus, Ent. durans, Ent. faecium, Staphylococcus Brevibacterium linens,*	i. Contains-aminobutyric acid (GABA). ii. Exopolysaccharides, peptides, vitamins, fatty acids, and organic acids. iii. Anticancer ability.	[19–21]

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	Propionibacterium freudenreichii, Debaryomyces hansenii, Geotrichum candidum, Penicillium camemberti, P. roqueforti		
Pla-khao-sug	*Ped. cerevisiae, L. brevis, Staphylococcus* sp., *Bacillus* sp.	i. Boost immune system ii. Suppression of pathogenic bacteria	[22]
Tapai Ubi	*Saccharomycopsis fibuligera*, *Amylomyces rouxii*, *Mu. circinelloides*, *Mu. javanicus*, *Hansenula* spp, *Rhi. arrhizus*, *Rhi. oryzae*, *Rhi. Chinensis*	i. Useful for nerve and muscle cells ii. Balancing microbial diversity and improving immunity	[23,24]
Tungrymbai	*B. subtilis*, *B. licheniformis*, *B. pumilus*	i. Isoflavones transformation and high antioxidants. ii. Cheap source of proteins.	[25,26]
Thua nao	*B. subtilis*, *B. pumilus*, *Lactobacillus* sp.	i. Contains pyrazine compounds and is rich in nutrients ii. Proteins supplement.	[27,28]
Yandou	*B. subtilis*		[29]
Sufu	*Actinomucor elenans, Mucor. silvatixus, Mu. corticolus, Mu. hiemalis, Mu. praini, Mu. racemosus, Mu. subtilissimus, Rhiz. Chinensis*	i. Healthy food because of its low cholesterol. ii. Sources of protein and calcium.	[30,31]
Miso	*Ped. acidilactici, Leuc. paramesenteroides, Micrococcus halobius, Ped. halophilus, Streptococcus* sp., *Sacch. rouxii, Zygosaccharomyces rouxii, Asp. Oryzae*	i. Reduces cancer cell growth. ii. Improve digestive system. iii. Lower cholesterol levels.	[32,33]
Koozh and gherkin	*Lactobacillus and Weissella*	i. Exhibited maximum cholesterol reduction. ii. Exopolysaccharide source.	[34]
Airag	*L. helveticus, L. kefiranofaciens, Bifidobacterium mongoliense*, and *Kluyveromyces marxianu*	i. Reduce thirst and hunger. ii. Improve metabolism. iii. Treat heart and lung troubles.	[35]
Chhurpi	*L. farciminis, L. paracasei, L. biofermentans, L. plantarum, L. curvatus, L. fermentum, L.*	High contents of protein and carbohydrates while low in fat	[36,37]

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	alimentarius, L. kefir, L. hilgardii, W. confusa, Ent. faecium, Leuc. Mesenteroides		
Somar	*L. paracasei, L. Lactis*		[38]
Boza	*Lactobacillus* sp., *Lactococcus* sp., *Pediococcus* sp., *Leuconostoc* sp.,	Contains Biogenic amine content	[39,40]
Suan-tsai and fu-tsai	*Ent. faecalis, L. alimentarius, L. brevis, L. coryniformis, L. farciminis, L. plantarum, L. versmoldensis, Leuc. citreum, Leuc. mesenteroides, Leuc. pseudomesenteroides, P. pentosaceus, W. cibaria, W. paramesenteroides*	i. Remove cholesterol *in vitro.* ii. Anti-oxidative and bile tolerance.	[41]
Nem-chua	*L. pentosus, L. plantarum, L. brevis, L. paracasei, L. fermentum, L. acidipiscis, L. farciminis, L. rossiae, L. fuchuensis, L. namurensis, Lc. lactis, Leuc. citreum, Leuc. fallax, P. acidilactici, P. pentosaceus, P. stilesii, Weissella cibaria, W. paramesenteroides*	Inhibit entrance of potentially pathogenic microorganisms.	[42]

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Table 2. Isolation of different bioactive compounds from fermented food by using various detection techniques.

