Received: 13 September 2021 | Revised: 5 January 2022 | Accepted: 5 January 2022

DOI: 10.1111/jam.15444

REVIEW ARTICLE

Journal of Applied Microbiology sfam

Preventive and therapeutic aspects of fermented foods

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Abstract

In recent times, the status of some fermented foods which are considered as functional foods that confer health benefits in certain disease conditions has grown rapidly. The health benefits of fermented foods are due to the presence of probiotic microbes and the bioactive compounds formed during fermentation. Microbes involved and metabolites produced by them are highly species specific and contribute to the authenticity of the fermented foods. Several studies pertaining to the effect of fermented foods on various disease conditions have been conducted in recent years using both animal models and clinical trials on humans. This review focuses on the impact of fermented foods on conditions such as diabetes, cardiovascular disease, obesity, gastrointestinal disorder, cancer and neurodegenerative disorders.

KEYWORDS

bioactive peptides, fermentation, fermented foods, prebiotics, probiotics

INTRODUCTION

Fermented foods have been a part of the human diet from ancient times and have been consumed in several forms across the world. Fermented foods are produced by controlled microbial fermentation in a food matrix resulting in the biotransformation of the original components. Various metabolites are produced from microbial fermentation in the food matrix such as lactic acid (lactic acid bacteria [LAB]), alcohol (yeast), acetic acid (*Acetobacter*), propionic acid (Propionibacteria), bacteriocin, bioactive peptides and exopolysaccharides. Recently, the genera *Lactobacillus*, an important group of bacteria seen in various fermented, was renamed into 23 different genera; however, they will be collectively referred to as *Lactobacillus* (Zheng et al., 2020). Fermented foods can be classified on the basis of their starting substrates, such as cereal-based fermented foods, vegetable and fruit-based fermented foods, dairy-based fermented foods, fish and meat-based fermented foods and fermented alcoholic or non-alcoholic beverages. Many of the fermented foods can contain health-promoting probiotic bacteria among other bacterial species, which, when consumed, can help to benefit human health. Probiotic bacteria are live micro-organisms that, when consumed in sufficient numbers, confer a health benefit on the host (FAO/WHO, 2001). Fermented foods can also contain prebiotics that is a non-digestible compound in food that can stimulate the growth of beneficial micro-organisms in the lower gastrointestinal (GI) tract, thereby conferring health benefits on the host (Gibson & Roberfroid, 1995).

In recent times, various clinical studies on humans involving fermented foods consumption have been carried out, and results have suggested a positive correlation to improving health in humans. Trials on the effect of long-term yoghurt consumption have shown a reduced risk of cardiovascular diseases (CVDs), type 2 diabetes (T2D) and overall mortality (Marco et al., 2017). Traditional Korean vegetable-based fermented food 'Kimchi' has been associated with anti-obesity and anti-diabetic activity (An et al., 2013). The purpose of this review is to highlight the therapeutic role of fermented foods on several types of diseases and health conditions in humans. It also describes the current research on the therapeutic effect of fermented foods.

FERMENTED FOODS AND HEALTH BENEFITS

Fermented foods can be considered as fermented functional foods that are beyond their nutritional functions by the delivery of health-promoting microbes and metabolites (Baruah et al., 2019).

Fermented foods are an excellent delivery system for probiotic cultures. Some of these cultures have been reported to benefit conditions such as lactose intolerance, inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis), irritable bowel syndrome, gastroenteritis, diarrhoea, depressed immune function, cancer and genitourinary tract infections (Table 1) (Stanton et al., 2005). The beneficial effects from these probiotic bacteria are observed in the presence of a high number of viable bacteria with a minimum of 10^7 colony forming unit (CFU)/mL at the end of the shelf life of the food (Ishibashi & Shimamura, 1993). Probiotic bacteria in fermented foods are protected against the GI tract barriers such as high acidity, bile salts and enzymes by the food matrix. This is especially seen in probiotic cheddar cheese, where probiotic bacteria were protected better from gastric acid as compared to yoghurt (Da Cruz et al., 2009).

Fermented foods have been associated with alleviating several health benefits in humans; these properties have been attributed to the bioactive compounds that are formed as a result of microbial fermentation (Table 2). Bioactive peptides produced from Faba bean fermentation using *Lactiplantibacillus plantarum* subsp. *plantarum* 299v (formerly *Lb. plantarum*) possessed antihypertensive (angiotensin-converting enzyme [ACE]-inhibitory) and anti-oxidative properties. Sample after 3 days of fermentation showed maximum activity against metabolic syndromes (Jakubczyk et al., 2019). Antimicrobial peptides like bacteriocins have been seen to be produced by microbes in fermented foods and have been associated with biosafety. These peptides inhibit the growth of pathogenic micro-organisms in fermented foods like sausages increasing its stability and shelf life (Şanlier et al., 2019). The therapeutic effect of microbial enzymes such as bile-salt hydrolase has been reported to influence systemic lipid and cholesterol metabolism, energy metabolism, immune homeostasis and intestinal electrolyte balance (Joyce & Gahan, 2016). Microbes in fermented foods also produce exopolysaccharides that contribute to the texture and flavour of the food product, but they are also reported to act as prebiotics and have hypocholesterolaemic, antioxidants and anti-microbial activities (Lynch et al., 2018). Short-chain fatty acids (SCFA) are produced by gut microbiota and probiotic microbes through the fermentation of dietary fibres; these can be acetate, lactate, propionate and butyrate. These SCFA extend their health benefits to protect against diseases like colon cancer and IBD by suppressing the growth of pathogenic bacteria, modulating cholesterol and lipid metabolism and providing energy for the colonic epithelium (Figure 1) (Prasad & Bondy, 2019). Next-generation sequencing technologies have been employed to elucidate the complex microbial diversity present in many fermented foods such as kefir, buttermilk, *koumiss, dahi*, *kurut* (de Melo Pereira et al., 2020). Metaproteomics studies in fermented fish revealed the role of microbial groups such as *Streptococcus* sp., *Bacillus* sp., *Escherichia* sp. and *Pseudoalteromonas* sp to be responsible for aroma formation due to the presence of 63 amino acid degradation proteins (Balkir et al., 2021).

