

# A Review of Fermented Foods with Beneficial Effects on Brain and Cognitive Function

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**ABSTRACT:** Around the world, fermentation of foods has been adopted over many generations, primarily due to their commercial significance with enriched flavors and high-profile nutrients. The increasing application of fermented foods is further promoted by recent evidence on their health benefits, beyond the traditionally recognized effects on the digestive system. With recent advances in the understanding of gut-brain interactions, there have also been reports suggesting the fermented food's efficacy, particularly for cognitive function improvements. These results are strengthened by the proposed biological effects of fermented foods, including neuroprotection against neurotoxicity and reactive oxygen species. This paper reviews the beneficial health effects of fermented foods with particular emphasis on cognitive enhancement and neuroprotective effects. With an extensive review of fermented foods and their potential cognitive benefits, this paper may promote commercially feasible applications of fermented foods as natural remedies to cognitive problems.

**Keywords:** fermentation, functional food, cognition, neuroprotection, gut-brain axis

## INTRODUCTION

Fermentation is a metabolic process, which is induced by a microorganism and characterized by the anaerobic breakdown of carbohydrates to alcohol or organic acids (1). A wealth of literature has focused on the beneficial physiological effects of fermented foods on enteral nutrient absorption and on digestive tract health (2,3). More recently, there has been a considerable increase in research and publications on how the gut microbiota is tied to the host's immune system, energy metabolism, and even to brain function like stress response (4). Studies which have focused on bidirectional communication between the brain and gut have received attention. There are reports showing that dysbiosis of gut microbiota is associated with anxiety and depression, and administration of probiotics produces anxiolytic- and anti-depressant-like activities in animal studies (5-7). Moreover, probiotic-rich diets, either prepared naturally or with industrial fermentation processes, showed positive effects on stress relief and memory enhancement, potentially via gut microbiota improvement (8).

There is much scientific evidence documenting the pro-

biotics' potential health effect on gut microbiota ecosystems in relation to brain function. Because of their health promoting benefits, probiotics-included diet plans would be an effective strategy to boost one's health and to manage disease risk (9). Beyond their nutritional value, probiotics hold a great marketing potential because they tend to meet consumer's demand better than other medicinal products. In other words, probiotics are easy to obtain because most of them are already available with added value from health claims (10). When taken as a part of a balanced diet, they could be contributing factors to disease prevention in a convenient way.

Taken together, a growing body of evidence indicates the potential of fermented foods as functional foods for the brain and cognitive health promotion. However, most of the studies mainly focused on certain functional foods associated with emotion- and stress-related health promotion and overlooked their role in cognition modulation as well as product diversity. Thus, careful investigation of products with a focus on their effects on cognition and neuroprotection was highlighted in this review.

This paper comprehensively reviews the beneficial effects of fermented foods on brain and cognitive function.

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Literature searches were performed for articles published up to May 2016 on MEDLINE, EMBASE, and the Cochrane Library. The search terms included “fermented”, and “fermentation” in combination with the search terms “cognitive”, “cognition”, “learning”, “memory”, “neuroprotective”, “neuroprotection”, “dementia”, and “Alzheimer”.

The searches from the three electronic databases yielded 312 records after removing duplicate entries. The administration of any fermented product as the target intervention was regarded as eligibility criteria for inclusion. Studies including any standardized outcome measures of neuroprotection, learning, memory, or cognitive function were included. All types of studies were considered for inclusion in the review including clinical trials, animal experimental studies, and *in vitro* studies using neuronal/glia cell models. In the process, the manuscript included references with no language or site restriction.

Initial screening of titles and abstracts identified 78 potentially relevant references. Of the 78 records retrieved, five studies were excluded because their focus was not on fermented products. Twenty-five studies were excluded as their outcomes were not related to brain or cognitive function. We also excluded one article, which was not available online and other two review articles. As a result, a total of 45 articles were selected and summarized (Table 1).

## EVALUATION OF NEUROPROTECTION AND COGNITIVE FUNCTION

The pathogenesis of cognitive dysfunction is multifaceted and complicated. Cholinergic dysfunction in the brain, including hydrolysis of acetylcholine from increased acetylcholinesterase (AChE) activity, has been suggested to be attributable to this pathogenesis (11,12). Dysregulation of the cholinergic system also disrupts hippocampal neurogenesis by modulating the mechanism involving brain-derived neurotrophic factor (BDNF) and cyclic adenosine monophosphate response element-binding protein (CREB) (11,12). Oxidative stress induces neuronal cell death and may cause cognitive dysfunction. Brain structures supporting memory are highly sensitive to oxidative stress partly due to their high demand for oxygen (13). Another possible cause of cognitive dysfunction is the accumulation of amyloid  $\beta$  (A $\beta$ ) and phosphorylated tau protein in the brain (14). Increased A $\beta$  formation and tau hyperphosphorylation are known to cause memory impairments in neurodegenerative diseases such as Alzheimer’s disease (AD) (14). These findings highlight some typical biomarkers for evaluating neuroprotection and neurodegeneration models, and suggest that these could be used as indirect indicators of cognitive function (15,

16).

