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Review Article

Inducing Agents for Alzheimer's Disease in Animal Models

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Abstract

The most prevalent form of dementia, Alzheimer's disease (AD), is a neurological disorder that causes gradual memory loss. AD is characterized by amyloid-beta plaques, neurofibrillary tangles, and neuron loss. While preclinical and clinical trials are underway to reduce the generation and overall brain disease load, current treatment focuses on alleviating symptoms. Animal studies are essential for advancing our understanding of AD, identifying potential drug targets, and testing experimental therapies. An ideal animal model not only exhibits the same symptoms and pathological changes as a human disease but also follows the same sequence of pathological events. This review highlights the various inducing agents used to model AD in animals, such as streptozotocin, aluminium chloride, trimethyltin, lipopolysaccharide, scopolamine, and others, along with their underlying mechanisms. The outcomes of some studies that used such inducing agents to develop AD are discussed briefly. Among chemically induced models, streptozotocin and amyloid-beta are the most frequently used, while d-galactose, scopolamine, and aluminium-induced models are being used because they are non-invasive, reproducible, and compatible. However, none of the chemical/drug-induced models fully capture the scope of AD pathology and cognitive impairment. Overall, further research is necessary to establish the stability of the models in terms of consistency and reproducibility.

Introduction

Alzheimer's disease (AD) is widely recognized as the most prevalent form of dementia, accounting for 60–70% of cases globally. Its incidence is projected to increase due to the aging demographic trends worldwide.[1] AD is a debilitating neurological condition characterized by a gradual decline in cognitive abilities, including memory loss and decreased logical reasoning skills. Over 55 million individuals worldwide have dementia, with more than 60% living in low- and middle-income countries.[2] Every year, about 10 million new cases are reported. The deposition of amyloid-beta (Aβ) plaques and neurofibrillary tangles (NFTs) of hyperphosphorylated tau are hypothesized as the underlying pathologies of AD.[3–5] Deposition of Aβ plaques results from the cleavage of a protein termed amyloid precursor protein (APP), with Aβ 42 identified as potentially hazardous.[6,7] Abnormal amounts of this naturally occurring protein gather between neurons in Alzheimer's patients' brains, forming plaques that damage cell function.[8,9] Hyperphosphorylated tau detaches from microtubules and sticks to other tau molecules, generating threads that eventually unite to create tangles inside neurons, known as NFTs.[10,11] These tangles impair synaptic transmission between neurons by interfering with the transport system inside the neuron.[12]

The International Classification of Diseases-10 identifies different types of AD-related dementia: early onset (familial AD), late-onset (sporadic AD), mixed or atypical, and unspecified. Familial AD is characterized by rapid disease progression, while sporadic AD progresses more gradually.[13] The cut-off age for familial AD and sporadic AD is usually 65 years. The genetic component of familial AD is well understood and heritable, unlike sporadic AD, which affects more than 95% of AD patients and remains poorly understood.[14] This lack of understanding contributes to the poor prognosis and therapeutic challenges associated with sporadic AD.

While there was no cure for AD, several non-medical approaches aimed to support individuals with AD and potentially slow disease progression. These approaches focus on enhancing cognitive function, promoting overall well-being, and improving quality of life.[15,16] For example, cognitive stimulation can be achieved by engaging in mentally stimulating activities such as puzzles, games, brain exercises or encouraging reading, storytelling, and discussions. Regular physical activity walking, swimming, and gentle exercises can improve overall health and well-being. Another approach is encouraging a balanced and nutritious diet rich in antioxidants, omega-3 fatty acids, and vitamins. Lifestyle changes,

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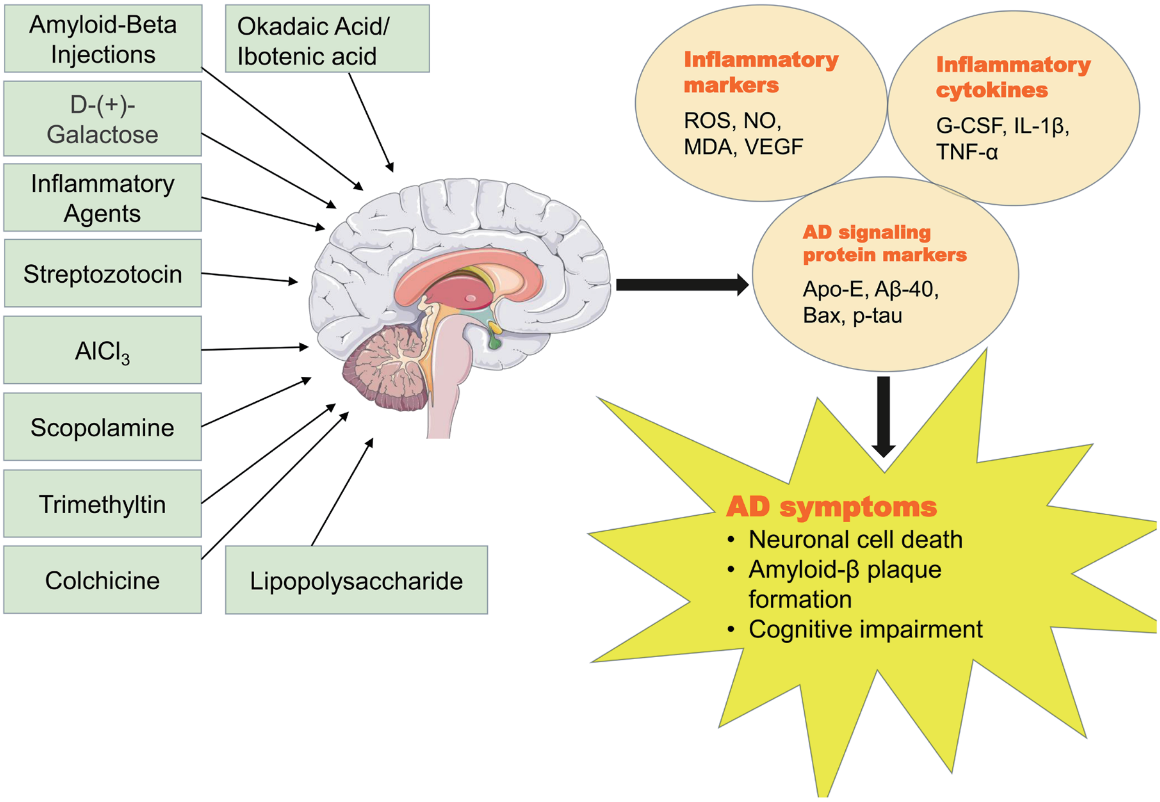

Fig. 1. Various approaches and agents used in animal studies to induce AD. $AlCl_3$: Aluminium chloride; Apo-E: Apolipoprotein E; Aβ-40: amyloid β-40; Bax: Bcl-2-associated X protein; G-CSF: granulocyte-colony stimulating factor; IL-1β: Interleukin-1 beta; MDA: malondialdehyde; NO: nitric oxide; p-tau: phosphorylated tau; ROS: reactive oxygen species; TNF-α: Tumor necrosis factor alpha; VEGF: Vascular endothelial growth factor.

such as maintaining social connections, engaging in music therapy and creative activities such as painting, crafting, ensuring a regular sleep routine and addressing any sleep-related issues, and creating a safe and supportive environment, may help manage the behavioral and psychological symptoms associated with AD.

Researchers conducted various studies on animal models to better understand AD and develop potential treatments or interventions. These studies used substances to induce specific pathological features associated with AD rather than inducing the disease as it naturally occurs in humans. Instead, researchers aimed to replicate certain aspects of the disease process to study its mechanisms and test potential therapeutic approaches. Various approaches and agents are used in animal studies related to AD (Fig. 1). Transgenic mouse models in which researchers often use genetically modified mice that express human genes associated with AD, such as mutant forms of the APP or presenilin genes.[13,17–19] These mice can develop amyloid plaques and other pathological features of Alzheimer's disease. Another approach is the Aβ injections, where synthetic or purified Aβ protein is injected into the brains of animals, usually rodents,[20–23] leading to amyloid plaque formation and neuroinflammation, mimicking aspects of Alzheimer's pathology. Tau protein abnormalities are another hallmark of AD. Researchers may also use animal models that overexpress abnormal tau proteins or inject tau aggregates to study their role in the disease.[24–26] Some studies investigate the effects of environmental toxins or chemicals, such as aluminium or certain pesticides, on the development or progression of Alzheimer's-like pathology in animal models.[27,28] Along with Aβ and NFTs, chronic inflammation is a critical underlying factor in the pathogenesis of AD,[29] and researchers have used agents to induce neuroinflammation in animals to study its impact on the brain and cognitive function.