FERMENTED FOODS AGAINST DIABETES

Diabetes or diabetes mellitus results in chronic high blood sugar levels in the body. It is characterized into two types, type 1 diabetes, where the pancreas fails to produce hormone insulin due to lack of beta cells caused by an autoimmune disorder. Insulin resistance is said to be the cause of T2D, where the cells fail to respond to insulin properly. More than 90% of diabetes cases are type 2 and are considered one of the most prevalent illnesses. There is another form of diabetes called gestational diabetes mellitus (GDM), which is characterized by the onset of glucose intolerance after or during pregnancy (Cabello-Olmo et al., 2019; Malchoff, 1991). Several fermented food products in recent times have been studied for anti-diabetic effects.

Traditional Chinese fermented food Red mould rice inoculated with mould *Monascus* into steamed rice has been shown to have anti-diabetic effects. During fermentation, *Monascus* sp. produces several secondary metabolites such as monacolin K, monascin (MS), ankaflavin (AK) and γ-aminobutyric acid (GABA) that confer several health benefits in humans. Upon administration of Red mould rice on diabetic rats for 8 weeks, there was increased insulin secretion and showed improved lipid profiles (Shi & Pan, 2012). Fermented soybean products popular in Asian countries have been associated with anti-diabetic effects due to the presence of compounds in fermented soybean products such as phytoestrogen, bioactive soy peptides and isoflavonoids. Plant-based fermented foods consisting of soya flour, alfalfa meal and barley sprouts and inoculated with LAB suggest the significant influence of gut microbiota on T2D with decreased glucose levels and more active beta cells in rat models (Cabello-Olmo et al., 2019). Fruit juice of *Punica granatum* fermented with *Lacticaseibacillus casei*

TABLE 1 Different fermented foods and their therapeutic effects

Fermented foods	Raw material	Micro-organisms involved	Therapeutic effects	References
Red Mould Rice (RMR)	Rice	*Monascus* spp.	Anti-diabetic, reduction in Alzheimer's disease	Shi and Pan (2012); Akbari et al. (2016)
Fermented fruit juice of *Punica granatum*	*Punica granatum*	*Lacticaseibacillus casei* NRRL-B-1922	Anti-diabetic	Mustafa et al. (2020)
Yoghurt	Milk	*Str. thermophiles, Lb. bulgaricus*	Anti-diabetic, reduces IBD	Fernandez and Marette (2018)
Fermented fruit juice of bitter melon	Bitter melon (*Momordica charantia*)	*Lactiplantibacillus plantarum subsp. plantarum*	Anti-diabetic	Gao et al. (2019)
Nato	Soybeans	*Bacillus subtilis var. natto*	Anti-hypertensive and protect against CVD and prevents IBD	Lee, Lai, et al. (2015); Fujisawa et al. (2006)
Kombucha tea	Tea	Various LAB	Inhibits CVD and reduces inflammation	Dufresne and Farnworth (2000)
Kefir	Milk	Consortia of LAB and yeasts	Anti-hypertensive and protects against CVD, reduces obesity, prevents gastric cancer, prevents Crohn's disease	Friques et al. (2015); Kim et al. (2017); Yilmaz et al. (2019)
Sourdough	Wholemeal wheat	*Levilactobacillus brevis* CECT 8183	Anti-hypertensive, Reduces IBD	Peñas et al. (2015)
Cheese	Milk	*Lactiplantibacillus plantarum subsp. plantarum* TENSIA	Anti-hypertensive and reduces obesity	Sharafedtinov et al. (2013)
Fortified yoghurt	Milk	*Str. thermophiles, Lb. bulgaricus*, and *Bif. lactis* Bb-12	Reduces obesity	Mohammadi-Sartang et al. (2018)
Kimchi	Assorted Vegetables	Various LAB	Reduces obesity, reduces IBD	Chilton et al. (2015)
Fortified rice beverage	Rice	*Bifidobacterium* sp MKK4	Reduces obesity	Ray et al. (2018)
Sauerkraut	Cabbage	Various LAB	Reduces IBD	Nielsen et al. (2018)
Fermented aged black garlic	Black garlic	*S cerevisiae* (KCTC 7910)	Reduces obesity	Lee, Lee, et al. (2017)
Miso	Soybean paste	*Aspergillus oryzae*	Reduces gastrointestinal disorder	Mano et al. (2018)
Haria	Rice	*Bifidobacterium* sp MKK4	Reduces gastrointestinal disorder	Ray et al. (2016)

Abbreviations: CVD, cardiovascular disease; IBD, inflammatory bowel disease; LAB, lactic acid bacteria.