Fermented foods	**Metabolites and bioactive compounds**	**Techniques use**	**References**
Fermented cantaloupe juice	Isoleucine, valine, lactic acid, alanine, β-alanine, sucrose, erythritol, gluconic acid, GABA, alpha-aminobutyric acid, methionine, acetoin, acetoacetate, and phenylpropanoid acid,	H NMR	[43]
Fermented soybeans	Glucosyringic acid, engeletin, glycitin, dihydroxy-4-phenyl coumarin, ediflavone, histidine, leucine, lysine, methionine, phenylalanine, and tryptophan	UHPLC Q-TOF MS/MS	[44]
Nozawana-zuke	Isothiocyanates, hexanoic acid, lactic acid, acetic acid, acetoin, and 2,3- butanedione, glutamine, valine, leucine, isoleucine, choline, and methionine	NMR, SPME-GC/MS	[45]
Fermented milk	Fatty acids, peptides, amino acids, carbohydrates, vitamins, aldehyde, ketone	*UPLC-Q-TOF-MS/MS*	[46]
Fermented coffee brews	aromatic amino acid, catabolites, and hydroxydodecanoic acid	LC-QTOF-MS/MS	[47]
Fermented camel and bovine milk	Fatty acyls, benzenoids, organ heterocyclic, organic acids and derivatives, phenylpropanoids, polyketides, glycerophospholipids, sterol lipids, polyketides, prenol lipids, organic oxygen, glycerolipids, organooxygen, alkaloids and derivatives, sphingolipids, hydrocarbons, nucleosides, nucleotides, and analogues, lignans, neolignans and related compounds, organosulfur compounds, hydrocarbon derivatives, organic nitrogen compounds	UPLC-QTOF:	[48]
Fermented goat milk	1-stearoyl-lysophosphatidylcholine, gaboxadol, guanine, cytosine, 4 acetamidobenzoic acid, taurochenodeoxycholic acid, 2,6-dimorpholinopyrimidine-4-carboxylic acid, D-proline, DL-Glutamic acid, O-beta-D-glucosyl-*trans*-zeatin, N2-1-Carboxyethyl-N5 diaminomethyleneornithine,	Q-HRMS-UPLC	[49]
Meju	Citric acid, pipecolic acid, glutamic acid, Isoleucine, Leucine, methionine, phenylalanine, tyrosine, proline, threonine, valine	UPLC-Q-TOF MS and PLS-DA	[50]
Cereal-based fermented foods	Volatiles (5 alcohols, 6 carbonils, dodecanoic acid, and 1,3-hexadiene) and the polyphenolic compounds gallic acid, epigallocatechin-gallate, epigallocatechin,	SPME–GC	[51]

	flavonoids, protocatechuic acid, and total polyphenols		
Soymilk fermented	Amino acids, Organic acids, Sugars, Amines, Phenolic compounds, Lipids, Choline, Trigonelline, Pterin, 2,3-butanedione	H NMR	[52]
Fermented Barley	Galactosamine, Maltose, Phenylacetic acid, Cuminaldehyde, Adenosine, Glucose 1-phosphate, Cafestol, Aspartic acid, Lysine, Tryptophan, Citric acid, Glucose 6-phosphate, Methionine, Asparagine, Docosahexaenoic acid methyl ester, Histidine, tyrosine, D-glucosamine-6-phosphate, arginine, fumaric acid, benzaldehyde	UPLC-HRMS	[53]
Gochujangs	Amino acids, organic acids, sugar and sugar alcohol, flavonoids, soyasampnins, lipids, and alkaloids	UPLC-Q-TOF-MS	[54]
Dry-fermented sausages	Amino acids, peptides, and analogues; carbohydrates; organic acids and derivatives; nucleosides, nucleotides and analogues; fatty acids and miscellaneous	1H HR-MAS NMR	[55]
Sunki	Amino acids, organic acids, aldoses, alditoles, and alcohol	HNMR and GC/MS	[56]
Koumiss	Glycerophospholipids, fatty acyls, sphingolipids, 1glycerolipids, prenol lipids, organic acids and derivatives, organic oxygen, organoheterocyclic, benzenoids, organic nitrogen compounds, phenylpropanoids and polyketides, nucleosides and analogues, alkaloids and derivative, glycerophospholipids and fatty acyls, included amino acids, carboxylic acids and derivatives, benzenoids, glycosides, organoheterocyclic compounds, glycerolipids, alcohols, lactones, carbonyl compounds	UPLC-Q-TOF-MS	[57]

Table 2. The list of fermented agents fermented with probiotics increases bioactive compounds.