This review provided an overview of the several inducing agents employed in animal models to simulate AD, including streptozotocin, aluminium chloride, trimethyltin, lipopolysaccharide, and scopolamine, along with their underlying mechanisms. The discussion briefly encompassed the outcomes of several investigations that employed these inducing approaches in AD development.

Inducing approaches for Alzheimer's disease

Aluminium chloride ($AlCl_3$)

Prolonged exposure or chronic administration of heavy metals to mice has been observed to induce significant toxicity, leading to the development of many diseases, including neurotoxicity. Most studies have focused on the effects of aluminium, among other heavy metals, on biological systems.[30,31] Abnormally high quantities of aluminium are found in the brains of Alzheimer's patients, which has toxicological consequences, including encephalopathy, bone disease, and anemia.[32] It was documented that oxidative stress, cholinergic insufficiency, and the accumulation of Aβ and NFTs occurred in the brains of rats following oral administration of aluminium at a dosage of 300 mg/kg body weight.[33] Oxidative stress and mitochondrial malfunction are the major causes in an $AlCl_3$ model, manifested by blocking the NADH dehydrogenase enzyme in the electron transport chain of the cortical and hippocampal regions.[34] In addition, neurodegeneration results from changes in neuroinflammatory mediators and proinflammatory cytokines in an $AlCl_3$ model.

Neuronal cell death may result from aluminium ion-induced calcium homeostasis dysregulation, which causes an aberrant increase of Ca^{2+} in mitochondria and disrupts normal cellular physiological processes. Aluminium ions can lead to the accumulation of Aβ and hyperphosphorylation of Tau proteins, resulting in neuronal death in the brain.[35]

Z. Firdaus *et al*.[36] examined the impact of *Centella asiatica* ethanolic extract on $AlCl_3$-induced neurological disorders in rats. The study's findings demonstrated that $AlCl_3$ causes cognitive impairment (memory and learning deficits, anxiety, and reduced locomotion) as well as oxidative stress, cholinergic impairment, and histological changes in the brains of rats.[36] Similarly, Zhao Y *et al*.[37] 2020 studied the neuroprotective potential of syringic acid on $AlCl_3$-stimulated behavioral deficits and neuroinflammation in rat AD models. The results showed that AD rats displayed reduced memory and learning impairments, augmented short-term memory loss, and diminished locomotion activity.[37] The syringic acid supplementation appreciably stabilized the AD rats' neurobehavioral impairments. Furthermore, Chen X. *et al*.[38] induced AD in Sprague Dawley rats by oral administration of 175 mg/kg of $AlCl_3$ for 25 days to study the protective effect of ononin treatment on AD (Table 1).[36–57] The result showed that ononin treatment effectively modulated the $AlCl_3$-triggered behavioral alterations in AD animals. The levels of interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), p38 mitogen-activated protein kinases (p38MAPK), acetylcholine esterase, malondialdehyde (MDA), and nuclear factor kappa B (NF-κB) were suppressed, while the brain-derived neurotrophic factor (BDNF) and peroxisome proliferator-activated receptor-γ (PPAR-γ) contents were elevated in the brain tissues of AD animals.[38] Other studies used $AlCl_3$ in doses of 17 mg/kg for four successive weeks and 50 mg/kg/day in rats to induce AD.[58,59] Taken together, the variation in $AlCl_3$ dose and duration of administration to induce AD necessitate further studies to determine the most suitable dose and route of administration.

Streptozotocin (STZ)

Streptozotocin (STZ), or 2-deoxy-2-(3-(methyl-3-nitrosoureido)-D-glucopyranose), is a naturally occurring antibiotic produced by Streptomyces achromogenes and derived from glucosamine nitrosourea.[60] The most widely used model for sporadic AD in rodents is based on the effects of STZ, which matches the sporadic form in humans.[61] The intracerebroventricular (ICV) administration of STZ elicits a distinct influence on the central nervous system (CNS) without noticeable effects on peripheral regions.[62] Brain biochemistry, metabolism, and functions, including glucose uptake and energy consumption, oxidative tissue stress, cholinergic deficiency, and cognitive capacities, are severely and persistently impacted by ICV treatment with STZ. These effects lead to hippocampus-dependent cognitive loss, including difficulties with spatial learning and memory, as well as neurodegeneration, inflammation, and synaptic malfunction.[63] Moreover, STZ induces neuronal injury and hyperphosphorylation of tau, leading to the release of reactive oxygen species (ROS) and reactive nitrogen species.[64] In addition, the neuroinflammation associated with sporadic AD is related to changes in the number and shape of astrocytes and microglia in particular brain areas following STZ injection.[65,66] Overall, these features validate the relevance of animal models of Alzheimer's disease, as loss of spatial memory and disorientation are fundamental markers of the progressive cognitive decline exhibited in AD patients. Various studies have used STZ to induce AD in rodents (Table 1).[39–42] For example, A. Gáspár *et al*. demonstrated the effect of a high dose of STZ (4.5mg/kg) on the learning and memory of Long-Evans rats (23 and 10 months old)[39] using the 5-choice serial reaction time task, the Morris watermaze, and the "pot-jumping" exercise. The 5-choice serial reaction time task(attention) and the pot jumping test (procedural learning) showed significant changes in young STZ-treated rats, while the phospho-tau/tau protein ratio in the hippocampus of aged rats showed a substantial increase. In contrast, cooperative (social) and competitive (visual) memory tests and Aβ levels in the hippocampus were not significantly different. Alvei M. *et al*.[40] studied the pharmacological effect of three doses of levetiracetam (50, 100, and 150mg/kg) on STZ-induced AD rats (3 mg/kg). The results of the passive avoidance and Morris watermaze tasks demonstrated that levetiracetam (100 and 150 mg/kg) considerably reduced STZ-induced learning and memory deficits.

Trimethyltin (TMT)

Trimethyltin (TMT) is an organometallic potent neurotoxic compound that promotes considerable neurodegeneration and neuronal cell death in the central nervous system in the cerebral cortex and hippocampus.[42,43] TMT has been detected in a variety of water sources, including those used for human consumption, as well as in marine ecosystems and aquatic organisms. Environmental exposures during plastic production and other industrial activities where plastic is heated account for most reported cases of TMT poisoning.[67] Neuronal cell death results from TMT's ability to disrupt neuronal membranes. TMT-induction induces intracellular Ca^{2+} overload, mitochondrial damage, and oxidative stress. In addition, TMT exposure can trigger neuroinflammatory responses, characterized by increased levels of pro-inflammatory cytokines such as TNF-α, IL-1β, and nitric oxide, and increased gene expression of the glial fibrillary acidic protein and activated microglia in the brain.[68] Furthermore, TMT signals the development of several components critical to the pathophysiology of AD, including APP, presenilin 1, and others.[43]

However, it's essential to clarify that while TMT can lead to cognitive impairments and neurodegeneration in animal models, it is not considered a direct causative agent for AD in humans. While TMT-induced neurotoxicity and cognitive impairments in animal models can provide insights into certain aspects of neurodegeneration and memory deficits, AD is a complex and multifactorial disease with genetic, environmental, and age-related factors playing significant roles. TMT-induced damage does not replicate the full spectrum of AD pathology, including the aggregation of Aβ and tau proteins, hallmark AD features in humans.

Lipopolysaccharide (LPS)

LPS is a common non-genetically manipulated neuroinflammation model for AD. LPS is an endotoxin found in the cell walls of Gram-negative bacteria, which can cause systemic inflammation, amyloidogenesis, and neuronal cell death.[69] It was hypothesized that LPS elevates Aβ levels, damages oligodendrocytes, and causes myelin destruction in the AD brain by acting on leukocyte and microglial TLR4-CD14/TLR2 receptors, triggering an NF-kB-mediated rise in cytokines.[70] A dose-dependent response of activated microglia and astrocytes was seen following direct LPS infusion into the fourth ventricle of the brains of male rats.[71] Neuroglial activation could be induced at dosages as low as 0.05 ng/h of LPS infusion, while the loss of choline acetyltransferase-positive cells in the basal forebrain was induced only at doses of 50 ng/h or higher.[72]

Table 1. AD studies were conducted in animal models using various inducing agents