TABLE 2 Bioactive metabolites found in fermented foods and their activity

Bioactive metabolite	Micro-organism	Associated fermented food	Therapeutic effects	References
Monacolin K	*Monascus* spp.	Red mould rice	Anti-diabetic	Shi and Pan (2012)
Phytoestrogen	--	Fermented soybean products	Anti-diabetic	Kwon et al. (2010)
Angiotensin-converting enzyme (ACE) inhibiting peptides	*Lb. helveticus* R0389 and *Lacticaseibacillus rhamnosus* R0011	Fermented milk	Anti-hypertensive	Adams et al. (2020)
Lactic acid	*Lactobacillus* spp, *Lb. acidophilus* and *Lacticaseibacillus rhamnosus*	Fermented milk	Inhibits gastric cancer	Nair et al. (2016)
Short-chain fatty acids (SCFA)	Various LAB and Bifidobacterium	Various fermented foods products	Inhibits colorectal cancer	Elfahri et al. (2016)
Casein-derived peptides: β-Casomorphins, κ-casecidin and casein phosphopeptides	Various LAB	Fermented milk	Inhibits cancer	Sah et al. (2015)
Kefiran (EPS)	*Lb. kefiranofaciens*	Kefir	Inhibits cancer	Utz et al. (2017)
Prebiotic oligosaccharides and exopolysaccharides	*W. cibaria*	Sourdough	Inhibits gastrointestinal disorders by gut microbiota modulation	Baruah et al. (2017)
γ-aminobutyric acid (GABA)	*Monascus* spp	Red mould rice	Inhibits neurodegenerative diseases	Lee and Pan (2011)

Abbreviation: LAB, lactic acid bacteria.

NRRL-B-1922 (formerly *Lactobacillus casei*) showed anti-diabetic properties. Quercetin-3-glucoside was produced after fermentation with a dipeptidyl peptidase-4 (DPP-4) inhibition rate of 80% showing the high anti-diabetic potential of the fermented product (Mustafa et al., 2020).

Fermented milk product like yoghurt has been studied for various health benefits, among which there is T2D. Meta-analysis of nine cohort studies suggested upon consumption of 244 g of yoghurt per day, there was 18% lower risk of T2D (Fernandez & Marette, 2018). Five meta-analyses on the association between fermented dairy food products with the risk of T2D conducted between 2013 and 2018 suggest the positive impact of fermented dairy like yoghurt on the risk of T2D (Gille et al., 2018).

Novel fermented foods like Bitter melon (*Momordica charantia*) juice fermented with *Lactiplantibacillus plantarum* subsp. *plantarum* showed anti-diabetic potential in a high-fat-diet and low-dose streptozocin-induced type 2 diabetic rat model. Fermented bitter melon juice helped in conditions such as hyperinsulinaemia, hyperglycaemia, hyperlipidaemia and oxidative stress along with increased concentration of SCFA in rat model (Gao et al., 2019).

FERMENTED FOODS AGAINST CVD

Among several life-threatening disorders, CVD is one of the foremost causes of mortality worldwide, affecting approximately 23.6 million people globally by 2030 (iBenjamin et al., 2017; WHO, 2009, 2011). CVD has been associated with several disorders such as coronary heart illness, hypertension, the chance of heart failure, stroke and ischemic heart disease (Anandharaj et al., 2014; Drozdz & Kawecka-Jaszcz, 2014).

Gut dysbiosis additionally can induce CVD progression (Jin et al., 2019). Thushara et al. (2016) showed modified gut microbes composition could treat the CVD type metabolic syndrome. Probiotic dietary supplementation comes under a healthy diet, proved to lower the risk of CVD progression (Schwingshackl et al., 2017).

Administration of dairy-fermented foods such as cheese, sour milk and yoghurt with a healthy diet was inversely linked with the CVD progression due to the

