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REVIEW

Animal Models of Cognitive Deficits for Probiotic Treatment

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Abstract Cognitive dysfunction is a common symptom of neurodegenerative diseases, such as Alzheimer's disease, Parkinson's disease, and Huntington's disease, and is known to be caused by the structural and functional loss of neurons. Many natural agents that can improve cognitive function have been developed and assessed for efficacy using various cognitive deficit animal models. As the gut environment is known to be closely connected to brain function, probiotics are attracting attention as an effective treatment target that can prevent and mitigate cognitive deficits as a result of neurodegenerative diseases. Thus, the objective of this review is to provide useful information about the types and characteristics of cognitive deficit animal models, which can be used to evaluate the anti-cognitive effects of probiotics. In addition, this work reviewed recent studies describing the effects and treatment conditions of probiotics on cognitive deficit animal models. Collectively, this review shows the potential of probiotics as edible natural agents that can mitigate cognitive impairment. It also provides useful information for the design of probiotic treatments for cognitive deficit patients in future clinical studies.

Keywords cognitive deficits, probiotics, neurodegenerative disease, gut-brain axis

Introduction

With rapid social development and the continued introduction of new medical technology, human life expectancy is gradually increasing, causing many countries around the world to become aging societies. Although aging is closely associated with cognitive decline, a broad range of different cognitive abilities was found even in people of the same age, and severe cognitive impairment could be detected in patients suffering from neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease (Chiu et al., 2006; Christensen et al., 1999). This indicates that age-dependent cognitive decline may be controlled. It has been reported that the prevalence of dementia is doubling every 20 years and is expected to reach 131.5 million cases by 2050 (Alladi et al., 2011; Bowler et al., 1998). Therefore, huge social and economic costs will be incurred as a result. As such, there is increasing demand for the development

of efficient drugs that can treat dementia.

Many agents have been developed to mitigate cognitive deficits, a major effect of dementia. Since AD is the most common neurodegenerative disease, which manifests as severe cognitive impairments, researchers have focused on developing agents that can inhibit the amyloid beta (Aβ) peptide-mediated cascade events, such as oxidative stress, mitochondria dysfunction, and neuronal death in the brain. Many natural agents, which can attenuate Aβ-induced neurological disorder with cognitive declines, have been developed from foods (Ravi et al., 2019), plants (Akter et al., 2021; Deng et al., 2020), and seaweed (Kwon and Lee, 2020; Kwon and Lee, 2021). Recently, various studies have reported that the gut environment can interact closely with the brain via the nervous system (Collins et al., 2012) and chemicals (Briguglio et al., 2018). In the connection between the brain and gut, the so-called gut–brain axis, gut microbiota have been proven to be a major regulator since they can exchange information between the gut and brain and also produce neuromodulators, such as short-chain fatty acids, glutamate, and serotonin. These neuromodulators can reach the central neurons via the circulatory system, finally affecting neuronal activity and causing behavioral changes (Logsdon et al., 2018).

Probiotics, which are defined as “viable microbial food supplements that have beneficial effects on human health” (Salminen et al., 1998), have been studied for their effects on various diseases, such as inflammation (Vitetta et al., 2012) and immunological disorders (Vitetta et al., 2018). Since it is known that controlling the gut microbiota is important in regulating neurological disorders (Morais et al., 2021), many efforts have attempted to use probiotics to treat neurodegenerative diseases. Since a huge number of probiotic strains have been developed, the demand for an accurate estimating system to test each probiotic strain is gradually increasing. Therefore, the use of proper cognitive deficit animal models is important to evaluate the anti-cognitive deficit function of each probiotic strain. In this paper, we summarize various animal models and probiotic strains that have been used to test the effects of anti-cognitive deficits. These results provide useful information about ways to further the development of probiotic-based drugs for human treatments.

Chemical-Induced Cognitive Deficit Animal Models for Probiotic Treatment

Various chemical-induced cognitive deficit animal models have been developed and used to test the anti-cognitive deficit activities of probiotics. The characteristics of each animal model are summarized in Table 1.