AD induction agents/ animal species	Dose of the inducing Agent	Drug/treatment model	Main findings	Reference
$AlCl_3$/Rat	i.p. injection of 100 mg/kg for 60 days	*Centella asiatica* ethanolic extract (CAE) (Oral Daily dose of 150 and 300 mg/kg for 60 days)	$AlCl_3$ causes cognitive impairment, oxidative stress, increased activity of the enzyme AChE, and changes in cellular architecture, although CAE significantly mitigates these effects	36
$AlCl_3$/Rat	100 mg/kg i.p. for 60 days	Syringic acid (25 & 50 mg/kg/day for 30 days)	Syringic acid supplementation in AD rats attenuated the expression of NF-κB, IL-1β, IL-6, and TNF-α.	37
AlCl3/Rat	Oral dose of 175 mg/kg for 25 days.	Ononin (Ononin 30 mg/kg orally from day 25 to day 36)	In the brain tissues of AD rats, ononin significantly reduced acetylcholine esterase, Aβ1-42, and MDA while increasing SOD and overall antioxidant activity	38
Streptozotocin/ Aged and young rat	1.5 mg/kg/day for three days by ICV injection	–	Icv STZ generated impulsive-like behavior, but it did not affect fear learning/memory, visual discrimination, or social learning.	39
Streptozotocin/Rat	3mg/kg/day for three days by ICV injection	Levetiracetam (Treatment regimens of 50, 100, and 150 mg/kg i.p. for 28 days)	The death of neurons in the hippocampus caused by STZ was prevented. hyperphosphorylation of tau was reversed, and oxidative stress markers such as lipid peroxides, glutathione, and AChE activity were all normalized	40
Streptozotocin/ Male Wistar rat	3 mg/kg/day by ICV injection	Galantamine plus methacrylated gelatin (10 mg/kg)	Loss of hippocampal neurons, oxidative stress, and neuroinflammatory alterations were observed in ICV-STZ-treated rat brains, as well as increases in AChE and LPO activity levels.	41
Trimethyltin/ Male Wistar rats	i.p. (8mg/kg)	Crocin (25 or 50 mg/kg)	Successful development of the model and analysis of the results revealed a protective benefit for crocin, as evidenced by an uptick in hippocampal neuronal density and a reduction in inflammatory mediators.	47
Trimethyltin/ Male and female C57BL/6 mice	–	Trans-anethole (10–50 µM dissolved in ethanol)	Trans-anethole inhibits TMT's effect on long-term potentiation (LTP).	43
Trimethyltin/ Male and female C57BL/6 mice	i.p. (2.6 mg/kg)	H_2 gas (2% by inhalation)	TMT-treated mice that inhale 2% H_2 gas show improved memory performance and a reduction in AD, OS, and inflammatory-related markers.	42
Scopolamine/ male Wistar rats.	2mg/kg/day, i.p. for 6 weeks	–	Impaired antioxidative defense systems, increased oxidative stress, mitochondrial dysfunction, apoptosis, and neuroinflammation are just some of the cellular changes induced by scopolamine.	44
Scopolamine/Rats.	0.4 mg/kg by i.p.	Rivastigmine (1.5 mg/kg)	These findings suggest that brain targeting using RT-loaded PLGA and PBCA NP could significantly improve Alzheimer's disease treatment.	48
Scopolamine/Rats.	1mg/kg for 9 days by i.p.	Embelin (0.6 mg/kg)	Embelin has nootropic and neuroprotective properties against scopolamine-induced amnesia in rats.	49
Scopolamine/Rats.	0.7 mg/kg by i.p.	Oleoresins and donepezil by oral (50 mg/kg and 0.5 mg/kg)	When compared to donepezil, oleoresins from spices are more effective at boosting antioxidant levels and decreasing lipid peroxidation caused by scopolamine.	50

(continued)

Table 1. *(continued)*

AD induction agents/ animal species	Dose of the inducing Agent	Drug/treatment model	Main findings	Reference
D-galactose/Mice	1.25 mg/kg, s.c., once daily for 40 days.	Aerobic treadmill exercise (40 days)	D-galactose reduces the SOD and AChE activities. The number of EGF-positive cells and neurons in the CA1 and CA3 areas of the hippocampus was reduced.	51
D-galactose+ $AlCl_3$/Rats	D-galactose (60 mg/kg i.p.) and $AlCl_3$(200 mg/kg orally) OD for 10 weeks.	WIN55,212-2 (cannabinoid agonist; 0.5, 1 and 2 mg/kg/day)	Cognitive impairments and marked neuronal loss in the CA1. A decrease in the expressions of GFAP and Nestin, including increased levels of MDA and decreased levels of SOD and GSH.	52
D-galactose+ $AlCl_3$/Mice	D-galactose (120 mg/kg) and AlCl3 (20 mg/kg) by gavage for 8 weeks	Nervonic acid (10.95 and 43.93 mg/kg)	D-galactose+ AlCl3 decline the locomotion and learning ability through decreased levels of neurotransmitters, such as dopamine, serotonin, and GABA.	45
Colchicine/Rats	–	Donepezil (1mg/kg) and Resveratrol (10mg/kg)	Microglia numbers increased whereas astrocyte count showed no change.	46
Colchicine/Rats	15 µg	Naproxen (10 mg/kg, orally)	Chromatolysis and Plaque formation in the hippocampus was observed. neurodegeneration is time-dependent and mediated by cyclooxygenase-induced neuroinflammation.	53
Okadaic Acid/Mice	100 ng/µL (ICV)	Evodiamine (50 or 100 mg/kg) intragastrically	Increased oxidative stress, is characterized by increased MDA and decreased GSH levels.	54
Okadaic Acid/Rats	100 ng/side (ICV)	India Royal jelly (100, 200, and 400 mg/kg, per oral dose)	Higher free radicals and cytokines that caused inflammation	55
Ibotenic acid/Rats	10 µg/5 µL (ICV)	flavonoids of *Herba Epimedii* (8 and 16 mg/kg)	Impaired learning and memory, neuronal injury and loss, and a pro-apoptotic response were all effects of injecting ibotenic acid into the hippocampus.	56
Ibotenic acid/Rats	5 µg/µL (ICV)	Thymoquinone (5 mg/kg)	Behavioral changes, Hyperplastic astrocytes, necrosis, and severe neuroinflammation induced by the ICV administration of ibotenic acid.	57

$AlCl_3$, Aluminium chloride; AChE, acetylcholinesterase; TMT, Trimethyltin; ROS, reactive oxygen species; NO, nitric oxide; MDA, malondialdehyde; VEGF, Vascular endothelial growth factor; OS, oxidative stress; G-CSF, granulocyte-colony stimulating factor; NF-κB, Nuclear factor kappa B; IL-1β, Interleukin-1 beta; TNF-α, Tumor necrosis factor alpha; Apo-E, Apolipoprotein E; Aβ-40, amyloid β-40; Bax, Bcl-2-associated X protein; p-tau, phosphorylated tau; SOD, Superoxide dismutase; CWS, Cold water stress; i.p., Intraperitoneal injection; ICV, intracerebroventricular; EGF, epidermal growth factor; OD, once daily; CA1, hippocampal conus ammonis 1; GFAP, glial fibrillary acidic protein; GSH, glutathione.

Scopolamine

Scopolamine is a compound that blocks acetylcholine receptors, leading to cholinergic dysfunction and resulting in cognitive impairments reminiscent of those seen in AD.[73] This drug interferes with the cholinergic pathways in brain regions involved in cognition and memory.[74] Recent research indicated that scopolamine causes the buildup of ROS, leading to oxidative stress and memory impairment. The cholinergic theory can be implemented through the intraperitoneal or ICV injection of scopolamine, which causes cognitive abnormalities similar to those seen in AD. Notably, rats show a twofold rise in Aβ protein levels and APP expression levels after six weeks of intraperitoneal administration of scopolamine. Additionally, the activity of tau kinase, which causes tau hyperphosphorylation, and the amount of pTau protein were increased.[44] The scopolamine-induced model has the advantage of not requiring complicated surgical procedures, unlike the ICV model.

Aβ Injections

The accumulation of external amyloid plaques, intracellular NFTs, and a cholinergic deficiency are the main features of AD. In rodent studies, Aβ peptide accumulation in the hippocampus has been linked to worse learning and memory due to alterations in hippocampal long-term potentiation. Dendritic spine and excitatory synapse loss have been related to Aβ oligomers and oxidative stress.[75,76] Results from studies in which synthetic- Aβ 1-42 species were injected into various regions of the brains of non-transgenic rats were often unreliable because of a lack of genuine characterization of the administered Aβ aggregates. Afterward, well-characterized hazardous soluble Aβ 1-42 species (oligomers, protofibrils, and fibrils) were ICV injected into the rat brain to create a more robust model. Studies of the distribution of fluorescently tagged Aβ 1-42 showed that soluble Aβ species spread to all areas of the rat brain. Spatial memory was impaired in the Morris water maze test, and long-term plasticity was damaged in acute hippocampal slices from Aβ-treated mice after seven days.[77] Shahidi S *et al*.[75] used behavioral and electrophysiological techniques to assess the protective effect of N-acetyl cysteine on learning and memory in an Aβ-induced AD model in adult male rats. Passive avoidance test step-through latency was shortened after intrahippocampal Aβ injections, and the amplitude and slope of excitatory postsynaptic potentials in the hippocampal neuron population were also reduced. If Aβ-treated rats were also given N-acetyl cysteine, the deficits caused by Aβ injection were reduced compared to the Aβ-only group.[75] Co-injection of Aβ with another inducing agent, such as ibotenic acid, has been reported,[78,79] leading to significant neuronal death in the injection site and faraway regions, such as CA1, CA4, and the dentate gyrus compared to a single inducing approach.