To mimic neurodegeneration, oxidative injury leading to neuronal death is provoked by neurotoxic chemicals such as glutamate or hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) in cellular models. In animal models, intracerebroventricular injection of A $\beta$  or intraperitoneal injection of scopolamine, a cholinergic antagonist, are widely applied to induce cognitive impairment (17,18). Various biomarkers are examined in these neurodegenerative models before and after treatment of neuroprotective agents. Cell viability, AChE level, neurotrophic factors, expression of antioxidant-related proteins such as superoxide dismutase (SOD), and inflammation indices are commonly measured both *in vitro* and *in vivo* to investigate neuroprotective effects (19).

Memory-related performance has been evaluated by established behavioral tests. Morris water maze (MWM) and passive avoidance test are broadly used, while there are numerous tests to assess cognition (20). In clinical studies, cognitive function is usually evaluated by cognitive assessment tools. Neuroprotection in humans can be evaluated by measuring oxidative stress or other biomarkers from peripheral blood and urinary samples (15). In some cases, antioxidant activities such as 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity and H<sub>2</sub>O<sub>2</sub> scavenging activity can be assessed to identify neuroprotective agents.

## THE EFFECTS OF FERMENTED FOODS ON COGNITIVE FUNCTION

### Fermented dairy products

Nearly every country has developed traditional fermented dairy products of some type within their farming system. Some of the oldest records suggest that dairy products date back to 9,000 B.C (21). Implied by a long and comprehensive history of dairy products use in many civilizations, consuming fermented dairy products might be considered as an attempted practice of healthy diet choice. Indeed, several epidemiological studies even report that consumption of fermented dairy products reduces a cognitive deficit in the elderly (22,23). Furthermore, there is scientific evidence to indicate that fermented dairy products may have neuroprotective effects (21).

Studies of cells and animals show that fermented dairy products tend to prevent neurotoxicity, indicating its neuroprotective effect. Compounds with camembert cheese extracts suppressed neuronal cell death that was induced by excessive microglia activation (24). In a transgenic mouse model of AD, the accumulation of A $\beta$  in the brain was reduced after feeding camembert cheese extract (25). In addition, production of chemokine and neurotrophic factor in the hippocampus were remarkably increased when the mice were fed with the camembert

Table 1. Studies of fermented foods on brain and cognitive function

Fermented product	Subject	Measurements	Effects	References
Fermented dairy products				
Camembert cheese extract	Primary microglia cells, NZA cells	Cytokine production, Neurotoxicity	Suppressed microglial TNF- $\alpha$ production; transformation of microglia to anti-inflammatory phenotype; reduced neurotoxicity	24
Camembert cheese extract	AD model transgenic mice, primary microglia cells	A $\beta$ deposition, cytokine production, neurotrophic factor	Reduction of A $\beta$ accumulation and hippocampal inflammation; enhanced hippocampal neurotrophic factors	25
Fermented soymilk	PC-12 cells, VaD model rats	Cell viability, MWM	Protective effect on H <sub>2</sub> O <sub>2</sub> <sup>-</sup> and OGD-induced damage in PC-12 cells; Improvement in learning and memory of VaD rats	26
Fermented milk	ddY mice	Y-maze, NOR	Improvement in scopolamine-induced memory impairment and novel object recognition in mice	27
Fermented milk	Healthy individuals	Physiological parameters in saliva, plasma, and fecal sample, physical symptoms	Reduced salivary cortisol and plasma L-tryptophan levels; attenuated physical symptoms	28
Legume- and cereal-based fermented foods				
Cheonggukjang extract	ICR mice	PA, NOR, AChE, MDA, SOD, NGF	Ameliorated memory defects and neuronal cell death in TMT-treated mice; suppression of AChE activity; activation of the NGF receptor signaling pathway; inhibition of oxidative stress	29
Cheonggukjang extract	SD rats	PA, MWM, A $\beta$ deposition	Decreased A $\beta$ accumulation, improved cognitive function and glucose regulation in AD diabetic rats	30
Fermented soybean powder	ICR mice	PA, Y-maze, MWM, AChE	Ameliorated the scopolamine-induced memory impairment and hippocampal BDNF reduction; suppression of AChE activity	31
Tempeh	Healthy elderly individuals	HVLT	Positive relation between high tempeh consumption and better memory	32
Red mold rice	IMR32 cells, PC-12 cells, Wistar rats	MWM, PA, cell viability, MDA, SOD, AChE, iNOS, ROS, A $\beta$ deposition	Protection against A $\beta$ -induced neurotoxicity <i>in vitro</i> and <i>in vivo</i> potentially ameliorated memory deficit and A $\beta$ accumulation in A $\beta$ -infused rats; suppressed $\beta$ -secretase activity	33-35
Red mold rice	Wistar rats	MWM, PA, antioxidant enzymes, ROS, corticosterone	Significant improvement in memory and antioxidant activity in Zn-deficient rats	36
Red mold rice	SH-SY5Y cells, SD rats	Cell viability, EBST, ROS, MDA, antioxidant enzymes, NO, TNF- $\alpha$	Neuroprotective effects in the $\delta$ -OHDA induced-PD model <i>in vitro</i> and <i>in vivo</i>	37
Rice vinegar	AD model mice	MWM, antioxidant activity, A $\beta$ deposition	Ameliorated cognitive dysfunction and A $\beta$ accumulation in the AD mice	41