D-Galactose (D-gal)-induced accelerated aging mouse model

Since D-gal, a normal carbohydrate, can be found in various foods, such as cheese, butter, and honey, D-gal is absorbed into the body through the intake of these foods and used in the biochemical pathways to produce metabolic energy. However, high levels of D-gal in the body are considered an oxidative stressor to cells because D-gal can be oxidized by galactose oxidase, resulting in aldehyde and hydrogen peroxide production. Thus, the chronic administration of D-gal to rodents could lead to oxidative damage to cells, including those in the brain, resulting in a progressive loss of memory. Many studies have shown that mitochondrial dysfunction, oxidative stress, neuronal death, and cognitive deficits occur in mouse brains when excess D-gal is supplied (Kumar et al., 2009; Prakash and Kumar, 2013; Rehman et al., 2017). Therefore, a D-gal-induced rodent model could be used to test the anti-cognitive deficit effects of new agents, including probiotics.

To make D-gal-induced cognitive deficit rodent models, 100–200 mg/Kg body weight/day of D-gal should be injected for 6–10 weeks, which seems to be enough doses to cause progressive loss of memory (Lu et al., 2010; Shwe et al., 2018). In most reports, the candidate materials were continuously fed from the time D-gal was injected to the end of the D-gal injection

Table 1. **Chemical-induced cognitive deficit animal models**

	Name	Doses/methods	Major phenotypes	Refs
Chemical-induced cognitive deficit animal models	D-Galactose-induced mice	IP injection of D-galactose (100–120 mg/kg·bw/d) for 6–12 wk.	Cognitive impairment Mitochondrial dysfunction Neuronal degeneration Apoptosis Depression and anxiety	(Liu et al., 2021; Parameshwaran et al., 2010; Woo et al., 2014)
	Aβ-induced mice	ICV injection of Aβ peptide solution (500–3,000 μg). Aβ peptide aggregation occurs within 3–28 d.	Cognitive impairment Aβ accumulation Neuronal loss	(Ali et al., 2015; Kobayashi et al., 2017; Kwon and Lee, 2020)
	Scopolamine-induced mice	IP injection of scopolamine (1–1.5 mg/kg·bw/d) to mice could induce cognitive impairment within 1 h, but repetitive administration of scopolamine (once/d) is recommended during behavioral tests.	Cognitive impairment Neuronal degeneration Apoptosis	(Choi et al., 2021; Kim et al., 2021b; Yadang et al., 2020)
	LPS-induced mice	IP injection of LPS (0.25–1 mg/kg·bw/d) in the abdominal cavity for 5–7 consecutive d.	Cognitive impairment Mitochondrial dysfunction Neuroinflammation	(Kamdi et al., 2021; Shoemark and Allen, 2015; Yang et al., 2020a)
		ICV injections of LPS (2–12 μg). Cognitive deficiency due to neuroinflammation occurs 1–7 d after LPS injection.	Cognitive impairment Mitochondrial dysfunction Neuroinflammation	(Zhao et al., 2019; Zhou et al., 2006)

IP, intraperitoneal; Aβ, amyloid beta; ICV, intracerebroventricular; LPS, lipopolysaccharides.

period. A few reports have demonstrated the anti-cognitive deficit function of probiotics by using the D-gal-induced cognitive deficits model. For example, *Lactobacillus paracasei* PS23, which is isolated from human feces, has been reported to have an anti-cognitive deficit function. *L. paracasei* PS23 (10^9 CFU/d/mice) was administrated to D-gal (100 mg/kg·bw/d)-injected mice for 10 weeks to attenuate anxiety-like behavior and prevent the loss of long-term memory induced by D-gal (Cheng et al., 2022). The oral administration of *Lactobacillus pentosus* var. *plantarum* C29 (10^{10} CFU/d/mice) isolated from kimchi, a traditional Korean food, to D-gal-injected mice (100 mg/kg·bw/d of D-gal for 10 weeks) ameliorated D-gal-induced memory impairment (Woo et al., 2014). Song et al. (2022) reported that the oral administration of *Bacillus coagulans* JA845 (10^9 CFU/d/mice) to D-gal-induced cognitive deficit mice (injected with 120 mg/kg·bw/d of D-gal for 10 weeks) inhibited oxidative stress in the brain, loss of hippocampal neurons, and loss of long-term memory. Collectively, these data suggest that probiotics other than the above strains have great potential for attenuating D-gal-induced cognitive impairment.