D-(+)-Galactose

D-galactose, a reducing sugar, is an aldohexose found in many foods, including dry figs, honey, and milk products. Naturally occurring amounts of aldohexose D-galactose are present in the brain and the rest of the body, with a maximum daily recommended amount of 50 g.[80] Nevertheless, it is well-established that exceeding the usual concentration of exogenous D-galactose can cause oxidative stress, apoptosis, and inflammation, producing aging effects in several organs, including the brain.[81] Mitochondrial failure and elevated oxidative stress are significant indicators of brain aging. Long-term injections of D-galactose result in a rise in AGE, RAGE, AR, SDH, telomere length shortening, telomerase activity, BACE-1, and $A\beta_{1\text{-}42}$.[82,83] One of the underlying mechanisms proposed is that when the amount of D-galactose rises, it is converted to H_2O_2 by the enzyme galactose oxidase, causing a drop in SOD. Subsequently, reduced Iron (Fe) reacts with the increased H_2O_2 to produce OH^-.[84] These ROS can harm neurons by impairing redox equilibrium and causing lipid peroxidation in cell membranes.

Several recent studies used D-Galactose combined with another agent, such as $AlCl_3$ or $A\beta_{25–35}$, to induce AD-like symptoms, including cognitive and memory impairments, oxidative damage, and inflammation.[35,45,85,86] D-galactose can accelerate the overproduction of ROS, and $AlCl_3$ intervention can cause neurotoxicity.[45] The body's metabolism of D-galactose and $AlCl_3$ results in D-galactitol, which the organism fails to metabolize. This leads to an increase in osmotic pressure, disrupting the typical morphology of hippocampus neurons and causing a gradual decline in neurological function.[45,87,88]

Colchicine

Colchicine is a medication commonly used to treat gout and arthritis. It works by reducing inflammation and pain. However, colchicine has been associated with neurological side effects, including cognitive impairment and memory loss, which can resemble symptoms seen in AD.[89] The exact mechanism by which colchicine might induce AD-like symptoms is not completely clear. However, proposed mechanisms include disruption of microtubule function, potential impact on inflammation in the brain, interference with mitochondrial function, contribution to oxidative stress, and possible disruption of the blood-brain barrier.[46,90]

Colchicine has been used for the induction of AD in animal models in several research (Table 1).[46,91–94] It has been proposed that the inflammatory action could be caused by cycloxygenase-2 (COX-2), prostaglandin E2 (PGE2), IL-1β, and TNF-α. The expression of COX-2 mRNA in dentate gyrus granule cells is significantly upregulated, and morphological changes associated with cell death are observed in rats following intrahippocampal injection of colchicine.[95] It's important to note that no research has examined this model's specific sequence of pathogenic events and cognitive impairment. As a result, whether the observed alterations in the colchicine-induced model align with the inflammatory hypothesis of AD remains an open question.

Okadaic acid

Okadaic Acid (OA) is a marine toxin produced by certain types of dinoflagellates, and it is well-known for its inhibitory effect on protein phosphatases, particularly protein phosphatase 1 and protein phosphatase 2A.[96] The disruption of normal protein phosphorylation and dephosphorylation processes can have various cellular effects, including alterations in the cytoskeleton, cell cycle progression, and apoptosis. In neurodegenerative diseases, disruptions in protein phosphorylation are often associated with the formation of abnormal protein aggregates, such as tau tangles in AD. Research has shown that OA causes cellular death and tau phosphorylation, produces intracellular ROS, and activates MAPK signaling.[97] In addition, cultured hippocampus neuronal cells exposed to OA increased Ca2+ through ionotropic excitatory amino acid receptors, resulting in neuronal cell death.[98]

To investigate the effect of IMM-H004 on OA-induced learning and memory deficits in rats, a prior study used 200 ng/5 µL of OA administered unilaterally via ICV injection.[99] The results showed that OA-treated rats demonstrated substantial impairments in spatial memory in the Morris water maze test. In addition, the hippocampus showed considerable increases in tau phosphorylation, Aβ protein deposition, and cell death. Another study found that rats that received a single ICV injection of OA (200 ng/10 µL) on both sides exhibited notable behavioral impairments, including nesting behavior, short-term working, image discrimination, and spatial discrimination memory.[100] Moreover, the hippocampus and prefrontal cortex showed a substantial increase in the frequency of pT231-tau immunoreactive cells, along with other abnormalities such as an expanded cell body and highly stained cytoplasm. Furthermore, a significant increase in the protein expression of pS396-tau, pT231-tau, and pS202/205-tau and a decreased number of neurons in the hippocampus and prefrontal cortex were observed.

Ibotenic acid

Ibotenic acid is a naturally occurring amino acid found in certain mushrooms, particularly in species of the Amanita genus. Researchers use ibotenic acid to create lesions or induce specific patterns of neural damage in laboratory animals, allowing them to study the effects on behavior, cognition, or cellular processes. Research has demonstrated that ibotenic acid causes considerable neuronal death in the cortex, substantia nigra, striatum, and hippocampus, as well as intense gliosis around the sites of neuronal death.[101] Ibotenic acid shares structural similarities with glutamate, an excitatory neurotransmitter, and is a potent N-methyl-D-aspartate receptor agonist, resulting in sustained activation and excitotoxicity.[102] The outcome is increased water entry into the neurons caused by osmotic lysis and an overabundance of chloride and calcium ions.[103] Additionally, ibotenic acid affects cholinergic cells in the ventral pallidum and substantia innominate complex and causes neuronal death throughout the nucleus basalis of the Meynert complex. Research has shown that rats can experience neuroinflammation and neurodegeneration due to cortical cholinergic dysfunction caused by ICV injections of ibotenic acid.[102,104] The proposed mechanism for neuroinflammation and neuronal cell death involves influencing both local microglia and protoplasmic astrocytes. The advantage of this toxin model is the similarities between the pathophysiology in AD models in rodents and the cholinergic situation in human patients. However, the invasive method and high mortality rate are two drawbacks of this model.

Future directions

Scientists are continually refining and developing new animal models that better recapitulate the complexity of AD, including the genetic and environmental factors contributing to the disease's heterogeneity. It's important to highlight that these studies aim not to induce AD in animals but to create models that recapitulate specific aspects of the disease's pathology. Animal studies are essential for advancing our understanding of AD, identifying potential drug targets, and testing experimental treatments. However, findings from animal studies must be interpreted cautiously, as they may not always translate directly to humans.

The complicated pathophysiology of AD means that there are currently no reliable models of early-stage AD. In the intermediate to late stages of AD, most models show that pathogenic events and cognitive impairment emerge rapidly. Most people with AD first experience mild cognitive impairment and subjective cognitive decline before the disease progresses to definitive AD, which can take many years in humans. To better understand the early pathological changes associated with AD and to find potential treatments, further animal models of mild cognitive impairment and subjective cognitive decline are required since late-onset sporadic AD is the most prevalent form of AD. These animal models should not only display clinical episodes comparable to actual AD but also undergo gradual cognitive deterioration over an extended period. Additionally, some limitations require to be addressed in future research. The surgical techniques, dosage of the inducing agent, and the efficacy of the therapeutic molecule can differ among researchers. Repeated administration of the therapeutic molecule within animal models may not consistently yield the anticipated outcomes. While amyloid infusion may benefit therapeutic research, it fails to elucidate the underlying causes and solely concentrates on the neurotoxic effects induced by amyloid oligomers. Furthermore, the utilization of excitotoxins is not exclusive to cholinergic neurons in the basal nuclear projections into the cortex, thus not adequately depicting the observed pathology in AD. Overall, further research is necessary to establish the stability of the models in terms of consistency and reproducibility.

Conclusion

AD is a progressive neurological condition, and its exact causes are still not fully understood. Aβ plaques and tau tangles are two aberrant proteins that accumulate in the brain of people with AD, causing cognitive decline and memory loss. While various studies and experiments have been conducted on animals to better understand the disease, these studies typically involve genetic manipulation or the administration of substances that mimic some of the pathological features of AD. These studies aim to gain insights into the disease's mechanisms and develop potential treatments. Thus, these AD-inducing agents are helpful pharmacological tools to study, to some extent, the cellular and molecular changes related to AD pathogenesis. Further research is required to optimize the inducing dose and to discover models that can cover the full scope of AD pathogenesis.