Table 1. Continued

Fermented product	Subject	Measurements	Effects	References
Fermented plant root products				
Fermented <i>Codonopsis lanceolata</i>	HEK293 cells, ICR mice	Antioxidant activity, PA, cytotoxicity	Ameliorated the scopolamine-induced memory impairment: Showed antioxidant activity and lowered cytotoxicity	43
Fermented <i>Codonopsis lanceolata</i>	HT22 cells, ICR mice	Cell viability, MWM, PA, AChE, neurotrophic factor, ROS, antioxidant enzymes, NO	Ameliorated scopolamine-induced memory impairments: neuroprotective effects against glutamate-induced cytotoxicity <i>in vitro</i> suppression of AChE activity and increased BDNF expression in hippocampus; upregulation of antioxidant enzyme's activity	44-48
Fermented ginseng	AD model HeLa cells, ICR mice, AD model transgenic mice	PA, MWM, A $\beta$ deposition	Significantly reduced A $\beta$ level <i>in vitro</i> and <i>in vivo</i> ameliorated memory impairment	50
Fermented ginseng	N2A cells, ApoE knockout mice	Tau, MWM	Inhibited the APP and tau IRES activities; improvement on memory function	51
Fermented garlic	Wistar rats	MWM, pyramidal neuronal cell number	Increased total number of pyramidal neurons and the spatial memory function in MSG-exposed rats	52
Fermented yellow onion	HT22 cells	Antioxidant activity, cell viability	Enhances the antioxidative and neuroprotective effect against glutamate-induced neurotoxicity <i>in vitro</i>	53
Fermented fruits and vegetables				
Fermented papaya	PC-12 cells, AD model SH-SY5Y cells	Cell viability, antioxidant activity, ROS, iNOS, nNOS, SOD, apoptotic proteins	Reduced oxidative stress-induced cell damage and inflammation; significantly increased cell viability and SOD expression	54,55
Fermented papaya preparation	Mice	Spontaneous alternation, PA	Significant improvement in scopolamine-induced memory impairment	56
Fermented papaya	Patients with AD	Urinary 8-OHdG	Decreased urinary 8-OHdG, oxidative stress biomarker in AD patients	57,58
Fermented grape marc	Human PBMC	Cytokine production, granzyme B, FoxP3	Increased the release of cytokine and induction of FoxP3: reduced the production of granzyme B	59
Kimchi extract	ICR mice	PA, MWM, Y-maze, BDNF, pCREB	Prevented memory deficit and increased hippocampal BDNF and pCREB expressions in scopolamine-injected mice	64
Other fermented plant products				
Fermented <i>Rhus verniciflua</i> bark	ICR mice	Apoptotic cell death, microglial activation	Attenuated KA-induced neuronal cell death and microglial activation	66
Fermented tea	Healthy elderly individuals	MMSE	Association between regular consumption of fermented tea and lower risks of cognitive deficiency	67
Fermented fungi				
Fermented <i>Ganoderma lucidum</i> extract	SD rats	PA, MWM, hippocampal AChE	Improved scopolamine-induced memory impairment in rats: Lowered hippocampal AChE activity	68
Fermented <i>Antrrodia cinnamomea</i> extract	PC-12 cells	Cell viability, MAPK proteins	Prevented serum deprivation-induced cell apoptosis	69
Fermented <i>Xylaria nigripes</i> extract	SH-SY5Y cells, BV-2 cells	Cell viability, NO	Protected A $\beta$ -induced injury in SH-SY5Y cells: Inhibitory effect against LPS-stimulated NO production in BV-2 cells	71

Table 1. Continued

Fermented product	Subject	Measurements	Effects	References
Fermented traditional oriental medicines				
Fermented Oyaksungisan	HT22 cells	Cell viability, antioxidant activity	Improved antioxidant activity: neuroprotective activity on glutamate-induced neurotoxicity <i>in vitro</i>	74
Fermented Insampaedok-san	HT22 cells	Cell viability, antioxidant activity	Improved antioxidant activity: neuroprotective activity on glutamate-induced neurotoxicity <i>in vitro</i>	75
Fermented Chongmyung-tang	ICR mice	Antioxidant activity, PA	Improved scopolamine-induced memory impairment in mice; showed strong antioxidant activity	77
Fermented Bozhougyiqi-tang	HT22 cells, ICR mice	MWM, PA, cell viability, antioxidant activity	Enhanced neuroprotective effect against glutamate-induced neurotoxicity <i>in vitro</i> ; ameliorated the scopolamine-induced memory impairment in mice	78
Fermented Gumiganghwal-tang	HT22 cells, ICR mice	Cell viability, AChE, ROS, MWM, PA	Enhanced neuroprotective effect against glutamate-induced neurotoxicity <i>in vitro</i> ; ameliorated the scopolamine-induced memory impairment in mice; suppression of AChE activity <i>in vitro</i> and <i>in vivo</i>	79,80
Fermented Hwangryunhaedok-tang	HT22 cells	Cell viability, antioxidant activity	Improved antioxidant activity: neuroprotective activity on glutamate-induced neurotoxicity <i>in vitro</i>	81
Fermented Sipjeondaebo-tang	C57BL/6 mice	PA, MWM, AChE, ROS, BDNF, pCREB, pAkt	Ameliorated the scopolamine-induced memory impairment in mice; promoted hippocampal neurogenesis and attenuated scopolamine-induced ROS and AChE activity; prevented scopolamine-induced suppression of BDNF	82