Amyloid beta (Aβ)-induced cognitive deficits model

Aβ is a 4 kDa peptide of 36–43 amino acids generated from the amyloid precursor protein (APP) by the proteolytic reaction of β-secretase and γ-secretase (Wang et al., 2021). Aβ aggregates to form amyloid plaques, which can induce toxicity to neuronal cells, and amyloid plaques are easily detected in the brains of AD patients. Therefore, Aβ-mediated neurotoxicity is considered a major target in developing anti-AD drugs. To make a cognitive deficit animal model that mimics AD, intracerebroventricular (ICV) injection of Aβ has been used, and once Aβ is injected into the mice brain directly, neuronal death followed by loss of learning and memory function could be detected from 3–6 d after injection (Ali et al., 2015;

Kobayashi et al., 2017; Kwon and Lee, 2020). To construct the Aβ-induced cognitive impairment animal model, stereotaxic apparatuses are often used to accurately inject Aβ into the bregma region without brain damage. However, the direct injection method without stereotaxic apparatuses is also used to introduce cognitive deficits in mice by the direct injection of Aβ peptide (Kim et al., 2016). Most reports injected 100 μmol of Aβ peptide, and cognitive impairment could be detected with a single injection. Therefore, Aβ-injected mouse can be used to estimate the anti-AD activity of drug candidates.

Probiotics have been reported to be a potential candidate for preventing Aβ-mediated neurodegeneration (Kobayashi et al., 2017). The oral administration of *Bifidobacterium breve* A1 (1×10^9 /d/mice) to Aβ-injected mice for 10 d inhibited Aβ-mediated cognitive dysfunction (Kobayashi et al., 2017). Zhu et al. (2021) reported that oral treatment with *B. breve* CCFM1025 and WX (0.6×10^9 /d/mice) for 6 weeks recovered Aβ-mediated synaptic plasticity decrease through the regulation of the gut microbiome. Thus, these results suggest that a cognitive deficit animal model induced by Aβ injection could be used to evaluate the regulatory function of probiotics in cognitive impairments.

Scopolamine-induced cognitive deficits in mice

Acetylcholine is a neurotransmitter that plays an important role in cortical development, sleep–wake cycles, and memory and cognitive function (Bruel-Jungerman et al., 2011; López-Sobaler et al., 2021; Van Erum et al., 2019). Reduced cholinergic activity with a loss of cortical cholinergic neurons in the hippocampus is often detected in neurodegeneration, and it has been considered a cause of memory impairment in AD (Whitehouse et al., 1981; Whitehouse et al., 1982). Therefore, inhibiting the central cholinergic system has been proposed as a way to build an animal model with limited cognitive function. Scopolamine is an anti-cholinergic drug that blocks the binding between acetylcholine and muscarinic receptors, resulting in the excess release of acetylcholine (Lazareno et al., 2000). Thus, the administration of scopolamine to mice results in the loss of hippocampus neurons and learning and memory impairments. A single intraperitoneal injection of scopolamine (1–1.5 mg/kg bw) to mice could induce cognitive impairment within 1 h, but repetitive administration of scopolamine (once/d) is recommended during behavioral tests (Choi et al., 2021; Kim et al., 2021b; Yadang et al., 2020).

Several studies have shown that scopolamine-induced cognitive impairment can be attenuated by probiotic treatment. For example, the administration of *Lactobacillus johnsonii* CJLJ103 (1×10^9 CFU/d/mice) for 5 d restored the scopolamine-induced decrease of spontaneous alteration (%) estimated by the Y-maze test (Lee et al., 2018). Patel et al. (2020) reported that the oral administration of *Lactobacillus rhamnosus* UBLR-58 (1×10^9 CFU/d/mice) for 10 d enhanced curcumin's effects against scopolamine-induced cognitive deficits. Collectively, these studies suggest that probiotics could be active agents that control for cognitive deficits induced by the impairment of the cholinergic system.

Lipopolysaccharide (LPS)-induced cognitive deficits in mice

Systemic inflammation induced by infectious agents has been recognized as a cause of cognitive dysfunctions (Banks et al., 2002; Konsman et al., 2002), and elevated inflammatory responses increase the amount of circulating proinflammatory cytokines that can change the central nerve system (Perry, 2004). In addition, it has been suggested that inflammatory cytokines can stimulate Aβ production and attenuate the secretion of APPs (Blasko et al., 1999; Buxbaum et al., 1992). Thus, the association between chronic infection and AD has been intensively studied to prevent cognitive deficits (Panza et al., 2019). Since neuroinflammation can occur via infiltration from Gram-negative bacteria, such as *Chlamydia pneumoniae* and *Porphyromonas gingivalis* (MacIntyre et al., 2003; Shoemark and Allen, 2015), LPS, which is a cell wall component of