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Conflict of interest

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Author contributions

Concept and design (KK, YS), acquisition of data (KK, NAE), drafting of the manuscript (KK, NAE), critical revision of the manuscript for important intellectual content (KK, NAE, YS), and study supervision (YS). All authors have made significant contributions to this study and have approved the final manuscript.

References

[1] Weller J, Budson A. Current understanding of Alzheimer's disease diagnosis and treatment. F1000Res 2018;7(F1000 Faculty Rev):1161. doi:10.12688/f1000research.14506.1, PMID:30135715.
[2] World Health Organization. Dementia. Geneva: WHO; 2023.

[3] Guan PP, Cao LL, Wang P. Elevating the Levels of Calcium Ions Exacerbate Alzheimer's Disease via Inducing the Production and Aggregation of β-Amyloid Protein and Phosphorylated Tau. Int J Mol Sci 2021;22(11):5900. doi:10.3390/ijms22115900, PMID:34072743.
[4] Jorfi M, Maaser-Hecker A, Tanzi RE. The neuroimmune axis of Alzheimer's disease. Genome Med 2023;15(1):6. doi:10.1186/s13073-023-01155-w, PMID:36703235.
[5] Alzobaidi N, Quasimi H, Emad NA, Alhalmi A, Naqvi M. Bioactive Compounds and Traditional Herbal Medicine: Promising Approaches for the Treatment of Dementia. Degener Neurol Neuromuscul Dis 2021;11:1–14. doi:10.2147/DNND.S299589, PMID:33880073.
[6] Sehar U, Rawat P, Reddy AP, Kopel J, Reddy PH. Amyloid Beta in Aging and Alzheimer's Disease. Int J Mol Sci 2022;23(21):12924. doi:10.3390/ijms232112924, PMID:36361714.
[7] Patel R, Aschner M. Commonalities between Copper Neurotoxicity and Alzheimer's Disease. Toxics 2021;9(1):4. doi:10.3390/toxics9010004, PMID:33430181.
[8] Boix CP, Lopez-Font I, Cuchillo-Ibañez I, Sáez-Valero J. Amyloid precursor protein glycosylation is altered in the brain of patients with Alzheimer's disease. Alzheimers Res Ther 2020;12(1):96. doi:10.1186/s13195-020-00664-9, PMID:32787955.
[9] Atoki AV, Aja PM, Ondari EN, Aja PM, Nyakundi E. Advances in Alzheimer's disease therapeutics: biochemistry , exploring bioactive compounds and novel approaches. Int J Food Prop 2023;26(1):2091–2127. doi:10.1080/10942912.2023.2243050.
[10] Khan MI, Hasan F, Hasan Al Mahmud KA, Adnan A. Domain focused and residue focused phosphorylation effect on tau protein: A molecular dynamics simulation study. J Mech Behav Biomed Mater 2021; 113:104149. doi:10.1016/j.jmbbm.2020.104149, PMID:33125954.
[11] Pradhan B, Jit BP, Maharana S, Ramchandani S, Jena M. Bio-nano Interface and Its Potential Application in Alzheimer's Disease. In: Arakha M, Pradhan AK, Jha S (eds). Bio-Nano Interface. Singapore: Springer; 2022:209–224. doi:10.1007/978-981-16-2516-9_12.
[12] Guo Y, Li S, Zeng LH, Tan J. Tau-targeting therapy in Alzheimer's disease: critical advances and future opportunities. Ageing Neurodegener Dis 2022;2(3):11. doi:10.20517/and.2022.16.
[13] Ulaganathan S, Pitchaimani A. Spontaneous and familial models of Alzheimer's disease: Challenges and advances in preclinical research. Life Sci 2023;328:121918. doi:10.1016/j.lfs.2023.121918.
[14] Chen C, Lu J, Peng W, Mak MS, Yang Y, Zhu Z, *et al*. Acrolein, an endogenous aldehyde induces Alzheimer's disease-like pathologies in mice: A new sporadic AD animal model. Pharmacol Res 2022;175:106003. doi:10.1016/j.phrs.2021.106003, PMID:34838693.
[15] Kivipelto M, Mangialasche F, Ngandu T. Lifestyle interventions to prevent cognitive impairment, dementia and Alzheimer disease. Nat Rev Neurol 2018;14(11):653–666. doi:10.1038/s41582-018-0070-3, PMID:30291317.
[16] Kuo CY, Stachiv I, Nikolai T. Association of Late Life Depression, (Non-) Modifiable Risk and Protective Factors with Dementia and Alzheimer's Disease: Literature Review on Current Evidences, Preventive Interventions and Possible Future Trends in Prevention and Treatment of Dementia. Int J Environ Res Public Health 2020;17(20):7475. doi:10.3390/ijerph17207475, PMID:33066592.
[17] Sasaguri H, Hashimoto S, Watamura N, Sato K, Takamura R, Nagata K, *et al*. Recent Advances in the Modeling of Alzheimer's Disease. Front Neurosci 2022;16:807473. doi:10.3389/fnins.2022.807473, PMID: 35431779.
[18] Sanchez-Varo R, Mejias-Ortega M, Fernandez-Valenzuela JJ, Nuñez-Diaz C, Caceres-Palomo L, Vegas-Gomez L, *et al*. Transgenic Mouse Models of Alzheimer's Disease: An Integrative Analysis. Int J Mol Sci 2022;23(10):5404. doi:10.3390/ijms23105404, PMID:35628216.
[19] Chen C, Ma X, Wei J, Shakir N, Zhang JK, Zhang L, *et al*. Early impairment of cortical circuit plasticity and connectivity in the 5XFAD Alzheimer's disease mouse model. Transl Psychiatry 2022;12(1):371. doi:10.1038/s41398-022-02132-4, PMID:36075886.
[20] Varshavskaya KB, Mitkevich VA, Makarov AA, Barykin EP. Synthetic, Cell-Derived, Brain-Derived, and Recombinant β-Amyloid: Modelling Alzheimer's Disease for Research and Drug Development. Int J Mol Sci 2022;23(23):15036. doi:10.3390/ijms232315036, PMID:36499362.
[21] Baerends E, Soud K, Folke J, Pedersen AK, Henmar S, Konrad L, *et al*. Modeling the early stages of Alzheimer's disease by administering intracerebroventricular injections of human native Aβ oligomers to rats. Acta Neuropathol Commun 2022;10(1):113. doi:10.1186/s40478-022-01417-5, PMID:35974377.
[22] Gomez-Gutierrez R, Ghosh U, Yau WM, Gamez N, Do K, Kramm C, *et al*. Two structurally defined Aβ polymorphs promote different pathological changes in susceptible mice. EMBO Rep 2023;24(8):e57003. doi:10.15252/embr.202357003, PMID:37424505.
[23] Hu Z, Yu P, Zhang Y, Yang Y, Zhu M, Qin S, *et al*. Inhibition of the ISR abrogates mGluR5-dependent long-term depression and spatial memory deficits in a rat model of Alzheimer's disease. Transl Psychiatry 2022;12(1):96. doi:10.1038/s41398-022-01862-9, PMID:35260557.
[24] Umeda T, Uekado R, Shigemori K, Eguchi H, Tomiyama T. Nasal Rifampicin Halts the Progression of Tauopathy by Inhibiting Tau Oligomer Propagation in Alzheimer Brain Extract-Injected Mice. Biomedicines 2022;10(2):297. doi:10.3390/biomedicines10020297, PMID:35203506.
[25] Tok S, Maurin H, Delay C, Crauwels D, Manyakov NV, Van Der Elst W, *et al*. Neurophysiological effects of human-derived pathological tau conformers in the APPKM670/671NL.PS1/L166P amyloid mouse model of Alzheimer's disease. Sci Rep 2022;12(1):7784. doi:10.1038/s41598-022-11582-1, PMID:35546164.
[26] Hosokawa M, Masuda-Suzukake M, Shitara H, Shimozawa A, Suzuki G, Kondo H, *et al*. Development of a novel tau propagation mouse model endogenously expressing 3 and 4 repeat tau isoforms. Brain 2022;145(1):349–361. doi:10.1093/brain/awab289, PMID:34515757.
[27] Nisa FY, Rahman MA, Hossen MA, Khan MF, Khan MAN, Majid M, *et al*. Role of neurotoxicants in the pathogenesis of Alzheimer's disease: a mechanistic insight. Ann Med 2021;53(1):1476–1501. doi:10.1080/07853890.2021.1966088, PMID:34433343.
[28] Singh T, Yadav S. Role of microRNAs in neurodegeneration induced by environmental neurotoxicants and aging. Ageing Res Rev 2020;60:101068. doi:10.1016/j.arr.2020.101068, PMID:32283224.
[29] Ozben T, Ozben S. Neuro-inflammation and anti-inflammatory treatment options for Alzheimer's disease. Clin Biochem 2019;72:87–89. doi:10.1016/j.clinbiochem.2019.04.001, PMID:30954437.
[30] Alasfar RH, Isaifan RJ. Aluminum environmental pollution: the silent killer. Environ Sci Pollut Res Int 2021;28(33):44587–44597. doi:10.1007/s11356-021-14700-0, PMID:34196863.
[31] Fernandes RM, Eiró LG, Chemelo VDS, Alvarenga MOP, Lima RR. Aluminum toxicity and oxidative stress. Toxicology: Oxidative Stress and Dietary Antioxidants. New York, NY: Academic Press; 2021:127–135. doi:10.1016/B978-0-12-819092-0.00014-5.
[32] Exley C, Clarkson E. Aluminium in human brain tissue from donors without neurodegenerative disease: A comparison with Alzheimer's disease, multiple sclerosis and autism. Sci Rep 2020;10(1):7770. doi:10.1038/s41598-020-64734-6, PMID:32385326.
[33] Chiroma SM, Mohd Moklas MA, Mat Taib CN, Baharuldin MTH, Amon Z. d-galactose and aluminium chloride induced rat model with cognitive impairments. Biomed Pharmacother 2018;103:1602–1608. doi:10.1016/j.biopha.2018.04.152, PMID:29864948.
[34] Martinez CS, Piagette JT, Escobar AG, Martín Á, Palacios R, Peçanha FM, *et al*. Aluminum exposure at human dietary levels promotes vascular dysfunction and increases blood pressure in rats: A concerted action of NAD(P)H oxidase and COX-2. Toxicology 2017;390:10–21. doi:10.1016/j.tox.2017.08.004, PMID:28826906.
[35] Xue JS, Li JQ, Wang CC, Ma XH, Dai H, Xu CB, *et al*. Dauricine alleviates cognitive impairment in Alzheimer's disease mice induced by D-galactose and AlCl3 via the Ca2+/CaM pathway. Toxicol Appl Pharmacol 2023;474:116613. doi:10.1016/j.taap.2023.116613, PMID:37414289.
[36] Firdaus Z, Kumar D, Singh SK, Singh TD. Centella asiatica Alleviates AlCl3-induced Cognitive Impairment, Oxidative Stress, and Neurodegeneration by Modulating Cholinergic Activity and Oxidative Burden in Rat Brain. Biol Trace Elem Res 2022;200(12):5115–5126. doi:10.1007/s12011-021-03083-5, PMID:34984596.
[37] Zhao Y, Dang M, Zhang W. Neuroprotective effects of Syringic acid against aluminium chloride induced oxidative stress mediated neuroinflammation in rat model of Alzheimer's disease. J Funct Foods 2020;71:104009. doi:10.1016/j.jff.2020.104009.
[38] Chen X, Zhang M, Ahmed M, Surapaneni KM, Veeraraghavan