Fermented agent	**Probiotic strains**	**Promotes compounds availability**	**References**
Carrot pulp	*L. plantarum* NCU 116	Rhamnogalacturonan-I-type polysaccharides break down	[58]
Semen vaccariae and	*L. casei*, *Enterococcus faecalis*, and *Candida utilis*	Increasing the total flavonoids, alkaloids, crude polysaccharides, and saponins contents	[59]

Leonurus artemisia			
Lespedeza cuneata	*L. pentosus,*	Quercetin and kaempferol contents increased	[60]
Daucus carota L	*L. plantarum* NCU116	Effective regulation of glucose and lipid metabolism	[61].
Longan pulp	*L. fermentum*	Lower polysaccharide molecular weight, viscosity, and particle size while higher solubility	*[62].*
Lily bulbs	*L. plantarum*	β-glucans and glycans degraded into tri- and tetra-saccharides	[63]
Tea Plant	*Saccharomyces boulardii* and *L. plantarum*	Improves the methyl salicylate, geraniol, and 2-phenyl ethyl alcohol	[64]
Barley beverage	*L. casei*	Increase total polyphenols and flavonoid contents	[65].
Lily bulbs	*L. lancifolium and S. cerevisae*	Increasing protein contents	[66].
Puerariae radix	*Bifidobactericum breve*	Increase daidzein and genistein	[67]
Soybean	*Bacillus licheniformis*	Increase the insulin-sensitizing action	[68]
Artemisia princeps	*L. plantarum* SN13T	catechol and seco-tanapartholide C	[69]
Panax notoginseng	*Streptococcus salivarius, L. helveticus, L.rhamnosus L. acidophilus , B. longum , B. catenulatum , B. breve* and *B. bifidum*	Increased ginsenosides Rh (1) and Rg (3)	[70]
Artemisia princeps	*L. plantarum*	Produce catechol and seco-tanapartholide C,	
Polygonum cuspidatum	*Aspergillus niger* and Yeast	Production of resveratrol	[71]
Radix astragalus	*Aspergillus* spp	3,4-di(4′-hydroxyphenyl) isobutyric acid	[72]
Cordyceps militaris	*Pediococcus pentosaceus*	Increase β-glucan and cordycepin	[73]

3. Probiotic fermentation increases the bioactive compound in fermented food

The bioactive compounds rich in plants, animals, and microorganisms have a wide range of biological protentional for example antidiabetic [7,103], immunity regulation [104], anticancer agents [105], and antiviral [106]. The functionality of the bioactive compounds is based on their structure. The triple helical *β*-glucans having low molecular weight and higher m stiffness showed strong anti-tumor ability as compared to the lower and higher molecular weight and stiffness β-glucans [107]. Similarly, the higher molecular weight (~10 MDa) of the *β*-(1-4)-D-mannans have the ability of higher

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immune stimulation than (~1.3 MDa) of lower molecular weight [108]. The fermentation of food with probiotics bacteria improves the nutritional values, chemical structure, and availability of bioactive compounds as compared to the unfermented and traditional fermentation process [7]. In the plant cell wall cellulose, hemicellulose, and lignin which give a compact structure to the cell wall are hard to hydrolyze while in the probiotic bacteria fermentation, these substances break into the sub united and promote bioactive compound contents levels [109]. The rhamnogalacturonan-I-type polysaccharides were degraded in the process of probiotic fermentation in the carrot pulp and increased their biological function than unfermented carrot [7]. *L. casei, Enterococcus faecalis*, and *Candida utilis* were used in the fermentation of the *Semen vaccariae* and *Leonurus artemisia* Chinese herbal medicine which increased 55.14 %, 127.28 %, 55.42 %, and 49.21 %, respectively of total flavonoids, alkaloids, polysaccharides, and saponins, compared with the natural herbs [110]. In the fermentation of the *Lespedeza cuneata* with the *Lactobacillus pentosus*, quercetin, and kaempferol were enhanced by 242.9% and 266.7%, respectively, and promoted the potential and antiaging functions [111].