Gram-negative bacteria, has been widely used to construct cognitive deficit animal models. Injection of LPS (0.25–1 mg/kg·bw/d) in the abdominal cavity of mice for 4–7 consecutive d could produce neuroinflammatory responses with cognitive impairments. LPS can also be administered directly to brain tissue via ICV injection (Kamdi et al., 2021; Shoemark and Allen, 2015; Yang et al., 2020a). A single ICV injection of LPS (2–12 μg) solution using a micro syringe or stereotaxic coordinates could induce neuroinflammatory responses with cognitive deficits from 1–7 d after injection (Zhao et al., 2019; Zhou et al., 2006). Therefore, an LPS-induced animal model could be used to evaluate the anti-cognitive deficit effects of probiotics. In fact, the *L. plantarum* NK51 and *Bifidobacterium longum* KN173 strains were reported to have preventive activity against LPS-induced neuroinflammation (Lee et al., 2021), and probiotic mixtures (*Lactobacillus helveticus* R0052 and *B. longum* R0175) were also proven to have anti-cognitive deficit effects on LPS-induced rat models (Mohammadi et al., 2019). In addition, it was reported that an oral gavage of *Lactococcus lactis* subsp. *cremois* LL95 (1×10^9 CFU/d/mice) for 7 d ameliorated mood disorders in an LPS-induced depression-like mice model (Ramalho et al., 2022), and the administration of a probiotic mixture (*Bifidobacterium animalis* subsp. *lactis* BL03, *B. animalis* subsp. *lactis* BI04, *B. breve* BB02, *Lactobacillus acidophilus* BA05, *L. helveticus* BD08, *L. paracasei* BP07, *L. plantarum* BP06, and *Streptococcus thermophilus* BT01; 1×10^9 CFU/d/mice) for 15 d attenuated LPS-induced pro-inflammatory responses and sickness behavior (Petrella et al., 2021). These reports suggest that probiotics could be developed as effective agents that can ameliorate LPS-mediated neuroinflammation and cognitive deficits.

Transgenic Animal Models that Have Cognitive Deficit Phenotypes

Various transgenic animal models that show cognitive impairment have been developed. Each mouse line showed subtly different characteristics in neuronal development and behavior disorders. The characteristics of the cognitive deficit transgenic animal models used for evaluating the anti-cognitive deficit effects of probiotics are summarized in Table 2, and the probiotic strains, treatment conditions, and behavior changes are listed in Table 3.

Senescence-accelerated mouse (SAM)

The senescence-accelerated mouse prone 8 (SAMP8) mouse line is derived from mice that have a naturally accelerated aging phenotype (Takeda et al., 1981). The SAMP8 mouse line shows an age-dependent increase in Aβ in the hippocampal area from 4 to 12 months after birth. SAMP8 mice exhibit age-associated cognitive impairment (from 8 to 10 months), reduced anxiety-like behavior, and reduced lifespan (Miyamoto et al., 1986; Miyamoto et al., 1992). Although the detailed molecular mechanisms behind early senescence in SAMP8 mice have not been fully elucidated, excessive oxidative stress has been suggested as a cause of cognitive dysfunction in the SAMP8 mouse line (Morley et al., 2012). Therefore, the SAMP8 mouse line could be an excellent animal model for studying age-dependent cognitive deficits.

Intriguingly, reports have shown that short- and long-term memory loss in SAMP8 mice was attenuated through the oral administration of a probiotic mixture (Yang et al., 2020b). SAMP8 mice (9-month-old males) were orally administered ProBiotic-4, a mixture of *B. lactis* (50%), *Bifidobacterium bifidum* (12.5%), *L. acidophilus* (12.5%), and *Lacticaseibacillus casei* (25%), for 12 weeks, and showed that memory deficits and neuronal injury were improved, and aging-related disruption of the intestinal barrier was attenuated. These results suggest that SAMP8 mice could be used as an animal model to evaluate probiotic effects on age-related cognitive impairment.