AD, Alzheimer's disease; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ ; A $\beta$ ,  $\beta$ -amyloid; VaD, vascular dementia; MWM, Morris water maze; H<sub>2</sub>O<sub>2</sub>, hydrogen peroxide; OGD, oxygen-glucose deprivation; NOR, novel object recognition; PA, passive avoidance; AChE, acetylcholinesterase; MDA, malondialdehyde; SOD, superoxide dismutase; TMT, trimethyltin; NGF, nerve growth factor; SD, Sprague-Dawley; BDNF, brain-derived neurotrophic factor; HVT, Hopkins verbal learning test; 6-OHDA, 6-hydroxydopamine; PD, Parkinson's disease; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; EBST, elevated body swing test; NO, nitric oxide; ApoE, apolipoprotein E; APP, amyloid precursor protein; IRES, internal ribosome entry site; MSG, monosodium glutamate; nNOS, neuronal nitric oxide synthase; PBMC, peripheral blood mononuclear cells; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; FoxP3, forkhead box P3; MAPK, mitogen-activated protein kinase; LPS, lipopolysaccharide; pCREB, phosphorylated cyclic adenosine monophosphate response element-binding protein; MMSE, mini mental state examination; KA, kainic acid; pAkt, phosphorylated Akt.

cheese extract. Dehydroergosterol and oleamide were found as active components of camembert cheese, enhancing microglial anti-inflammatory activity (25).

Soy milk fermented with *Lactobacillus plantarum* strain exhibited a protective effect on H<sub>2</sub>O<sub>2</sub>- and oxygen-glucose deprivation (OGD)-induced damage in PC-12 cells. In addition, oral administration of fermented soy milk extract improved learning and memory in deoxycorticosterone acetate-salt-stimulated rat models of vascular dementia (26).

Calpis sour milk is a Japanese beverage prepared by fermenting skim milk with *Lactobacillus helveticus* and *Saccharomyces cerevisiae*. Oral administration of Calpis sour milk whey powder significantly improved scopolamine-induced memory deficits and novel object recognition in mice (27). Fermented milk also reduced plasma L-tryptophan and salivary cortisol levels in healthy subjects who were exposed to stressful situations. In the same study, the rate of subjects experiencing physical symptoms was reduced after consumption of fermented milk for 8 weeks (28).

#### Legume- and cereal-based fermented foods

Cereals and legumes have been important sources of carbohydrates and proteins. They have been widely consumed in various fermented forms in different parts of the world. These foods contain many bioactive compounds that are absent in unfermented foods. Soybeans and rice are the most popular ingredients used in the preparation of legume- and cereal-based fermented foods (21).

Asian countries developed their own methods to make fermented soybean products. Soy sauce, soybean paste such as *miso* and *doenjang*, *tempeh*, and *natto* are typical examples of fermented soybean products (21). Neuroprotective effects of fermented soybean have been reported in several animal studies. *Cheonggukjang* is one of the fermented soybean pastes used in Korean regional cuisine. In an animal study using *cheonggukjang* extract, a trimethyltin-treated group showed long- and short-term memory loss, whereas groups pretreated with *cheonggukjang* showed improved memory function in a dose-dependent manner (29). The number of cell death and AChE activity of the hippocampus were decreased in the *cheonggukjang*-treated group. Expression of nerve growth factor (NGF) and activation of the NGF receptor signaling pathway were also upregulated in the *cheonggukjang*-treated group. Additionally, the level of SOD activity was enhanced, whereas malondialdehyde was lower in the *cheonggukjang*-treated group compared to the vehicle-treated group (29). In another study with AD and type 2 diabetes-induced rats, 8-week administration of *cheonggukjang* extract improved cognitive function and glucose regulation (30). *Cheonggukjang* is usually prepared with *Bacillus*

strains such as *Bacillus licheniformis*, *Bacillus amyloferences*, and *Bacillus subtilis*. Similarly, fermented soybean powder with *Lactobacillus pentosus* var. *plantarum* C29 showed a protective effect against scopolamine-induced memory impairment in mice (31). Scopolamine-induced reduction of hippocampal BDNF expression was reversed, and AChE activity was inhibited after treatment with fermented soybean powder extract (31). A cross-sectional clinical study also reported that fermented soybean products oriented diets have a beneficial effect among this particular population. High consumption of *tempeh*, a mold-fermented soy product originated from Indonesia, had a positive association with improved memory function in elderly subjects, while *tofu* showed a negative association when analyzed together (32).