The active regulation and metabolism of glucose and lipids in the probiotic-fermented carrot (*Daucus carota* L) pulp increase the functionality against diabetic effects as compared to the unfermented pulp [112]. It was also stated that polysaccharides of the probiotic-fermented pulp are more effective for type II diabetic rats than unfermented carrot pulp [113]. This suggested that probiotic fermentation was found to change the structure and level of contents in the bioactive compounds. *L. fermentum* fermented the longan pulp and the polysaccharides have low molecular weight, viscosity, and particle size while higher solubility as compared to the unfermented longan pulp and polysaccharides. Therefore, *Leuconostoc mesenteroides* and *L. casei* were restored in the fermented longan pulp which stimulates macrophage secretion of the NO and IL-6 [114]. This indicates that the probiotic fermented food could cause modification and enhancement in the physicochemical structure of the bioactivity of bioactive compounds. The probiotic fermentation also increases the care, dietary, and life shelf of the food. *Bacteroides* spp could alter the structures of β-glucans, and glycans degraded into tri- and tetra-saccharides by *L. plantarum* [115]. The conversion of the baicalin to baicalein via its β-glucuronidase by L. brevis [116]. *Saccharomyces boulardii* and *L. plantarum* bacteria tea fermentation were observed to improve the bioactive constituents including methyl salicylate, geraniol, and 2-phenyl ethyl alcohol [117]. In the barley beverages, the contents of the total polyphenols and flavonoids were improved fermented with strain *L. casei* and raised antioxidant inhibitory function than unfermented barley beverage [118]. Similarly, the lily bulb extract of the *L. lancifolium* was cultivated with *S. cerevisae* increasing the polysaccharide production and the protein removal ratio to unfermented [119]. The carrot water-soluble and soybean-soluble polysaccharides, after the probiotic fermentation enhanced immune regulation function [7]. Lily bulb fermented with S. cerevisiae showed a 91.46% protein removal ratio [119], while *L. plantarum* decreased the water-soluble polysaccharides by degrading them into monosaccharides [115]. *Bacillus licheniformis* fermented soybean increases insulin action by triggering and promoting the peroxisome proliferator-activated receptor-g expression as compared to unfermented soybean [120]. *Puerariae radix* was fermented with the B. breve increased 785 % and 1010 % of the daidzein and genistein contents which promoted the production of the hyaluronic acid in the NHEK cells [121]. The use of probiotics bacterial in food fermentation can reduce or change the toxic effect of the food on human health.

4. Antiviral function of fermented food (Figure 1)

Fermented foods and probiotic bacterial strains have received great attention for having the ability of high antiviral potential. The consumption of fermented food promotes the T lymphocytes (CD3+, CD16+, CD56+) function and enhances pro-inflammatory cytokines to reduce the toxicity of the natural killers' cells [10], These functions of fermented food can control viral infection of the alimentary and respiratory tracts [11,127]. The probiotic fermented food also promotes the digestive system and protects the influenza A viral infection [128]. Moreover, viruses such as rotaviruses, noroviruses, and enteroviruses are gastrointestinal and could be controlled or minimized their

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infections by using functional fermented food [129,130]. However, the antiviral action of fermented are still not well elucidated but it was suggested that direct and indirect viral contact boosting the host's immunity was employed (Fig. 1). This mechanism showed that stimulation of the dendritic cells was increased because of the IgA secretion and IL-6 and IL-10 cells in the clinical trials by some probiotic strains from fermented food. IgA inhibition was caused to control the mucosal membrane attachment and attack of viruses [131]. Similarly, the lipopolysaccharides (LPS) prevent the viral ambition to the host cells [132] the detailed mechanism can be seen in Table 3. Probiotic strain *L. plantarum* in Japanese fermented foods [131], and kimchi [133] were found to inhibit influenza replication. The investigators stated that fermented foods comprising probiotics and bioactive compounds boost immune function and decrease casualty and viral infections [134].