Table 2. **Transgenic mouse models that have cognitive deficit phenotypes**

	Name	Promoter	Mutation(s)	Symptoms	Refs
Senescence-accelerated mouse prone (SAMP)	SAMP8 mice	–	–	Age-associated increase in Aβ deposition in hippocampal from 4 to 12 mon ⇒ Astrogliosis, microgliosis, and cognitive deficits	(Takeda et al., 1981)
Single *APP* knock-in	*App*$^{NL-G-F}$ mice	Endogenous *APP*	*APP*$^{KM670/671NL, E693G, I716F}$	Aβ plaque deposition observed starting at 2 mon and is nearly saturated by 7 mon ⇒ Gliosis and cognitive deficits	(Guerreiro et al., 2010; Mullan et al., 1992; Nilsberth et al., 2001)
Double transgenic *APP*-Tg × *PSEN1*-Tg	*APP/PS1* transgenic mice	Mouse Thy1 (*APP*, *PS1*)	*APP*$^{KM670/671NL}$ *PS1*^{I166P}	Aβ plaque deposition starting at approximately 6 wk of age in the neocortex ⇒ Astrogliosis, microgliosis, formation of dystrophic neuritis, neuronal loss, and cognitive deficits	(Maia et al., 2013; Radde et al., 2006)
	5xFAD transgenic mice	Mouse Thy1.2 (*APP*, *PS1*)	*APP*$^{KM670/671NL, I716V, V717I}$ *PS1*$^{M146L, L286V}$	Neuron loss occurs in multiple brain regions beginning at 6 mon of age ⇒ Astrogliosis, microgliosis, neuronal loss, and cognitive deficits	(Devi and Ohno, 2010; Oakley et al., 2006)
Triple transgenic	3xTg-AD mice	Mouse Thy1.2 (*APP*) Endogenous (*PS1*)	*APP*$^{K670N, M671L}$ *PS1*^{M146V} *MAPT*^{P301L}	Aβ deposition with intracellular immunoreactivity detected in some brain regions as early as 3–4 mon of age ⇒ Gliosis and cognitive deficits	(Oddo et al., 2003)

Aβ, amyloid beta; APP, amyloid precursor protein; Tg, transgenic; PS1, presenilin-1; Thy, promotor of Thy-1 cell surface antigen gene; FAD, familial Alzheimer's disease; MAPT, microtubule-associated protein Tau.

App^{NL-G-F} mice

The *App*$^{NL-G-F}$ mice are transgenic mice constructed by the knock-in of the *APP* gene containing four amino acids. In *App*$^{NL-G-F}$ mice, the lysine (K) and methionine (M) amino acids at the 670/671 positions of the *APP* gene are substituted with asparagine (N) and leucine (L), respectively (KM670/671NL). In addition, isoleucine (I) at the 716 position and glutamic acid (E) at the 693 position of the *APP* gene are mutated to phenylalanine (F) (I716F) and glycine (G) (E693G), respectively. These four mutation sites of the *APP* gene were found in human families that struggled with cognitive deficits (Guerreiro et al., 2010; Mullan et al., 1992; Nilsberth et al., 2001). The *App*$^{NL-G-F}$ mouse line shows aggressive Aβ amyloidosis in an age-dependent manner. *App*$^{NL-G-F}$ mice show Aβ deposition from 2 months after birth, and maximum memory impairment is shown at 12 months (Mehla et al., 2019; Saito et al., 2014). Therefore, *App*$^{NL-G-F}$ mice are considered to have cognitive deficits in animal models that represent the typical Aβ pathology.

It was reported that the oral administration of VSL#3, a probiotic mixture (1.28×10^9 CFU/d/mice) that consists of *L. plantarum*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *L. paracasei*, *L. acidophilus*, *B. breve*, *B. longum*, *Bifidobacterium infantis*, and *Streptococcus salivarius* subsp. *thermophiles*, for 8 weeks reduced intestinal inflammation and anxiety-like behavior in *App*$^{NL-G-F}$ mice (Kaur et al., 2020a; Kaur et al., 2020b). Although not many probiotic trials on *App*$^{NL-G-F}$ mice have been reported, *App*$^{NL-G-F}$ mice are thought to be an attractive animal model for estimating the probiotic effects on Aβ amyloidosis.

Amyloid precursor protein (APP)/presenilin-1 (PS1) transgenic mice

APP/PS1 transgenic mice are created by introducing a human *APP* gene containing KM670/671NL mutations and PS1