VP, Arulselvan P. Neuroprotective effects of ononin against the aluminium chloride-induced Alzheimer's disease in rats. Saudi J Biol Sci 2021;28(8):4232–4239. doi:10.1016/j.sjbs.2021.06.031, PMID:34354404.

[39] Gáspár A, Hutka B, Ernyey AJ, Tajti BT, Varga BT, Zádori ZS, *et al*. Performance of the intracerebroventricularly injected streptozotocin Alzheimer's disease model in a translationally relevant, aged and experienced rat population. Sci Rep 2022;12(1):20247. doi:10.1038/s41598-022-24292-5, PMID:36424423.

[40] Alavi MS, Fanoudi S, Hosseini M, Sadeghnia HR. Beneficial effects of levetiracetam in streptozotocin-induced rat model of Alzheimer's disease. Metab Brain Dis 2022;37(3):689–700. doi:10.1007/s11011-021-00888-0, PMID:35098412.

[41] Rajkumar M, Sakthivel M, Senthilkumar K, Thangaraj R, Kannan S. Galantamine tethered hydrogel as a novel therapeutic target for streptozotocin-induced Alzheimer's disease in Wistar rats. Curr Res Pharmacol Drug Discov 2022;3:100100. doi:10.1016/j.crphar.2022.100100, PMID:35510084.

[42] Jeong ES, Bajgai J, You IS, Rahman MH, Fadriquela A, Sharma S, *et al*. Therapeutic Effects of Hydrogen Gas Inhalation on Trimethyltin-Induced Neurotoxicity and Cognitive Impairment in the C57BL/6 Mice Model. Int J Mol Sci 2021;22(24):13313. doi:10.3390/ijms222413313, PMID:34948107.

[43] Chang W, An J, Seol GH, Han SH, Yee J, Min SS. Trans-Anethole Alleviates Trimethyltin Chloride-Induced Impairments in Long-Term Potentiation. Pharmaceutics 2022;14(7):1422. doi:10.3390/pharmaceutics14071422, PMID:35890317.

[44] Tang KS. The cellular and molecular processes associated with scopolamine-induced memory deficit: A model of Alzheimer's biomarkers. Life Sci 2019;233:116695. doi:10.1016/j.lfs.2019.116695, PMID:31351082.

[45] Aihaiti M, Shi H, Liu Y, Hou C, Song X, Li M, *et al*. Nervonic acid reduces the cognitive and neurological disturbances induced by combined doses of D-galactose/AlCl(3) in mice. Food Sci Nutr 2023;11(10):5989–5998. doi:10.1002/fsn3.3533, PMID:37823115.

[46] Rao YL, Ganaraja B, Suresh PK, Joy T, Ullal SD, Manjrekar PA, *et al*. Effect of resveratrol and combination of resveratrol and donepezil on the expression of microglial cells and astrocytes in Wistar albino rats of colchicine-induced Alzheimer's disease. 3 Biotech 2023;13(9):319. doi:10.1007/s13205-023-03743-4, PMID:37641690.

[47] Sadoughi D. The effect of crocin on apoptotic, inflammatory, BDNF, Pt, and Aβ40 indicators and neuronal density of CA1, CA2, and CA3 regions of hippocampus in the model of Alzheimer suffering rats induced with trimethyltin chloride. Comp Clin Path 2019;28(5):1403–1413. doi:10.1007/s00580-019-02981-4.

[48] Joshi SA, Chavhan SS, Sawant KK. Rivastigmine-loaded PLGA and PBCA nanoparticles: Preparation, optimization, characterization, in vitro and pharmacodynamic studies. Eur J Pharm Biopharm 2010;76(2):189–199. doi:10.1016/j.ejpb.2010.07.007.

[49] Bhuvanendran S, Kumari Y, Othman I, Shaikh MF. Amelioration of Cognitive Deficit by Embelin in a Scopolamine-Induced Alzheimer's Disease-Like Condition in a Rat Model. Front Pharmacol 2018;9:665. doi:10.3389/fphar.2018.00665, PMID:29988493.

[50] Rajashri K, Mudhol S, Serva Peddha M, Borse BB. Neuroprotective Effect of Spice Oleoresins on Memory and Cognitive Impairment Associated with Scopolamine-Induced Alzheimer's Disease in Rats. ACS Omega 2020;5(48):30898–30905. doi:10.1021/acsomega.0c03689, PMID:33324798.

[51] Guo C, Kong X, Fan Y, Zhang R. Aerobic Treadmill Exercise Upregulates Epidermal Growth Factor Levels and Improves Learning and Memory in d-galactose-Induced Aging in a Mouse Model. Am J Alzheimers Dis Other Demen 2023;38:15333175231211082. doi:10.1177/15333175231211082, PMID:37977137.

[52] Mahdi O, Chiroma SM, Hidayat Baharuldin MT, Mohd Nor NH, Mat Taib CN, Jagadeesan S, *et al*. WIN55,212-2 Attenuates Cognitive Impairments in AlCl(3) + d-Galactose-Induced Alzheimer's Disease Rats by Enhancing Neurogenesis and Reversing Oxidative Stress. Biomedicines 2021;9(9):1270. doi:10.3390/biomedicines9091270, PMID:34572456.

[53] Sil S, Goswami AR, Dutta G, Ghosh T. Effects of naproxen on immune responses in a colchicine-induced rat model of Alzheimer's disease. Neuroimmunomodulation 2014;21(6):304–21. doi:10.1159/000357735, PMID:24662962.