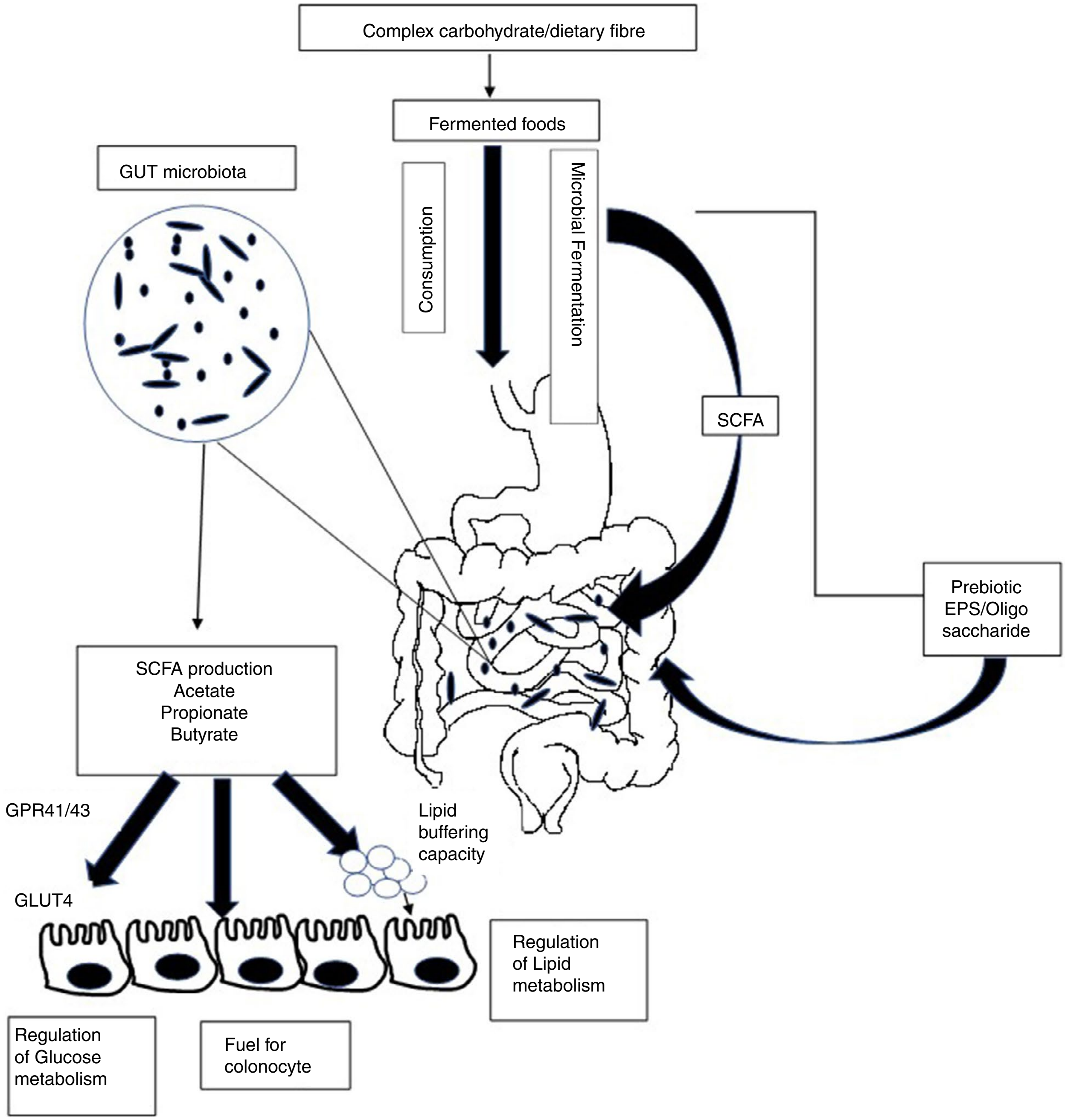

FIGURE 1 Health benefits of microbial metabolites produced in fermented foods

available beneficial compounds in fermented milk products known to improve and control glycaemic index, blood lipids, cholesterol concentrations and blood pressure in studied individuals (Buziau et al., 2019). A modern meta-analysis suggests that fermented dairy food consumption was linked with reduced CVD risk (Zhang et al., 2020). Natto, a *Bacillus subtilis* fermented soybean product of Japan, can significantly prevent CVD progression and hypertension. Nattokinase, the potent serine fibrinolytic enzyme present in *Natto*, exerts several health benefits, increases blood circulation via dissolving fibrin and their monomers, ultimately prevent CVDs by decreasing the blood clotting (Lee, Lai, et al., 2015). Kefir, a fermented milk product responsible for reducing various cardiometabolic complications such as hypertension, vascular endothelial dysfunction, dyslipidaemia, insulin resistance in individuals and reduced cardiac hypertrophy in spontaneously hypertensive rats (Friques et al., 2015; Pimenta et al., 2018). Kefir suggested providing the health-promoting effects by the recruitment of endothelial progenitor cells, development stability of vagal/sympathetic nervous system, and reduction of excessive generation of reactive oxygen species, angiotensin-converting enzyme inhibition, anti-inflammatory cytokines profile and modification of the intestinal microbiome composition (Pimenta et al., 2018). Administration of probiotics-fermented purple sweet potato yoghurt with diet enhanced cardiac survival rate and was activating anti-apoptotic trails in hypertensive hearts that could hinder hypertension-associated cardiac apoptosis and hypertension (Lin et al., 2013).

Fermented milk with *Lactobacillus delbrueckii* subsp. *lactis* (formerly *Lactobacillus lactis*) was suggested to reduce the systolic and diastolic blood pressure caused by hypertension; thus, the fermented milk exhibits anti-hypertensive effects (Rodrıguez-Figueroa et al., 2013). Peñas et al. (2015) studied the beneficial effect of whole-meal wheat sourdough (*Levilactobacillus brevis* CECT 8183 and protease enzyme) in lowering the blood pressure level. The fermentation enhanced the total antioxidant activity of whole bread, increased GABA content, small peptides (<3 kDa) and angiotensin I-converting enzyme inhibitory activity. The reduced sodium content after fermentation might be responsible for lowering the blood pressure. Studies have reported that pre-treatment with fermented garlic extract rich in nitrite and reduced glutathione exhibits cardioprotective impacts against ischemia–reperfusion injury in H9c2 cells and myocardium (Lee, Lee, et al., 2017).

Bioactive peptides formed as a result of proteolytic cleavage during dairy fermentation can have anti-hypertensive effect, as seen in casein-derived peptides having ACE inhibiting activity. In a study, peptides produced from *Lb. helveticus* R0389 and *Lacticaseibacillus rhamnosus* R0011 in both media and milk had shown 79% inhibition of ACE activity which result in high anti-hypertensive effect (Adams et al., 2020).

FERMENTED FOODS AGAINST OBESITY

Accumulation of immoderate or abnormal fat in the body creates overweight and obesity like metabolic syndrome that may impair the health status (Obesity and overweight, WHO, 2019). Obesity is altered metabolic health trouble ensured from high consumption rate, fallacious energy utilization, and alteration of the gut microbiome, improper food habit, inappropriate lifestyle, less physical exercise, and different environmental factors (Hou et al., 2017). Fermented foods may be an alternative to nutritional, medicinal supplements due to its various bioactive components, which exert beneficial health effects. Fermented foods containing probiotic help to lower blood cholesterol to reduce body weight, to induce cellular immunity, to shield against pathogens, anti-carcinogenic, helps against osteoporosis, diabetes, downregulate obesity, allergies, atherosclerosis, and solve the problem of lactose intolerance (Tamang & Kailasapathy, 2010).