Table 3. Effects of probiotics on cognitive deficits in animal models

Animal models		Strains (age, sex)	Proposed disease models	Probiotics (sources)	Doses	Effects	Behavior experiments	Refs
Chemical-induced cognitive deficit animal models	D-Galactose induced mice	C57BL/6J (20-wk-old males)	Alzheimer's disease	*Lactobacillus pentosus* var. *plantarum* C29 (Kimchi)	1×10^{10} CFU/d/mouse for 5 wk	Improvement of spatial memory and non-declarative connecting memory functions	Y-maze Morris water maze Passive avoidance	(Woo et al., 2014)
		C57BL/6J (8-wk-old males)	Alzheimer's disease	*Lactobacillus paracasei* PS23 (Fermented milk)	1×10^{10} CFU/d/mouse for 9 wk	Improvement of spatial memory	Morris water maze Open field	(Cheng et al., 2022)
		ICR (males)	Alzheimer's disease	*Bacillus coagulans* JA845 (Fermented pickle)	1×10^{9} CFU/d/mouse for 10 wk	Improvement of spatial memory	Morris water maze	(Song et al., 2022)
	Aβ induced mice	ddY mice (10-wk-old males)	Alzheimer's disease	*Bifidobacterium breve* A1 (Yogurt)	1×10^{9} CFU/d/mouse for 10 d	Improvement of spatial memory and non-declarative connecting memory functions	Y-maze test Passive avoidance	(Kobayashi et al., 2017)
		C57BL/6J (8-wk-old males)	Alzheimer's disease	*B. breve* NMG *B. breve* MY *B. breve* CCFM1025 *B. breve* XY *B. breve* WX (Human feces)	0.6×10^{9} CFU/d/mouse for 6 wk	Improvement of spatial memory and non-declarative connecting memory functions	Y-maze Morris water maze Passive avoidance	(Zhu et al., 2021)
	Scopolamine induced mice	Swiss albino (Females)	Alzheimer's disease	*Lactobacillus rhamnosus* UBLR-58 (Kimchi)	1×10^{9} CFU/d/mouse for 10 d	Improvement of spatial memory	Morris water maze	(Patel et al., 2020)
		ICR (6-wk-old males)	Alzheimer's disease	*Lactobacillus johnsonii* CJLJ103 (Human feces)	1×10^{9} CFU/d/mouse for 5 d	Improvement of spatial memory and non-declarative connecting memory functions	Y-maze Passive avoidance	(Lee et al., 2018)
	LPS-induced mice	C57BL/6 (8-wk-old males)	Alzheimer's disease	*Lactococcus lactis* subsp. *cremoris* LL95 (Mozzarella cheese)	1×10^{9} CFU/d/mouse for 7 d	Improvement of spatial memory	Sucrose preference Open field Forced swim	(Ramalho et al., 2022)
		C57BL/6 (6-wk-old males)	Alzheimer's disease	*Bifidobacterium longum* NK173 *L. plantarum* NK151 (Human feces)	1×10^{9} CFU/d/mouse for 5 d	Improvement of spatial memory	Y-maze, Novel object recognition	(Lee et al., 2021)
		C57BL/6J, (8-wk-old males)	Alzheimer's disease	*Bifidobacterium animalis* subsp. *lactis* BL03 *B. animalis* subsp. *lactis* BI04 *B. breve* BB02 *Lactobacillus acidophilus* BA05 *Lactobacillus helveticus* BD08 *L. paracasei* BP07 *L. plantarum* BP06 *Streptococcus thermophilus* BT01 (Human feces)	1×10^{9} CFU/d/mouse for 15 d	Improvement of spatial memory Finding space well has the effect of reducing anxiety symptoms	Open field Plus maze	(Petrella et al., 2021)
Transgenic mouse models which have cognitive deficits phenotypes	SAMP8 mice	9-mon-old (Male)	Alzheimer's disease	ProBiotic-4 (*B. lactis*, *Lacticaseibacillus casei*, *Bifidobacterium bifidum*, *L. acidophilus*) (Fermented milk)	2×10^{9} CFU/d/mouse for 12 wk	Improvement of spatial memory and non-declarative connecting memory functions	Y-maze Passive avoidance	(Yang et al., 2020b)

Table 3. Effects of probiotics on cognitive deficits in animal models (continued)