[54] Chou CH, Yang CR. Neuroprotective Studies of Evodiamine in an Okadaic Acid-Induced Neurotoxicity. Int J Mol Sci 2021;22(10):5347. doi:10.3390/ijms22105347, PMID:34069531.

[55] Dubey R, Sathiyanarayanan L, Sankaran S, Arulmozhi S. Nootropic effect of Indian Royal Jelly against okadaic acid induced rat model of Alzheimer's disease: Inhibition of neuroinflammation and acetylcholineesterase. J Tradit Complement Med 2024;14(3):300–311. doi:10.1016/j.jtcme.2023.11.005, PMID:38707922.

[56] He L, Deng Y, Gao J, Zeng L, Gong Q. Icariside II ameliorates ibotenic acid-induced cognitive impairment and apoptotic response via modulation of MAPK pathway in rats. Phytomedicine 2018;41:74–81. doi:10.1016/j.phymed.2018.01.025, PMID:29519323.

[57] Ittiyavirah SP, Ramalingam K, Sathyan A, Rajasree RS, Kuruniyan MS, Quadri SA, *et al*. Thymoquinone-rich black cumin oil attenuates ibotenic acid-induced excitotoxicity through glutamate receptors in Wistar rats. Saudi Pharm J 2022;30(12):1781–1790. doi:10.1016/j.jsps.2022.10.007, PMID:36601514.

[58] Yassin NAZ, El-Shenawy SMA, Mahdy KA. Effect of Boswellia serrata on Alzheimer's disease induced in rats. J Arab Soc Med Res 2013;8(1):74439570. doi:10.7123/01.JASMR.0000429323.25743.cc.

[59] Ismail MF, Elmeshad AN, Salem NA. Potential therapeutic effect of nanobased formulation of rivastigmine on rat model of Alzheimer's disease. Int J Nanomedicine 2013;8:393–406. doi:10.2147/IJN.S39232, PMID:23378761.

[60] Nizamutdinova IT, Jin YC, Chung JI, Shin SC, Lee SJ, Seo HG, *et al*. The anti-diabetic effect of anthocyanins in streptozotocin-induced diabetic rats through glucose transporter 4 regulation and prevention of insulin resistance and pancreatic apoptosis. Mol Nutr Food Res 2009;53(11):1419–29. doi:10.1002/mnfr.200800526, PMID:19785000.

[61] Wan Chik M, Ramli NA, Mohamad Nor Hazalin NA, Surindar Singh GK. Streptozotocin mechanisms and its role in rodent models for Alzheimer's disease. Toxin Rev 2023;42(1):491–502. doi:10.1080/15569543.2022.2150646.

[62] Moreira-Silva D, Carrettiero DC, Oliveira ASA, Rodrigues S, Dos Santos-Lopes J, Canas PM, *et al*. Anandamide Effects in a Streptozotocin-Induced Alzheimer's Disease-Like Sporadic Dementia in Rats. Front Neurosci 2018;12:653. doi:10.3389/fnins.2018.00653, PMID:30333717.

[63] Bassani TB, Bonato JM, Machado MMF, Cóppola-Segovia V, Moura ELR, Zanata SM, *et al*. Decrease in Adult Neurogenesis and Neuroinflammation Are Involved in Spatial Memory Impairment in the Streptozotocin-Induced Model of Sporadic Alzheimer's Disease in Rats. Mol Neurobiol 2018;55(5):4280–4296. doi:10.1007/s12035-017-0645-9, PMID:28623617.

[64] Karami F, Jamaati H, Coleman-Fuller N, Zeini MS, Hayes AW, Gholami M, *et al*. Is metformin neuroprotective against diabetes mellitus-induced neurodegeneration? An updated graphical review of molecular basis. Pharmacol Rep 2023;75(3):511–543. doi:10.1007/s43440-023-00469-1, PMID:37093496.

[65] Hernández-Rodríguez M, Clemente CF, Macías-Pérez ME, Rodríguez-Fonseca RA, Vázquez MIN, Martínez J, *et al*. Contribution of hyperglycemia-induced changes in microglia to Alzheimer's disease pathology. Pharmacol Rep 2022;74(5):832–846. doi:10.1007/s43440-022-00405-9, PMID:36042131.

[66] Humphrey CM, Hooker JW 4th, Thapa M, Wilcox MJ, Ostrowski D, Ostrowski TD. Synaptic loss and gliosis in the nucleus tractus solitarii with streptozotocin-induced Alzheimer's disease. Brain Res 2023;1801:148202. doi:10.1016/j.brainres.2022.148202, PMID:36521513.

[67] Kumar B, Tharumasivam SV, Boominathan V. A Pilot Study on Nanotherapy of Momordica charantia against Trimethyltin Chloride-Induced Neurotoxicity in Danio rerio (Zebrafish). J Nanomater 2021;2021:2180638. doi:10.1155/2021/2180638.

[68] Pompili E, Nori SL, Geloso MC, Guadagni E, Corvino V, Michetti F, *et al*. Trimethyltin-induced differential expression of PAR subtypes in reactive astrocytes of the rat hippocampus. Brain Res Mol Brain Res 2004;122(1):93–98. doi:10.1016/j.molbrainres.2003.12.001, PMID:14992820.

[69] Ganz T, Fainstein N, Ben-Hur T. When the infectious environment meets the AD brain. Mol Neurodegener 2022;17(1):53. doi:10.1186/