Rice (*Oryza sativa* L. *Gramineae*) is a principle ingredient in Asian foods. Red mold rice (RMR), also known as *hongqu* (Chinese) or *koji* (Japanese), is fermented rice which acquired its color from being cultivated with the mold *Monascus purpureus*. RMR has been used for many centuries to improve its color and flavor, as well as to promote digestion and blood circulation. Lee et al. have reported the neuroprotective effect of RMR ethanol extract *in vitro* and *in vivo* (33-35). RMR extract provided strong protection against A $\beta$ 40-induced neurotoxicity in PC-12 (35). It rescued cell viability as well as repressed inflammatory responses and oxidative stress. In AD rats infused with A $\beta$ 40 into the cerebral ventricle, administration of RMR extract potently reversed the cognitive dysfunction in the memory task and brain damage in the biochemical assay (34). Furthermore, RMR prevented A $\beta$  fibrils formation and decreased A $\beta$ 40 accumulation in the hippocampus (34,35). A further study reported that RMR extract treatment suppressed cholesterol-raised  $\beta$ -secretase activity and increased the neuroprotective soluble amyloid precursor protein (APP) R-fragment secretion *in vitro* and *in vivo* (33). Other studies revealed that RMR administration has a protective effect in a Zn-deficiency model (36) and Parkinson's disease model (37). The administration of RMR significantly ameliorated behavioral dysfunction and improved the activity of antioxidant enzymes including glutathione reductase, glutathione peroxidase, SOD, and catalase, which all lead to markedly reduced reactive oxygen species (ROS) production.

Monacolins are the major active functional compounds that are isolated from RMR (21). Monacolin K (also known as lovastatin) is one of the main monacolins that has been found to have various pharmacological activities, including lowering blood cholesterol levels and reducing oxidative damage. Several *in vivo* studies have indicated that Monacolins K can permeate the blood-brain barrier (38,39). In addition to monacolins, considerable amounts of gamma-aminobutyric acid (GABA) have also

been found in RMR, which is the main inhibitory neurotransmitter in the central nervous system (5). RMR also contains multiple functional components derived from the fermentation process (38). The protective effect of RMR might be caused by a synergism among these multiple bioactive components (35,38,40).

Rice vinegar is another fermented rice product which has been cultivated in Asian countries including China, Japan, Korea, and Vietnam. One variation of rice vinegar is *Kurozu*, a traditional Japanese rice vinegar. It is known that concentrated *Kurozu* feeding suppresses cognitive dysfunction and brain amyloid accumulation in senescence-accelerated P8 mice (41). Concentrated *Kurozu* increased mRNA expression of heat shock 70 kDa protein 1A (HSPA1A), a protein that stabilizes proteins against misfolding and aggregation, although the result was ambiguous in mice primary neurons. The expression of HSPA1A may be associated with the decreased accumulation of aggregated proteins in the brain (41).

#### Fermented plant root products

Several root and tuber crops are particularly fermented to produce foods with dense nutrients in a traditional practice of preservation as fermentation has the advantage of reducing the cyanogen content (21). Recently, a number of studies shifted its focus on the neuroprotective and functional improvement of fermented root products.

*Codonopsis lanceolata* is a herb mainly found in Asian countries. This plant has been broadly used in traditional medicine. The root of *C. lanceolata* contains various bioactive ingredients—polyphenols, saponins, alkaloids, steroids, tannins, and triterpenes—collectively; and, these are used to treat a broad range of illnesses—bronchitis, cough, spasm, psychoneurosis, cancer, and inflammation (42). Recent studies have revealed that the fermentation process can improve the functional properties of poor quality *C. lanceolata*. In the study by He et al. (43), the phenol amounts and DPPH scavenging activities in *C. lanceolata* extract were significantly increased after probiotic fermentation. Administration of fermented *C. lanceolata* effectively ameliorated a scopolamine-induced memory deficit in ICR mice. Weon et al. (44) also have reported the cognitive-enhancing effect of steamed and fermented *C. lanceolata* in animal and biochemical studies. Mice that were orally treated with steamed and fermented *C. lanceolata* extract (SFCE) exhibited enhanced memory performance compared to mice treated with original *C. lanceolata* extract in MWM and passive avoidance test. SFCE treatment showed a significant neuroprotective effect against glutamate-induced cell death in HT22 cells (44-47). In biochemical assays, AChE activity was decreased, and the level of CREB phosphorylation and BDNF expression were increased in the hippocampal tis-

sue of scopolamine-treated mice after the administration of fermented *C. lanceolata* (44). Additionally, treatment with SFCE reduced glutamate-induced ROS accumulation,  $\text{Ca}^{2+}$  influx, and nitric oxide (NO) formation in HT22 cells. SFCE upregulated the antioxidant enzyme's activity, and potentially ameliorated mitochondrial dysfunction by inhibiting Bax and caspase-3 expression in the hippocampal-derived cell line (48).

For thousands of years, ginseng root has been used as an East Asian medicinal herb for various diseases (49). Use of ginseng extract may enhance cognitive and psychomotor functions by stimulating the central nervous system. A study demonstrated that fermented ginseng reversed memory impairment and reduced A $\beta$  accumulation in the AD mouse model (50). Another study reported that NB34, a preparation of fermented *Radix notoginseng*, can serve in an alike functional manner to memantine, a drug used for the treatment of AD, by reducing the activities of both tau internal ribosome entry site and APP (51).

Garlic and onion have also been recognized for their medicinal properties for centuries. After the feeding of fermented garlic (black garlic) extract, the total number of pyramidal cells in the hippocampus and the spatial memory were enhanced in monosodium glutamate-exposed rats (52). When the hippocampal-derived HT22 cells were treated with fermented yellow onion (*Allium cepa*) extract, the glutamate-induced neurotoxicity was decreased (53).