In a study, administration of cheese containing probiotic bacteria *Lactiplantibacillus plantarum* subsp. *plantarum* TENSIA with a calorie restriction diet for 3 weeks could significantly downregulate the body mass index (BMI) and hypertension in obese sufferers than to the control group (patients fed a calorie-restricted diet supplemented with control cheese) due to anti-microbial activity of *Lactiplantibacillus plantarum* subsp. *plantarum* TENSIA, its ability to produce polyamines and nitric oxide, and provides anti-oxidative activity (Sharafedtinov et al., 2013). A 12-week intervention of fermented milk comprising *Lb. gasseri* SBT2055 notably decreased the visceral adiposity with extensively lowering body weight, BMI, and waist and hip circumferences of the healthy individuals than the control group (Kadooka et al., 2013). Long-term administration (12 weeks) of probiotic (*B. lactis* BB12 and *Lb. acidophilus* LA5) yoghurt in obese and overweight women can substantially lower the total cholesterol, low-density lipoprotein (LDL) and improve the lipid profile (Madjd et al., 2016). Another experimental study concluded that consuming a calorie-restricted diet with fortified yoghurt containing *Str. thermophiles, Lb. bulgaricus* and *Bifidobacterium lactis* BB-12 to obese persons appreciably reduced body weight and improved lipid metabolism (Mohammadi-Sartang et al., 2018). *Lactiplantibacillus plantarum* subsp. *plantarum* DK211 fermented high protein whey beverage, considerably reduced-fat composition, serum lipid level and eventually control of the body weight gain in high-fat diet (HFD)-induced obese rats (Hong et al., 2015). Fermented green tea consumption could attenuate obesity development via inducing energy spending, altering the expressions of lipid metabolism genes (Seo et al., 2017). Pre-treatment with *kombucha* tea could alter the levels of free cholesterol, triglycerides, free fatty acids and glycoprotein constituents in plasma and heart to near normal, indicating its lipid-lowering and glycoprotein-modulating effects (Lobo et al., 2017). Administration of *Kochujang*, a Korean soybean fermented red pepper paste, upregulates plasma triglyceride (TG) concentration in obese adults diminishing TG/high-density lipoprotein ratios for daily consumption in obese adults. Fermented *Kochujang* reported to upregulate the obesity-linked peroxisome proliferator activator receptor γ (PPARγ2) gene responsible for lipid metabolism (Marchesin et al., 2018; Lee, Cha, et al., 2017). The administration of soy-based probiotic (*B. longum* ATCC 15707 and *Enterococcus faecium* CRL 183) product positively influences the gut microbiota and immune system by increasing the IL6 and IL10 in the obese mice model (Marchesin et al., 2018). Kefir is another probiotic beverage, additionally responsible for reducing LDL cholesterol and preventing obesity via upregulating fatty acid oxidation gene PPARα in both the liver and adipose tissue. Kefir administration also decreases the concentration of pro-inflammatory markers in plasma (Kim et al., 2017). 'Kefir-fermented soymilk' supported favourable impacts on glucose and lipid metabolism were studied by the reduction of glucose, TG, and LDL-cholesterol and induction in high-density lipoprotein cholesterol in blood in the HFD-induced obesity and hyperglycaemia in rats (Tiss et al., 2020). It has been recommended that the level of conjugated linoleic acid (CLA) is increased during the milk fermentation with kefir, which provides a variety of beneficial health effects, along with anti-obesity and anti-inflammatory activities, and accelerate lean muscle mass deposition (Yang et al., 2015). Another study concluded that the produced phenolic compounds during fermentation from the fermented blueberry–blackberry beverage reduced the total weight gain, accumulation of fat mass and plasma triglycerides in diet-induced obese mice (Johnson et al., 2016). Fermented red ginseng could inhibit body weight gain, decrease the amount of body fat, advance blood lipid profile, improve the antioxidant status and suppress lipid peroxidation in rats fed with HFD, and that fermented red ginseng may, therefore, act as a potent hypolipidaemic and antioxidant functional food (Kim et al., 2016). *Bifidobacterium* sp MKK4-fortified rice beverage was able to suppress adipogenesis and lipogenesis, promote lipid catabolism, improved glucose–insulin homeostasis and prevent obesity (Ray et al., 2018). The anti-obesity effects of fermented rice beverages containing *Bifidobacterium* sp MKK4 were more profound, as the fermentation carries several nutraceuticals, such as phenolics, prebiotics, dietary fibres, vitamins, minerals, peptides, antioxidants nutraceuticals (Ray et al., 2017).

FERMENTED FOODS AGAINST CANCER

Cancer is a pathological condition where some cells of the body display abnormal or uncontrollable growth, which may result in tumours and can spread throughout the whole body. In recent times, cancer is a major cause of death worldwide. In spite of the existence of cancer chemotherapies, many cancer patients choose to consume food products that possess health benefits against cancer. These foods can include traditional or novel fermented foods containing probiotic micro-organisms.