Animal models		Strains (age, sex)	Proposed disease models	Probiotics (sources)	Doses	Effects	Behavior experiments	Refs
Transgenic mouse models which have cognitive deficits phenotypes	*App*$^{NL-G-F}$ mice	6–8 mon old (Female)	Alzheimer's disease	VSL#3 (*L. plantarum*, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *L. paracasei*, *L. acidophilus*, *B. breve*, *B. longum*, *Bifidobacterium infantis*, and *Streptococcus salivarius* subsp.) (Yogurt, fermented milk)	1.28×10^9 CFU/d/mouse for 8 wk	Finding space well has the effect of reducing anxiety symptoms	Cross-maze rodent behavior	(Kaur et al., 2020b)
		6–8-mon-old (Female)	Alzheimer's disease	VSL#3 (*L. plantarum*, *L. delbrueckii* subsp. *bulgaricus*, *L. paracasei*, *L. acidophilus*, *B. breve*, *B. longum*, *B. infantis*, and *S. salivarius* subsp.) (Yogurt, fermented milk)	1.28×10^9 CFU/d/mouse for 8 wk	Improvement of non-declarative connecting memory functions	Passive avoidance	(Kaur et al., 2020a)
		6-mon-old (ND)	Alzheimer's disease	*Clostridium butyricum* WZMC1016 (Milk and cheeses)	0.2×10^9 CFU/d/mouse for 4 wk	Improvement of spatial memory	Morris water maze Object recognition	(Sun et al., 2019)
		6-mon-old (Male)	Alzheimer's disease	*L. plantarum* ATCC 8014 (Fermented milk)	1×10^9 CFU/d/mouse for 12 wk	Improvement of spatial memory and working memory	Spontaneous locomotor activity test Nest building, Novel object recognition Morris water maze Shuttlebox	(Wang et al., 2020)
		4-mon-old (ND)	Alzheimer's disease	*B. lactis* Probio-M8 (Yogurt)	2×10^{10} CFU/d/mouse for 45 d	Improvement of spatial memory and working memory	Novel object recognition Y-maze	(Cao et al., 2021)
		8-wk-old (Male)	Alzheimer's disease	SLAB51 (*S. thermophilus*, *B. longum*, *B. breve*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, *Levilactobacillus brevis* [Yogurt])	4×10^9 CFU/d/mouse for 4 mon	Improvement of spatial memory and working memory and non-declarative connecting memory functions	Open field Novel-object recognition Passive avoidance	(Bonfili et al., 2017)
	3xTg-AD mice	12-wk-old (Male)	Alzheimer's disease	*Ligilactobacillus salivarius* CUL61, *L. paracasei* CUL08, *B. bifidum* CUL20, *B. animalis* subsp. *lactis* CUL34 (Fermented milk)	5×10^8 CFU/d/mouse for 12 wk	Improvement of spatial memory and working memory	Novel object recognition Open field	(Webberley et al., 2022)
		6-mon-old (Male)	Alzheimer's disease	*B. longum* NK46 (Human feces)	1×10^9 CFU/d/mouse for 8 wk	Improvement of spatial memory and non-declarative connecting memory functions	Y-maze Morris water maze Passive avoidance	(Lee et al., 2019)
	5xFAD-Tg mice	3-mon-old (ND)	Alzheimer's disease	*B. bifidum* BGN4 and *B. longum* BORI (Human feces)	1×10^9 CFU/d/mouse for 30 d	Improvement of spatial memory	A contextual fear conditioning test Y-maze Morris water maze	(Kim et al., 2021a)

Aβ, amyloid beta; LPS, lipopolysaccharide; SAMP8, senescence-accelerated mouse prone 8; ND, not determined; Tg, transgenic; FAD, familial Alzheimer's disease.

(PSEN1) possessing an L166P mutation. *APP/PS1* transgenic mice exhibit increased Aβ production in an age-dependent manner, and Aβ deposition is detected in the neocortex from approximately 6 weeks after birth. Aβ deposition on the hippocampus can be detected from 3 to 4 months of age, and *APP/PS1* transgenic mice are known to show spatial learning and memory impairment from 7 months of age (Lok et al., 2013; Radde et al., 2006).

APP/PS1 transgenic mice have also been used to estimate probiotics' effects on cognitive deficits. Oral administration of the *L. plantarum* ATCC 8014 strain (1×10^9 CFU/d/mice) to *APP/PS1* mice for 12 weeks ameliorated Aβ deposition in the hippocampus and cognitive impairment (Wang et al., 2020). The administration of *B. lactis* Probio-M8 (2×10^{10} CFU/d/mice) to *APP/PS1* transgenic mice for 45 d attenuated Aβ plaque formation and improved spatial working memory, which was estimated by using the Y-maze test (Cao et al., 2021). Sun et al. (2019) reported that the daily administration of *Clostridium butyricum* WZMC1016 (0.2×10^9 CFU/d/mice) for 4 weeks effectively ameliorated Aβ deposition, microglia activation, and cognitive impairments in *APP/PS1* transgenic mice. The evidence strongly suggested that *APP/PS1* transgenic mice could be used to evaluate probiotics' effects on age-dependent amyloid deposition accompanied by cognitive dysfunction.