#### Fermented fruits and vegetables

Keeping fruits and vegetables fresh to maintain their nutrient values needs special caution and can become demanding if without a proper refrigerating system. It seems that the practice of fruit and vegetable fermentation may have evolved from ancient times to keep the collected food fresh for longer periods of time, especially when natural resources and harvestings are limited.

Papaya is the fruit of the plant *Carcica papaya*. It is native to the tropics of the Central and northern South America and is now cultivated in many tropical regions including India, Australia, Malaysia, Indonesia, the Philippines, and Hawaii. Fermented papaya preparation (FPP) has been reported to possess free radical scavenging and antioxidative properties (54). A study in an AD cell model showed that the neurotoxicity of the A $\beta$  can be significantly attenuated by FPP. The expression of SOD was significantly upregulated after FPP treatment, while FPP post-treatment improved cell viability and attenuated the intracellular  $\text{Ca}^{2+}$  influx, ROS generation, and NO accumulation (54,55). In a mouse model of AD induced by scopolamine, PS-501, the extract of yeast-fermented papaya, significantly reversed short- and long-term memory impairment (56). There is further evidence to indicate

that FPP administration can improve memory functions in human studies. Barbagallo et al. assessed oxidative stress in AD patients by measuring urinary 8-hydroxy-2'-deoxyguanosine (8-OHdG). When FPP was consumed by patients for 6 months, 8-OHdG levels were significantly decreased, with no significant changes in that of the controls (57,58). Several studies suggested that the beneficial effect of FPP is possibly regulated by mitogen-activated protein kinase-mediated signaling pathway or Bax/bcl-2 sensitive pathway (54,55).

Fermented grape marc is the solid remains after the juice has been squeezed from grapes. In a study using human peripheral blood mononuclear cells, fermented grape marc was suggested as a potential therapeutic agent regarding its immunomodulatory activities. Fermented grape marc increased the intracellular content of cytokines and the induction of FoxP3, a biomarker of T regulatory cells while reducing the production of Granzyme B (59).

*Kimchi* is a long-established Korean traditional food made from green vegetables with various seasonings prepared after the natural fermentation process. Many studies have reported that the concentration of the bioactive components in *kimchi* changes during fermentation, suggesting its anti-carcinogenic, anti-bacterial, and anti-oxidative properties (60-63). Lactic acid bacteria are the main microorganisms responsible for *kimchi* fermentation. Lactic acid bacteria isolated from the supernatant of *kimchi* protected against scopolamine-induced mouse memory deficit as shown by the result of passive avoidance test. Particularly, the strain C29 of several lactic acid bacteria suppressed scopolamine-induced memory deficit related behaviors in Y-maze and MWM tests as well. Furthermore, C29 treatment increased hippocampal BDNF and phosphorylated CREB expressions, which were reduced by scopolamine injection (64).

#### Other fermented plant products

*Rhus verniciflua*, also commonly known as Chinese lacquer tree, is a member of the sumac family (*Anacardiaceae*) of flowering plants, which are native to East Asia. Its value for medicinal applications to treat diabetes mellitus and stomach diseases is underestimated and obscured by its allergic compound—urushinol—which was reported to cause irritation and inflammation (65). To detoxify the stem bark of *R. verniciflua*, a fermentation process involving mushroom species was applied, and it significantly attenuated allergic-induced responses as well as neuroprotective properties. In ICR mice, *R. verniciflua* extracts were orally administered for 7 days, followed by an intracerebroventricular injection of kainic acid resulting in apoptotic neuronal cells. Pretreatment with *R. verniciflua* extracts significantly reduced kainic acid-induced microglial activation and neuronal cell death

in the mouse hippocampus (66).

In an epidemiologic study, there was a significant association between total tea consumption and a lower risk of cognitive decline. The effect was most evident in diets with fermented black and oolong teas compared to that of regular green tea (67).

#### Fermented fungi

Medicinal fungi have long been used for its anticancer, antihepatotoxic, antihypertensive, anti-inflammatory, and antioxidative properties in a practice of traditional Chinese medicine. Several cell culture and animal studies investigated the potential effects of fermented medicinal fungi that would be beneficial for cognitive function.

*Ganoderma lucidum* is one of the most popular medicinal mushrooms used in China for more than 2,000 years (68). *G. lucidum* water extracts fermented by lactic acid bacteria significantly enhanced learning memory and cognitive function of scopolamine-induced rats in passive avoidance and MWM test. In parallel with behavioral changes, lower hippocampal AChE activities were apparent in the group treated with fermented *G. lucidum* extracts in a biochemical test (69).

*Antrodia cinnamomea*, also known as *Antrodia camphorate*, is a species of fungus native to Taiwan. It is commonly used to treat various diseases including cancer, cardiovascular disease, and inflammatory reaction. Lu et al. (70) reported that fermented *A. cinnamomea* extract protects neuron-like PC-12 cells from serum deprivation-induced cytotoxicity in a dose-dependent manner. During the serum deprivation, phosphorylation of extracellular signal-regulated kinase was decreased along with the increase in phosphorylated c-Jun NH<sub>2</sub>-terminal kinase level and p38, while *A. cinnamomea* reverses these apoptotic results.