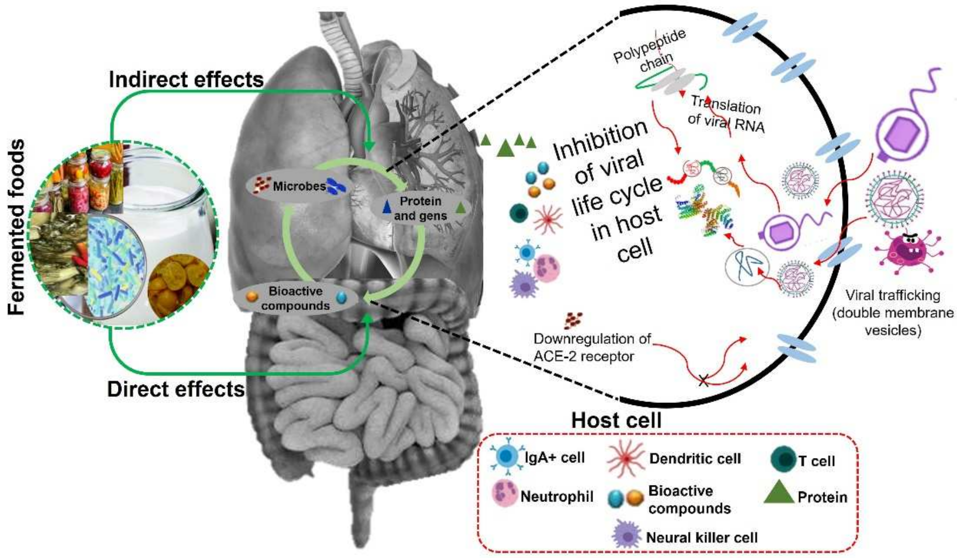

Figure 1. Fermented food promotes the immune system against viral infection via direct pathways (bioactive compounds such as organic acid, fatty acid, phenolic, and flavonoids) and indirect by probiotics and gut microbiota. .

Table 3. Probiotic strains isolated from fermented food are effective against various kinds of viral infections.

Antiviral agent	Target viruses	References
P. pentosaceus, W. cibaria, B. adolescentis	Noroviruses and, murine-1virus	[74,75]
L. brevis and Secoiridoid glucosides	Herpes simplex virus type 2	[76]
L. acidophilus, L. rhamnosus, L.plantarum, S. thermophiles and B. bifidum,	Hepatitis C, Influenza virus,	[77,78]
L. acidophilus, L. reuteri and L. salivarius	avian influenza virus	[79]
L. plantarum, Enterococcus faecium L3	Influenza virus, Coxsackie virus, Echovirus E7 and E19	[80]
Lactobacillus gasseri	Influenza A virus, Espiratory syncytial virus	[81]
L. reuteri ATCC 55730	Coxsackieviruses CA6, and Enterovirus 71	[82]
L. plantarum YU	Influenza A virus	[83]

L. plantarum DK119, *L. gasseri* SBT2055, *L. casei* DK128, Caffeic acid and glycyrrhizin	Influenza virus	[2,84,85]
Lactobacillus spp, Bifidobacteria	Vesicular stomatitis virus	[86,87]
Vitamin A, C D, omega-3, fatty acids, and docosahexaenoic acid	Influenza and COVID-19	[88,89]
Taurine, creatine, carnosine, anserine, and 4-hydroxyproline	COVID-19	[90]

4.1. Inhibition of respiratory and alimentary tracts viruses' infection

Influenza virus causes and leads to morbidity and mortality due to the cause of respiratory tract infection which could be controlled by fermented vegetables and dairy products and probiotic strains isolated from fermented food [135]. It has been reported that in the mice experiment the influenza virus infections were controlled and increased their survival rates by administration of the *Lactobacillus* [136]. Kimchi has a rich diversity of *L. caseai* Dk128 was employed in the mice experiment to control or protect against the influenza virus infection. The results showed that the mice treated with the log 9 CFU mL-1 of strain Dk128 had no significant weight loss as compared to the mice treated with log 7 and 8 CFU mL-1 which revealed 10-12% weight loss in the mice [46]. This data indicates that the dose-dependent treatment of fermented foods could also affect viral inhibition. Similarly, Korean fermented cabbage was screened with the *L. plantarum* DK119 to increase the cytokines IL-12 and IFN-c levels while decreasing the inflammation in the bronchoalveolar lavage fluids infected by the influenza virus [133]. *L. bulgaricus* OLL1073R-1 fermented yogurt was used by the old age (67-74 years) of people which can reduce the common cold by controlling the natural cell killers and protecting the immune system [137].

Additionally, it was stated that the use of fermented food inhibited the rotaviruses [129], noroviruses [130], and enteroviruses [138]. However, the viruses before their attachment and fusion to the host cells can destroy within secretion of protease enzymes and bile detergents and also at low pH levels [139]. Some of the alimentary tract infection viruses are also resistant to the above conditions. Similarly, the viruses at an early stage of infection are disturbed through fermented food rich in probiotic bioactive compounds [140]. Probiotic strains *L. ruminis* and *B. longum* SPM1205, and SPM1206 were observed in the fermented food to control the rotavirus infection by inhibiting the Caco-2 cells [141]. The replication of the murine norovirus-1 (MNV-1) was inhibited by cultured *Bifidobacterium adolecentis* with the RAW 264.7 cells [142].