s13024-022-00559-3, PMID:35986296.
[70] Zhan X, Stamova B, Sharp FR. Lipopolysaccharide Associates with Amyloid Plaques, Neurons and Oligodendrocytes in Alzheimer's Disease Brain: A Review. Front Aging Neurosci 2018;10:42. doi:10.3389/fnagi.2018.00042, PMID:29520228.
[71] Houdek HM, Larson J, Watt JA, Rosenberger TA. Bacterial lipopolysaccharide induces a dose-dependent activation of neuroglia and loss of basal forebrain cholinergic cells in the rat brain. Inflamm Cell Signal 2014;1(1):e47. doi:10.14800/ics.47, PMID:26052539.
[72] Zakaria R, Wan Yaacob WM, Othman Z, Long I, Ahmad AH, Al-Rahbi B. Lipopolysaccharide-induced memory impairment in rats: a model of Alzheimer's disease. Physiol Res 2017;66(4):553–565. doi:10.33549/physiolres.933480, PMID:28406691.
[73] Hosseini Z, Mansouritorghabeh F, Kakhki FSH, Hosseini M, Rakhshandeh H, Hosseini A, *et al*. Effect of Sanguisorba minor on scopolamine-induced memory loss in rat: involvement of oxidative stress and acetylcholinesterase. Metab Brain Dis 2022;37(2):473–488. doi:10.1007/s11011-021-00898-y, PMID:34982352.
[74] Yadang FSA, Nguezeye Y, Kom CW, Betote PHD, Mamat A, Tchokouaha LRY, *et al*. Scopolamine-Induced Memory Impairment in Mice: Neuroprotective Effects of Carissa edulis (Forssk.) Valh (Apocynaceae) Aqueous Extract. Int J Alzheimers Dis 2020;2020:6372059. doi:10.1155/2020/6372059, PMID:32934845.
[75] Shahidi S, Zargooshnia S, Asl SS, Komaki A, Sarihi A. Influence of N-acetyl cysteine on beta-amyloid-induced Alzheimer's disease in a rat model: A behavioral and electrophysiological study. Brain Res Bull 2017;131:142–149. doi:10.1016/j.brainresbull.2017.04.001, PMID:28411131.
[76] Tofighi N, Asle-Rousta M, Rahnema M, Amini R. Protective effect of alpha-linoleic acid on Aβ-induced oxidative stress, neuroinflammation, and memory impairment by alteration of α7 nAChR and NMDAR gene expression in the hippocampus of rats. Neurotoxicology 2021;85:245–253. doi:10.1016/j.neuro.2021.06.002, PMID:34111468.
[77] Kasza Á, Penke B, Frank Z, Bozsó Z, Szegedi V, Hunya Á, *et al*. Studies for Improving a Rat Model of Alzheimer's Disease: Icv Administration of Well-Characterized β-Amyloid 1-42 Oligomers Induce Dysfunction in Spatial Memory. Molecules 2017;22(11):2007. doi:10.3390/molecules22112007, PMID:29156571.
[78] Morimoto K, Yoshimi K, Tonohiro T, Yamada N, Oda T, Kaneko I. Co-injection of β-amyloid with ibotenic acid induces synergistic loss of rat hippocampal neurons. Neuroscience 1998;84(2):479–487. doi:10.1016/S0306-4522(97)00507-1.
[79] Feng C, Zhang C, Shao X, Liu Q, Qian Y, Feng L, *et al*. Enhancement of nose-to-brain delivery of basic fibroblast growth factor for improving rat memory impairments induced by co-injection of β-amyloid and ibotenic acid into the bilateral hippocampus. Int J Pharm 2012;423(2):226–234. doi:10.1016/j.ijpharm.2011.12.008, PMID:22193058.
[80] Shwe T, Pratchayasakul W, Chattipakorn N, Chattipakorn SC. Role of D-galactose-induced brain aging and its potential used for therapeutic interventions. Exp Gerontol 2018;101:13–36. doi:10.1016/j.exger.2017.10.029, PMID:29129736.
[81] Rahman MA, Shuvo AA, Apu MMH, Bhakta MR, Islam F, Rahman MA, *et al*. Combination of epigallocatechin 3 gallate and curcumin improves D-galactose and normal-aging associated memory impairment in mice. Sci Rep 2023;13(1):12681. doi:10.1038/s41598-023-39919-4, PMID:37542120.
[82] Bo-Htay C, Shwe T, Chattipakorn SC, Chattipakorn N. The role of d-galactose in the aging heart and brain. Mol Nutr Carbohydrates. Published online January 1 2019;12:285–301. doi:10.1016/B978-0-12-849886-6.00022-7.
[83] Yu Y, Bai F, Wang W, Liu Y, Yuan Q, Qu S, *et al*. Fibroblast growth factor 21 protects mouse brain against D-galactose induced aging via suppression of oxidative stress response and advanced glycation end products formation. Pharmacol Biochem Behav 2015;133:122–31. doi:10.1016/j.pbb.2015.03.020, PMID:25871519.
[84] Bryukhanov AL, Klimko AI, Netrusov AI. Antioxidant Properties of Lactic Acid Bacteria. Microbiology 2022;91(5):463–478. doi:10.1134/S0026261722601439.
[85] Haider S, Liaquat L, Ahmad S, Batool Z, Siddiqui RA, Tabassum S, *et al*. Naringenin protects AlCl3/D-galactose induced neurotoxicity in rat model of AD via attenuation of acetylcholinesterase levels and inhibition of oxidative stress. PLoS One 2020;15(1):e0227631. doi:10.1371/journal.pone.0227631, PMID:31945778.
[86] Deng S, Lu H, Chi H, Wang Y, Li X, Ye H. Neuroprotective Effects of OMO within the Hippocampus and Cortex in a D-Galactose and Aβ (25-35)-Induced Rat Model of Alzheimer's Disease. Evid Based Complement Alternat Med 2020;2020:1067541. doi:10.1155/2020/1067541, PMID:33101436.
[87] Oskouei Z, Mehri S, Kalalinia F, Hosseinzadeh H. Evaluation of the effect of thymoquinone in d-galactose-induced memory impairments in rats: Role of MAPK, oxidative stress, and neuroinflammation pathways and telomere length. Phytother Res 2021;35(4):2252–2266. doi:10.1002/ptr.6982, PMID:33325602.
[88] Wu HT, Yu Y, Li XX, Lang XY, Gu RZ, Fan SR, *et al*. Edaravone attenuates H2O2 or glutamate-induced toxicity in hippocampal neurons and improves AlCl3/D-galactose induced cognitive impairment in mice. Neurotoxicology 2021;85:68–78. doi:10.1016/j.neuro.2021.05.005, PMID:34004234.
[89] Saini N, Singh D, Sandhir R. Bacopa monnieri prevents colchicine-induced dementia by anti-inflammatory action. Metab Brain Dis 2019;34(2):505–518. doi:10.1007/s11011-018-0332-1, PMID:30604025.
[90] Sil S, Ghosh T, Gupta P, Ghosh R, Kabir SN, Roy A. Dual Role of Vitamin C on the Neuroinflammation Mediated Neurodegeneration and Memory Impairments in Colchicine Induced Rat Model of Alzheimer Disease. J Mol Neurosci 2016;60(4):421–435. doi:10.1007/s12031-016-0817-5, PMID:27665568.
[91] Bagchi A, Swain DK, Mitra A. Neuroprotective effect of organic and inorganically grown tea on oxidative damage in rat model of Alzheimer's disease. Adv Tradit Med 2020;20(3):439–450. doi:10.1007/s13596-020-00428-8.
[92] Anawal L, Shalavadi M, Chandrashekhar VM. Neuroprotective activity of Acanthus maderaspatensis L. against colchicine induced Alzheimer's disease rat model. Alzheimer's Dement 2023;19(S7):e060408. doi:10.1002/alz.060408.
[93] Hammadi SH, Hassan MA, Allam EA, Elsharkawy AM, Shams SS. Effect of sacubitril/valsartan on cognitive impairment in colchicine-induced Alzheimer's model in rats. Fundam Clin Pharmacol 2023;37(2):275–286. doi:10.1111/fcp.12837.
[94] Omar EM, Elatrebi S, Soliman NAH, Omar AM, Allam EA. Effect of icariin in a rat model of colchicine-induced cognitive deficit: role of β-amyloid proteolytic enzymes. Nutr Neurosci 2023;26(12):1172–1182. doi:10.1080/1028415X.2022.2140395, PMID:36342068.
[95] Sil S, Ghosh T. Role of cox-2 mediated neuroinflammation on the neurodegeneration and cognitive impairments in colchicine induced rat model of Alzheimer's Disease. J Neuroimmunol 2016;291:115–124. doi:10.1016/j.jneuroim.2015.12.003.
[96] Gan T, Liu X, Chen X, Shi Y, Wang W. Okadaic Acid Inhibits Protein Phosphatases to Suppress Spermatogonial Cell Proliferation. Biol Bull 2022;49(2):S12–S19. doi:10.1134/S1062359022140060.
[97] Ravindran J, Gupta N, Agrawal M, Bala Bhaskar AS, Lakshmana Rao PV. Modulation of ROS/MAPK signaling pathways by okadaic acid leads to cell death via, mitochondrial mediated caspase-dependent mechanism. Apoptosis 2011;16(2):145–61. doi:10.1007/s10495-010-0554-0, PMID:21082355.
[98] Kamat PK, Tota S, Shukla R, Ali S, Najmi AK, Nath C. Mitochondrial dysfunction: A crucial event in okadaic acid (ICV) induced memory impairment and apoptotic cell death in rat brain. Pharmacol Biochem Behav 2011;100(2):311–319. doi:10.1016/j.pbb.2011.08.019.
[99] Song XY, Wang YY, Chu SF, Hu JF, Yang PF, Zuo W, *et al*. A new coumarin derivative, IMM-H004, attenuates okadaic acid-induced spatial memory impairment in rats. Acta Pharmacol Sin 2016;37(4):444–452. doi:10.1038/aps.2015.132, PMID:26838073.
[100] Chu J, Wang J, Cui L, *et al*. Pseudoginsenoside-F11 ameliorates okadiac acid-induced learning and memory impairment in rats via modulating protein phosphatase 2A. Mech Ageing Dev 2021;197:111496. doi:10.1016/j.mad.2021.111496.
[101] Zong N, Li F, Deng Y, Shi J, Jin F, Gong Q. Icariin, a major constituent from Epimedium brevicornum, attenuates ibotenic acid-induced excitotoxicity in rat hippocampus. Behav Brain Res 2016;313:111–119. doi:10.1016/j.bbr.2016.06.055, PMID:27368415.

[102] Martínez-Torres NI, Vázquez-Hernández N, Martín-Amaya-Barajas FL, Flores-Soto M, González-Burgos I. Ibotenic acid induced lesions impair the modulation of dendritic spine plasticity in the prefrontal cortex and amygdala, a phenomenon that underlies working memory and social behavior. Eur J Pharmacol 2021;896:173883. doi:10.1016/j.ejphar.2021.173883, PMID:33513334.
[103] Karthick C, Periyasamy S, Jayachandran KS, Anusuyadevi M. Intrahippocampal Administration of Ibotenic Acid Induced Cholinergic Dysfunction via NR2A/NR2B Expression: Implications of Resveratrol against Alzheimer Disease Pathophysiology. Front Mol Neurosci 2016;9:28. doi:10.3389/fnmol.2016.00028, PMID:27199654.
[104] Ittiyavirah SP, Ramalingam K, Sathyan A, Rajasree RS, Kuruniyan MS, Quadri SA, *et al*. Thymoquinone-rich black cumin oil attenuates ibotenic acid-induced excitotoxicity through glutamate receptors in Wistar rats. Saudi Pharm J 2022;30(12):1781–1790. doi:10.1016/j.jsps.2022.10.007, PMID:36601514.