*Xylaria nigripes* is another medicinal fungus used in traditional Chinese medicine in attempts to resolve sleep, mood, and memory problems. Nineteen natural compounds were isolated from the ethanol extract of fermented *X. nigripes*. Among the products, compound 17 exhibited neuroprotective effects by attenuating A $\beta$ -induced neurotoxicity in SH-SY5Y neuroblastoma cells. Compound 15 exhibited anti-neuroinflammatory effects by inhibiting lipopolysaccharide-stimulated NO production in BV-2 microglial cells (71).

#### Fermented traditional oriental medicine

Traditional oriental medicines have been used for thousands of years. Unlike modern drugs, which contain a single active component, traditional oriental medicines consist of multiple components and are based on a multi-target approach (72). The fermentation process converts the components of traditional oriental medicines into active metabolites, hence it enhances their biological activity and improves nutrient absorption (72). Fer-



mentation also reduces the toxicity of traditional oriental medicines. Several studies reported the enhanced biological activity of fermented traditional oriental medicines (5,73).

A Korean traditional herbal formula, *Oyaksungisan*, has been used to treat rheumatoid arthritis and paralysis. It is composed of twelve herbs including *Citrus unshiu* peel, *Lindera* root, *Angelica Dahurica* root, and *Zingiberis rhizoma*, which are reported to have anti-cancer effects (74). The fermentation process changed the contents of *Oyaksungisan* and improved radical scavenging effects. Compared to original *Oyaksungisan*, treatment with fermented *Oyaksungisan* showed greater neuroprotective activity on glutamate-stimulated neurotoxicity in HT22 cells (74). Similarly, *Insam paedoksan*, a traditional oriental medication for antipyretic and anti-inflammatory diseases, exhibited more potent anti-oxidative and neuroprotective activity after fermentation with *Lactobacillus* (75).

*Chongmyung-tang* is a Korean herbal medicine, which has been frequently used for the therapy of memory improvement. It consists of three medicinal herbs of *Polygonae radix*, *Acori graminei rhizoma*, and *Hoelen* (76). Nam et al. (77) investigated the antioxidative and memory-enhancing effects of fermented *Chongmyung-tang*. Both, original *Chongmyung-tang* and fermented *Chongmyung-tang* treatments resulted in a significant memory enhancing effect in ICR mice. Both of them also exhibited strong radical scavenging activities. In comparison to the original *Chongmyung-tang* group, the fermented *Chongmyung-tang* group showed slightly greater memory function enhancement, although the result was not statistically significant.

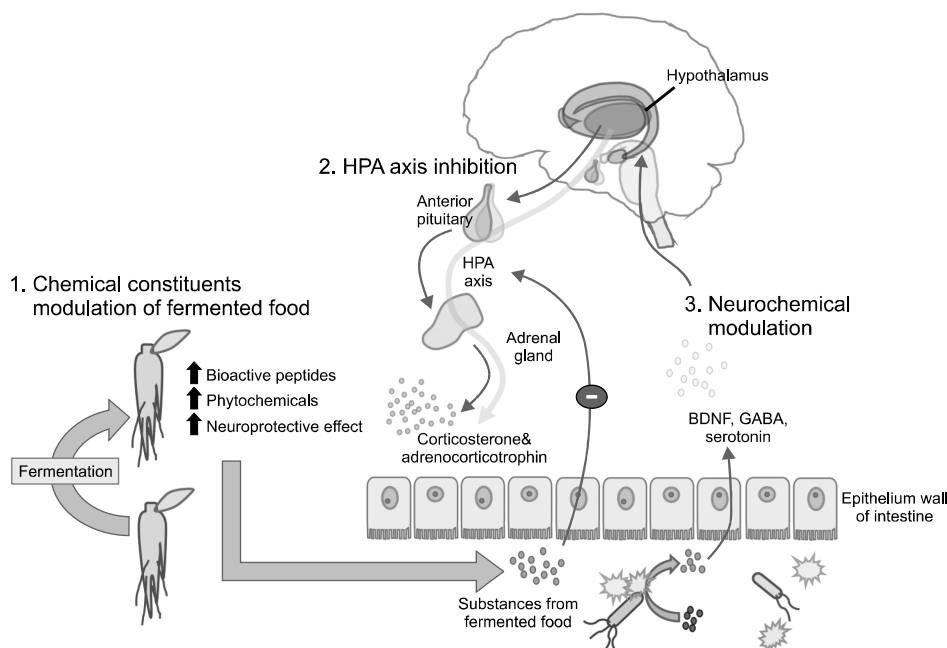
The neuroprotective effects of other decocted herbal medicines, which have been traditionally used for the

treatment of fatigue or inflammatory diseases, have also been investigated. Fermented *Bozhougyiqi-tang* (78), *Gumiganghwal-tang* (79,80), and *Hwangryunhaedok-tang* (81) showed more potent protective activities against glutamate-stimulated cell death in HT22 cells than the unfermented prescription. Moreover, several studies in scopolamine-treated mice reported that fermented *Sipjeondaebotang* (82), *Bozhougyiqi-tang* (78), and *Gumiganghwal-tang* (79,80) significantly ameliorated amnesic behaviors possibly through AChE inhibition. These results suggest that fermentation might improve the pharmacological activities of traditional oriental medicines.