3x Transgenic (Tg)-Alzheimer's disease (AD) mice

3xTg-AD mice are developed by integrating the three mutated AD-related genes, specifically *APP*, *PSEN1*, and microtubule-associated protein Tau (*MAPT*). 3xTg-AD mice harboring *APP* (KM670/671NL), *PSEN1* (M146V), and *MAPT* (P301L) genes showed progressive Aβ deposition from 3 to 4 months of age, and hyperphosphorylated tau protein could be detected at 12–15 months of age (Oddo et al., 2003). 3xTg-AD mice were reported to have mildly impaired spatial learning and memory function, and the Barnes maze test was determined to be the most sensitive way to estimate cognitive deficits in 3xTg-AD mice (Stover et al., 2015). Thus, 3xTg-AD mice have been recognized as a valuable animal model for estimating anti-AD therapeutics.

3xTg-AD mice have also been used to evaluate the anti-AD effects of probiotics. Bonfili et al. (2017) reported that oral treatment with SLAB51, a probiotic mixture that consists of *S. thermophilus*, *B. longum*, *B. breve*, *B. infantis*, *L. acidophilus*, *L. plantarum*, *L. paracasei*, *L. delbrueckii* subsp. *bulgaricus*, and *Levilactobacillus brevis*, to 3xTg-AD mice (8-week-old males) for 4 months attenuated Aβ aggregation, brain damage, and cognitive decline. Another probiotic mixture, Lab4b, which consists of *Ligilactobacillus salivarius* CUL61 (NCIMB 30211), *L. paracasei* CUL08 (NCIMB 30154), *B. bifidum* CUL20 (NCIMB 30153), and *B. animalis* subsp. *lactis* CUL34 (NCIMB 30172), was proven to have anti-AD effects on the 3xTg-AD mouse model. Oral treatment with Lab4b (5×10^8 CFU/d/mice) in 12-week-old 3xTg-AD mice for 12 weeks improved recognition memory sensitivity, which was estimated using the novel objection recognition test (Webberley et al., 2022). Collectively, these reports support the possibility of using 3xTg-AD mice to evaluate the anti-cognitive impairment effects of probiotics.

5x Familial Alzheimer's disease (FAD) mice

It has been reported that mutations in AD-related genes, such as *APP* and presenilins (PS1 and PS2), are closely associated with FAD, which express high levels of Aβ. 5xFAD mice is an *APP/PS1* transgenic mouse model that expresses five FDA mutations ($APP^{KM670/671NL}$, APP^{I716V}, APP^{V717I}, $PSEN1^{M146L}$, and $PSEN1^{L286V}$) that result in the rapid accumulation of cerebral Aβ. The advantage of 5xFAD mice is that intraneuronal Aβ accumulation was detected at 1.5 months of age, which is relatively early, and neuronal loss started from 6 months of age with amyloidosis. In addition, it was reported that the impairment of spatial working memory was detected at 4–5 months (Devi and Ohno, 2010; Oakley et al., 2006). Therefore,

5xFAD mice could be used as an animal model for estimating the effects of anti-cognitive deficit agents.

Several reports have assessed functional probiotics against AD-like phenotypes by using 5xFAD mice. Lee et al. (2019) reported that *B. longum* NK46, which is isolated from human fecal matter, has anti-AD effects. Oral administration of *B. longum* NK46 (1×10^9 CFU/mouse/d) to 5xFAD mice (6 months old) for 1 and 2 months attenuated the hippocampal accumulation of Aβ and cognitive decline. *B. bifidum* BGN4 and *B. longum* BORI were also reported to have anti-AD activities in 5xFAD mice. The administration of a probiotic mixture (*B. bifidum* BGN4+*B. longum* BORI; 1×10^9 CFU/mouse/d) to 5xFAD mice (3 months old) for 30 d inhibited the loss of hippocampal neurons and cognitive decline estimated by the Y-maze test (Kim et al., 2021a). These reports suggest that 5xFAD, which exhibits AD-like physiology at a relatively early stage, could be an excellent animal model for evaluating the anti-cognitive deficit activity of probiotics.

Conclusion

Several animal models for cognitive impairment have been developed. If these animal models are properly used to estimate the anti-cognitive deficit activity of probiotics, more efficient and powerful probiotic-based anti-neurodegenerative disease agents could be developed. Additionally, these approaches will shed light on the detailed molecular mechanisms behind how probiotics modulate the gut–brain axis to attenuate the cognitive impairments that occur as a result of neurodegenerative diseases.

Conflicts of Interest

The authors declare no potential conflicts of interest.

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Author Contributions

Conceptualization: Lee SH. Investigation: Kwon OY. Writing - original draft: Kwon OY. Writing - review & editing: Kwon OY, Lee SH.

Ethics Approval

This article does not require IRB/IACUC approval because there are no human and animal participants.

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