The health effect of fermented foods on gastric cancer has been an important topic of research in recent times. Some forms of gastric cancers are caused by micro-organism *Helicobacter pylori* which cause infection in the stomach. Probiotic bacteria show inhibitory activity against *H. pylori*, where the members of the former genus *Lactobacillus* have shown great potential in stopping *H. pylori* infections. *Lactobacillus acidophilus* culture supernatants have been shown to inhibit the growth of *H. pylori* on blood agar plates. *Lb. acidophilus* and *Lacticaseibacillus rhamnosus* (formerly *Lb. casei* subsp. *rhamnosus*) can inhibit *H. pylori* growth due to the production of lactic acid (Nair et al., 2016). Consumption of fermented foods containing specific probiotic bacteria can inhibit *H. pylori* infections. Yoghurt (112 g) containing *Lb. gasseri* were effective in treating patients with antibiotic-resistant *H. pylori* infections in 4 weeks (Deguchi et al., 2012).

Fermented milk products have been reported to have anti-carcinogenic activities towards colorectal cancers. The SCFA formed by fermentation have associated with these anti-cancer effects, SCFA plays a role in modulating the apoptosis of epithelial cells (Cousin et al., 2012). Several strains of *Lactobacillus helveticus* produced bioactive peptides by proteolytic cleavage milk proteins during fermentation. These peptides have antioxidant activity and inhibited the growth of colon cancer HT-29 cell line by 50.98%, and had no significant effect on normal primary colon cells T4056 (Elfahri et al., 2016). Antitumor peptides can be produced by proteolytic cleavage of milk protein casein; some of these peptides formed during milk fermentation are as follows. β-Casomorphins derived from β-casein is highly resistant to proteolytic cleavage, κ-casecidin derived from κ-casein and casein phosphopeptides which are phosphorylated peptides of casein peptides are the types of bioactive peptides derived from casein having anti-cancer properties (Sah et al., 2015). Antitumor peptides derived from whey proteins, α-lactalbumin, β-lactoglobulin and lactoferrin, have shown anti-carcinogenic activities in cancer cell lines (Sah et al., 2015). Kefir can have positive effects with respect to cancer prevention and contains probiotic micro-organism as well as bioactive compounds such as peptides, organic acids and exopolysaccharide (EPS) kefiran, play an essential role (Utz et al., 2017). Skim milk fermented with *Lacticaseibacillus paracasei* subsp. *paracasei* NTU 101, when administered in combination with chemotherapy, resulted in suppressed tumour growth and metastasis. These changes were achieved through regulating matrix metalloprotein-9, vascular endothelial growth factor and tissue inhibitor of matrix metalloproteinase-1 levels (Chang et al., 2019).

Fermented food products have been shown to have health benefits against breast cancer, which is prevalent worldwide. Probiotic LAB has played a part in inducing immune modulation in a location distant to the GI tract, possibly by means of CD4 + CD25+ lymphocytes stimulation (Lakritz et al., 2014). In another study, *Lacticaseibacillus* *casei* CRL 431 administered to metastatic stage breast cancer murine model through fermented milk resulted in diminished metastasis in the lungs. These effects were attributed to decreased pro-inflammatory cytokines like IL-10 and decreased F4/80+ cells locally in the lungs (metastatic organs) (Utz et al., 2019).

FERMENTED FOODS AGAINST GI DISORDER

The health-promoting effects of fermented foods were first supported as far back as 76 A.D by the Roman historian Pliny, who introduced the use of fermented milk for healing GI diseases (Ray et al., 2016). The different unfavourable conditions create disease within the GI tract. Fermented foods containing gut commensals are additionally able to modify intestinal permeability, gut barrier function in a positive way to treat several diseases such as metabolic syndrome, atherosclerosis, IBDs and colon cancer (Hiippala et al., 2018).

Kefir, a fermented milk product rich in bioactive metabolites containing probiotic, on consumption proved to modify the intestinal microbiome composition by increasing the concentration of *Bifidobacterium*, *Lactococcus*, and the former genus *Lactobacillus* population, and decrease in numbers of Proteobacteria and Enterobacteriaceae, increase the number of Firmicutes, Bacteroidetes and Prevotella in several studies on animal models (Jeong et al., 2017; Kim et al., 2019). Studies in humans with IBD reported *Lentilactobacillus kefiri* (formerly *Lactobacillus kefiri*) in their faeces after consuming kefir for 4 weeks and also suggestively increased the total count of faecal *Lactobacillus* compared to control patients with Crohn's disease (Yilmaz et al., 2019). Fermented milk like yoghurt containing *Bifidobacterium animalis* enriched with bioactive metabolites like SCFA may lower the risk of irritable bowel syndrome and reduce pathobiont richness (Veiga et al., 2014). *Bifidobacterium lactis* DN-173010 fermented milk consumption improved digestive discomforts by alteration of microbial flora in the gut than the control group in irritable bowel syndrome (IBS) patients with constipation (Harris & Baffy, 2017). Prebiotics are non-digestible carbohydrates like isomalto-oligosaccharides and exopolysaccharides formed during sourdough fermentation by *Bifidobacterium* spp, and *Lactobacillus* spp can positively influence gut microbiota populations via the production of SCFA in hosts with GI disorders (Baruah et al., 2017). Synbiotic (prebiotics and probiotics) administration by altering the gut microbiome can lower the risk of IBD, described by Crohn's disease and ulcerative colitis (Scaldaferri et al., 2013). Plé et al. (2016) concluded that cheese containing starter probiotics (*Lb. delbrueckii* subsp. *lactis* CNRZ327 and *Pro. freudenreichii* ITG) could treat against anti-inflammation, colitis and epithelial cell damage by lowering the inflammation marker and oxidative stress. Fermented milk containing *Lacticaseibacillus casei* (formerly *Lactobacillus casei*) has been reported to reduce colitis and inflammation in mice. Mutation in *Lacticaseibacillus casei* devoid of lipoteichoic acid D-alanine transfer protein or recombinase A cannot defend against the dextran sulphate sodium-induced murine model of ulcerative colitis (Lee, Yin, et al., 2015).