## POTENTIAL MECHANISMS OF FERMENTED FOODS

Although the underlying mechanisms of fermented foods on cognitive function is still unclear, emerging evidence indicates that ingestion of fermented food may influence the central nervous system (10). There are several hypotheses for the beneficial effects of fermentation, of which the major ones are described (Fig. 1).

One possible explanation is that fermentation modulates the chemical constituents, improving the activity and bioavailability of the food. As reviewed here, a number of studies have reported the chemical changes such as enriching bioactive peptides and creating phytochemicals during the fermentation process (5). It seems that substances obtained by the incubation of natural foods with microbes enhance their neuroprotective effects. Moreover, the components changed through fermentation may increase bioavailability involving intestinal absorption and utilization of the ingested nutrients within



**Fig. 1.** Potential mechanisms underlying the efficacy of fermented foods. The figure presents 3 hypotheses through which fermented foods can improve brain and cognitive function. (1) Chemical constituents modulation, (2) HPA axis inhibition, and (3) Neurochemical modulation. HPA, hypothalamic-pituitary-adrenal; BDNF, brain-derived neurotrophic factor; GABA, gamma-aminobutyric acid.

the body (5,21). Our intestinal epithelium is a selectively permeable barrier, preventing the access of harmful substances. The absorption of nutritional components in the intestines is therefore restricted and occasionally the components need to be converted to active forms by bacteria in the intestine (83). For example, a recent study found that short-chain fatty acids, which are fermented products formed by intestinal bacteria, positively influence host metabolism and play a key role in functions of the central nervous system (84). It is also reported that phytochemical absorption and its antioxidative and anti-inflammatory functions can be controlled by resident intestinal microbiota (4,85,86). In another study of germ-free (GF) mice, colonization with microbes was accompanied by marked changes in the transcription of genes associated with nutrient absorption and metabolism (83). These findings suggest that proper fermentation may amplify the beneficial contents of the food, promoting biological function and bioavailability.

In addition to changing constitutive properties, probiotics in fermented foods may also influence brain function via gut microbiota. The human intestine is inhabited by nearly  $10^{14}$  microorganisms (8). The relation between these microorganisms and their host, which is called commensal intestinal microbiota, begins shortly after birth and remains throughout life. The presence of commensal microbiota is important to the immune system, gastrointestinal homeostasis, and nutrient processing (9). Recently, a growing body of findings revealed that gut microbiota is also critical to the function of the central nervous system, resulting in altered brain function and behaviors (7-9).

The hypothalamic-pituitary-adrenal (HPA) axis is involved in the neurobiology of stress response. It is becoming clear that gut microbiota is significantly associated with the HPA axis. In GF animals, which have no commensal microbiota, restraint stress-induced HPA reactivity with exaggerated corticosterone and adrenocorticotrophin release were compared to the specific pathogen-free controls (87). On the other hand, early development of the gut microbiota reduced the exaggerated HPA axis response of GF mice over their lifetime (87). Feeding of probiotics can also attenuate the HPA-mediated stress responses (88,89). Considering that cognitive deficit is associated with HPA axis hyperactivity, administration of probiotics in fermented foods may improve cognitive function by normalization of HPA activity.

Other potential mechanisms through which fermented foods can influence cognitive function include neurochemical modulation. To date, several studies have provided evidence that neurotransmitter systems are affected by the gut microbiota. For example, reduced expression of hippocampal BDNF, which is important for the survival and differentiation of neurons, was observed in

the infected dysbiosis mice model (90) and male GF mice (87,91). Supplementation with probiotics returned BDNF expression to the control level. Alteration in GABA, the main inhibitory neurotransmitter, was also observed. Chronic treatment with the probiotic *Lactobacillus rhamnosus* changed the expression of certain GABA receptors in a regional-dependent manner, matching the known effects of anxiolytic agents. The changes related to *L. rhamnosus* treatment were extinguished with vagotomy, indicating a key route of communication from gut to brain (92). Interestingly, some probiotic bacteria are capable of producing GABA from glutamate in culture (93). Other experiments have shown that the administration of probiotics can alter serotonin turnover and related metabolites in the brain (94,95). Neurotransmitters, such as BDNF, glutamate, GABA, and serotonin are reported to be respectively involved in learning and memory. Therefore, it is hypothesized that fermented foods might improve cognitive function by modulating the release of neurotransmitters.

The fermented food's functional aspect of neuroprotective effects along with the improvement in brain and cognitive function is becoming more evident as studies of animals and humans with positive results are accumulating. The beneficial effects of fermented foods may be due to changes in chemical composition by probiotics and homeostasis in the gut microbiota community.

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## CONCLUSION

As the mechanisms underlying the beneficial effects of fermented foods are becoming more visible with accumulating results from clinical and animal studies, fermented foods are gaining popularity among consumers for their possible therapeutic and high marketing value. To our knowledge, this paper is the first research to conduct an extensive review on fermented foods and their cognitive enhancing effects, so to be used as a reference when studying the relevance of gut microbiota and fermented foods to brain functionality. Partly due to the paucity of clinical trials in humans using fermented functional foods, quantitative synthesis of these trial results could not be carried out. As more studies are published in the future, it would be possible to conduct a meta-analysis that may be helpful in confirming the beneficial effects of fermented functional foods.

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