4.2. Herpes simplex virus

HSV-2 and HSV-1 were most frequently developed in the body which causes herpes infection [143]. A group of probiotic strains including *L. lactis* subspecies lactis, *L. rhamnosus, L. brevis,* and *L. crispatus* respectively can inhibit HSV-1 and HSV-2 replication [144]. HSV-1 and HSV-2 activities were repressed by bacteriocins purified from the *L. lactis* because of their association with the cell-surface bacterial component and heat resistance [145]. In mammalian Vero and HeLa cell lines, the inhibitory activities of strain *L. crispatus* were investigated against HSV-2. The results showed that the viral entry was evaded due to the blockage of the HSv-2 in the cell surface during the colonization of *L. crispatus* [146] and (Table 3)

4.3. COVID-19

The COVID-19 outbreak has gained serious critical significance, not only in the form of casualties but also made financial crises worldwide back 2020-2021 and still [43,147]. It poses seasonal epidemics of mild illness or fatal disease related to pulmonary ailments and was eradicated with vaccination and viral treatment. Nonetheless, these treatments commonly have limited effectiveness in persons with immunity suppression. Therefore, the appropriate way is needed to investigate the natural compounds or agents that suppress SARS-CoV-2 activity and promotes the immune system

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because presently available antiviral agent is not efficacious and might have health side effect. fermented food and food additives rich in natural compounds may boost the immune function and control the COVID-19 infection. In such cases, for example, it was reported that fermented milk product used on a daily base is a capable choice to treat various viral infection [148]. The fermented foods are rich in the probiotic's community-related Lactobacilli genus which was found very effective against viral infection (Table. 3). The modification of the gut microbiota promotes the immune function in the COVID-19-infected patients The probiotics control the pathogenic communities over the friendly bacteria despite their age [149] because in the Covid-19 infected individual, the pathogenic microbes stress the immune function [150]. Hence, stress on the immune system could be minimized by the utilization of fermented food and probiotics which increase its anti-viral infection.

Kefir has attention at a commercial level which has healthy probiotics and natural compounds that could restore gut microbiota and promote the immune system [151]. For example, it boosting the production of the CD4+, CD8+, IgG+, IgA+, B, and T-cells, along with cytokines IL-2, IL-12, -γ. These cells have been found to work as cytokine storms in the COVID-19 treatment and other viral infections [152]. However, it was suggested that the use of probiotic fermented food to increase the bioavailability might be very effective and helpful for the cure of COVID-19 on a clinical scale.

5. Fermented food safety, conclusion, and future prospective

The demographic and economic developments of the people's migration to urban areas make several changes including the food organization. Therefore, it is significant to be concerned about the food security of the people not only from an unknown opinion of this alteration but surveys also of some outbreaks that happened recently [162]. In the food security drivers, there are various reasons such as optimization parameters, economic pressure, and specific training of the fermentation [163]. Amongst the many food products, fermented food is superior produced on a small scale, and is considered tasty and old worldwide [164], but also sometimes as risky. There are 3500 various types of fermented found worldwide among which up to 7.2 % of beverage contribution in the period of 2018-2020 [165]. To increase the interest of the consumers, entrepreneurs, and market demand innovative approaches and product formulation of fermented food need to improve. For example, fermented foods and beverages health a beneficial impact on public information and also need to improve nutritional values which can reduce cholesterol level, protect against carcinogenic effects and micro-flora of the gastrointestinal tract, and promotes immune function [166]. This might increase public demand and willingness to pay more attention to fermented food. The grains, legumes, fruits, and vegetables with rich sauces of nutrients are most commonly used in fermented food and beverages. Fermented food product integration is important in national and global markets to sustain food care and, production [167]. The implementation of an influential systematic protective technique for risk administration will keep defending public health, support free trade, and advance food safety, and quality. The numerous probiotic strains are responsible to make sure the improvement of a bioactive compound and restoring the beneficial microbiota of the fermented food.

Moreover, an understanding of the active associations for metabolite mediates and amicrobial diversity while a fermentative process supports predicting the consistent microbiome model appropriate in food quality and safety assessments. Future studies are suggesting to investigate and screen the fermented from various regions of the world for probiotics and bioactive compounds that improve and develop immune system function. Furthermore, fermented foods comprising probiotics and bioactive compounds need to be employed for viral infection in clinical trials. Another, based on the dose and duration are also important factors that should be identified for the consumption of fermented food. Nevertheless, the effects of bioactive compounds and probiotics in fermented food increase the antiviral activities on the host immune cells directly or indirectly. The additional challenge is the deficiency of an appropriate database to profile microbiota and bioactive compounds in the different fermented foods.

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