Lactic acid bacteria-fermented sauerkraut has positive effects on GI disease and gut microbiome alteration, especially emphasis on IBS patients (Nielsen et al., 2018). *Lacticaseibacillus paracasei* LS2 (formerly *Lactobacillus paracasei*), isolated from kimchi, Korean-fermented vegetables, suggested downregulating the cytokine induction, myeloperoxidase function, and the macrophage count and neutrophils in the lamina propria lymphocytes resulting in a potential anti-inflammatory effect (Park et al., 2017). Kimchi suggested to have anti-inflammatory, anti-mutagenesis effects; it also helps to maintain GI health and diseases such as gastric cancer, functional bowel disease, as well as helps in infection caused by *H. pylori*. Studies have approved that kimchi has beneficial effects to prevent diarrhoea and constipation (Chilton et al., 2015).

The red and white sorghum fermented products by malted sorghum flour with LAB enhanced GABA and other phenolic compounds. These enriched bioactive metabolites were more bioaccessible to the intestinal and colonic epithelium (Garzón et al., 2020). Miso, traditional Japanese soybean fermented paste, showed downregulation of GI disorder after consumption due to the presence of histidine, glutamate and aspartate observed in the miso soup (Mano et al., 2018). Sourdough is a fermented flour containing LAB and bioactive metabolites, including SCFA that have positive effects on gut microbiota and lowers the gas production in IBS patients (Costabile et al., 2014). The total gastric volume, flatulence, abdominal discomforts, bloating and nausea were significantly reduced with the consumption of sourdough (Polese et al., 2018).

Study reports suggested that fermented rice products restore healthy intestinal microbes and prevent different GI ailments such as duodenal ulcers, contagious ulcerative colitis, Crohn's disease, irritable bowel syndrome, celiac disease and candida infection (Ray & Swain, 2013). Haria, a rice-based fermented beverage, was known to protect against GI disorders such as dysentery, diarrhoea, amebiasis, acidity and vomiting (Ray et al., 2016).

FERMENTED FOODS AGAINST NEURODEGENERATIVE DISORDERS

Gut microbiota can influence other parts of the human body, such as the brain. There is communication between the gut and central nervous system (CNS) by the sympathetic and parasympathetic nervous system, which is termed as the gut–brain axis, and the CNS communicates with the gut by afferent and efferent autonomic pathways (ANS) with muscle and the mucosal layer of gut (Figure 2) (Sarkar & Banerjee, 2019). The gut microbiota can both positively and negatively modulate the pathogenesis of various neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD), etc., by the production of various neuroactive molecules and metabolites (Sarkar & Banerjee, 2019).

Gut dysbiosis has been associated with both PD and AD. The increase in Enterobacteriaceae population in the gut and the subsequent synthesis of lipopolysaccharides (LPS) are neurotoxic in nature. The LPS passes into the bloodstream through intestinal walls and affect different parts of the body, such as the brain (Guo et al., 2013). Patients with PD as a result of LPS dispersion in blood have been reported to have higher levels of LPS-binding proteins in their blood. Due to dysbiosis, the increase in circulation of harmful microbes and their metabolites such as LPS, β-*N*-methylamino-L-alanine and microbial amyloids could be responsible for the onset of neurodegeneration leading to AD in patients (Sarkar & Banerjee, 2019). Probiotic bacteria and their associated fermented foods products that help alleviate the symptoms of gut dysbiosis can be effective against combating these neurodegenerative diseases.

Patients with PD that regularly consume fermented milk containing probiotic *Lacticaseibacillus casei* Shirota have a reduced number of faecal Staphylococci, reduced abdominal pain and improved bowel movements (Cassani et al., 2011). Studies on the rat model for PD, which were fed the active metabolites of a traditional Chinese medicinal food that is, *Monascus purpureus*-fermented rice showed a reduction in neurodegeneration caused by antioxidative and anti-inflammatory mechanisms (Tseng et al., 2016).

A clinical trial on 60 AD patients was conducted where the test group ($n = 30$) was given probiotic milk containing *Bifidobacterium bifidum, Lacticaseibacillus casei, Lactobacillus acidophilus* and *Limosilactobacillus fermentum* (formerly *Lactobacillus fermentum*) 2×10^9 CFU/g for each for 12 weeks of 200 ml/day. The trial concluded that the consumption of probiotic milk could positively affect cognitive function and some metabolic statuses in AD patients (Akbari et al., 2016). Red mould rice viz. *Monascus*-fermented rice, as mentioned above, can help in the prevention of AD. By various in-vitro and in-vivo studies, a number of bioactive metabolites present in red mould rice have been reported to combat different metabolic statuses in the AD. These metabolites are Monacolins having the hypolipidemic ability, pigments such as ankaflavin and monascin, neurotransmitter GABA and antioxidant agents such as tannin, dimerumic acid, unsaturated fatty acids and phenol (Lee & Pan, 2011). Extracts of fermented tea (*Camellia sinensis* L.), namely catechin gallate, epicatechin gallate and epigallocatechin gallate, showed anti-amyloid-beta (Aβ) aggregation effects, thus showing protective effect against AD (Rho et al., 2019).

Clinical studies on 20 AD patients fed with fermented papaya (*Carica papaya* Linn) fermented by yeast as a nutritional supplement for 6 months. Studies suggest that fermented papaya has high antioxidant activity and help in reducing oxidative stress and preventing damage from Aβ, suggesting its preventive role in AD (Barbagallo et al., 2015). Peptides from fermented rice decreased memory impairment in the mice model. Mice were found to have upregulated levels of brain-derived neurotrophic factor and induced the phosphorylation of cAMP response element-binding protein and extracellular signal-regulated kinase in the hippocampus (Corpuz et al., 2019).

CONCLUSION AND FUTURE PERSPECTIVE

There is great importance in exploring less known traditional fermented foods for their effect on human health. With the advancement in food chemistry, new health-promoting components in fermented foods can be discovered and can be studied in depth using animal models followed by human trials. The microbiota associated with fermented foods is a great source of untapped knowledge in the field of food microbiology. Isolation, characterization and subsequent food applications of micro-organisms isolated from fermented foods have seen a rise in number in the last decade. Future research on fermented foods should explore its microbiota their metabolites using metagenomics, whole genome sequencing (WGS) and metabolomic technique focusing on probiotic markers and also conduct human trials of large numbers for establishing health benefits of some fermented foods.

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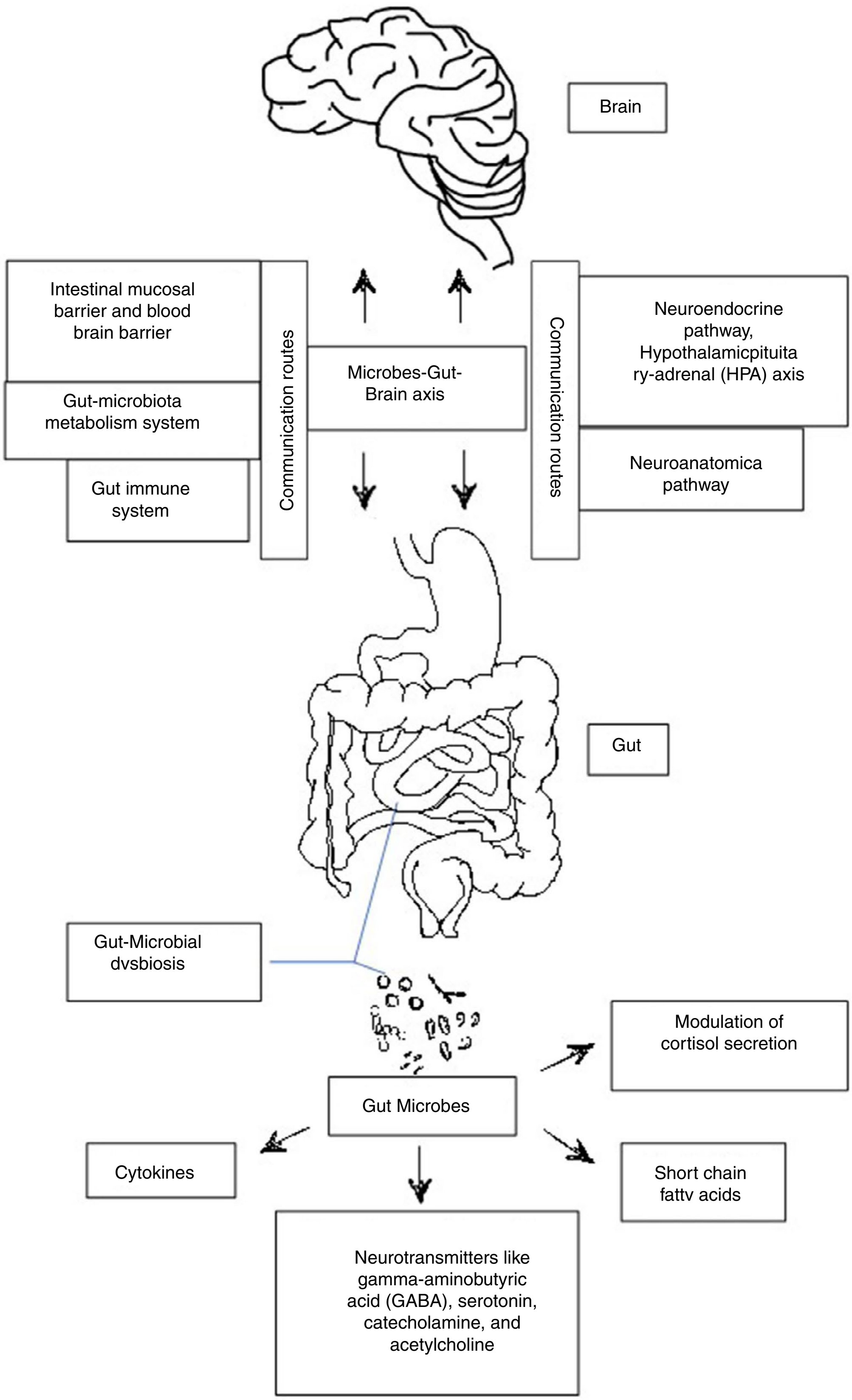

FIGURE 2 Gut–brain axis, their communication and mechanism of action (adapted from Misra & Mohanty, 2019)

CONFLICT OF INTEREST

There is no conflict of interest.

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How to cite this article: Baruah, R, Ray, M, Halami, PM (2022) Preventive and therapeutic aspects of fermented foods. *Journal of Applied Microbiology*. 132:3476–3489. https://doi.org/10.1111/jam.15444