International Journal of Pharmaceutics and Drug Research
ISSN: 2347-6346
Available online at http://ijpdr.com

Review Article

REVIEW ON ANIMAL MODEL FOR DEMENTIA ASSOCIATED DISEASE

Sanskar Jain*, Samrat Biswas, Sameer Khan, Rohit Sahu, Rituraj Singh Lodhi, Sunayana Kesharwani

Adina Institute of Pharmaceutical Sciences, Sagar (M.P.)

***Correspondence Info:**
Sanskar Jain
Adina Institute of Pharmaceutical Sciences, Sagar (M.P.)
Email:
jainsanskar7580@gmail.com

***Article History:**

Received: 12/04/2024
Revised: 28/04/2024
Accepted: 07/05/2024

ABSTRACT

Dementia-associated diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), and other neurodegenerative disorders, represent a significant burden on global health. To advance our understanding and develop effective treatments, animal models have been extensively utilized. These models, ranging from invertebrates like *Caenorhabditis elegans* and *Drosophila melanogaster* to vertebrates such as rodents and non-human primates, offer invaluable insights into the pathophysiology of dementia. Transgenic rodent models, in particular, have been instrumental in elucidating the genetic and molecular mechanisms underlying AD and PD, by replicating human-like amyloid-beta plaque formation, tau protein tangles, and alpha-synuclein aggregation. Additionally, these models are pivotal for preclinical drug testing and biomarker discovery. Despite their contributions, limitations such as differences in brain structure and function between humans and animals, and the complexity of human dementia, necessitate continuous refinement of these models. Future directions include the development of more sophisticated models that better mimic human disease pathology and the integration of multi-species data to enhance translational relevance.

Keywords: Dementia, Alzheimer's disease, Parkinson's disease, Animal models, Neurodegeneration, Transgenic rodents, Amyloid-beta, Tau protein, Alpha-synuclein, Preclinical testing, Biomarkers, Translational research

INTRODUCTION

Dementia is a disabling clinical syndrome characterised by a progressive deterioration of cognition associated with impairment in activities of daily living (Van der Flier and Scheltens, 2005). It is on the increase in high-income countries and even more so in low- and middle-income countries (Kalaria *et al*., 2008). At present, about 36 million people in the world live with dementia and this number will almost double in the next 20 years, thus imposing a great burden on patients, their families and society as a whole. Because the current dementia treatments are still limited, a broad understanding of risk factors is essential for the prevention of these diseases (Ferri *et al*., 2005; Silva *et al*., 2013). Affective disorders are associated with cognitive disturbances that are not just limited to acute mood episodes. Even after major depression has remitted, patients show impairment in executive function and attention (Paelecke *et al*., 2005). A wide gap prevailed between this observation made at the start of the twentieth century and the recent interest in affective disorders as risk factors for late-life dementia. A growing number of epidemiological studies have addressed this link, most of them

focused on depression as a risk factor for Alzheimer's disease. In fact, two meta-analyses found that having a history of depression approximately doubled the probability of developing Alzheimer's disease or dementia in general (Ownby *et al*., 2006; Jorm, 2001).

Although there are more than 70 diseases that cause dementia, Alzheimer' disease (AD) is the most common cause and accounts for 50-70% of dementia, and combination of Alzheimer's disease and vascular dementia account for between 80-90% of cases (Black *et al*., 2001). It is a brain disorder usually in elderly, associated with slow progressive loss of brain function notably lapses in memory, disorientation, confusion, mood swings, changes in personality, language problems, such as difficulty in finding the right words for everyday objects, loss of behavioral inhibitions, loss of motivation and paranoia. Other subtypes of dementia are vascular dementia associated with vascular risk factors (Hachinski *et al*., 2006), lewy body dementia associated with eosinophilic cytoplasmic inclusion (Wild *et al*., 1996) frontotemporal dementia most commonly caused by frontotemporal degeneration (Rosen *et al*., 2002) and mixed dementia a combination of Alzheimer's disease and vascular dementia (Zekry *et al*., 2002).

Dementia is a syndrome due to disease of the brain - usually of a chronic or progressive nature in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded, by deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in a large number of conditions primarily or secondarily affect- ing the brain (Deore *et al*., 2024).

Causes and types of Dementia

It is known that dementia is a progressive neurodegenerative disease so over the coming decades, it has become a set of the world's largest socio-economic healthcare burden issues. Alzheimer Society UK, claims that more than 60%-62% disease accounts as a Alzheimer's disease with the elderly followed by vascular dementia (17%), mixed (AD and vascular) dementia (10%), dementia with Lewy bodies (4%), fronto-temporal dementia (2%) and Parkinson's dementia (2%) (Ashraf *et al*., 2013)

There are many diseases that result in dementia. The most common types of dementia are outlined below:

Progressive dementias:

Alzheimer's disease: Alzheimer's disease (AD) accounts for around 60 percent of all cases of dementia (Fratiglioni *et al*., 2007). AD is a progressive neurodegenerative condition that may be of presenile or senile onset depending on whether the occurrence of disease is before or after the age of 65 years. These gene changes can be passed down from parent to child. While several genes are probably involved in Alzheimer's disease, one important gene that increases risk is apolipoprotein. Alzheimer's disease have plaques and tangles in their brains. Plaques are clumps of a protein called beta-amyloid. It's thought that these clumps damage healthy brain cells and the fibers connecting them.

Vascular dementia: Vascular dementia (VaD) remains the second most common form

of dementia (upto 20% of all cases) in the elderly after AD (Roman, 2002). This type of dementia is caused by damage to the vessels that supply blood to the brain. Blood vessel problems can cause stroke or affect the brain in other ways, such as by damaging the fibers in the white matter of the brain. It is the result of brain injury produced by cerebrovascular disease, either hemorrhagic or ischemic, or by hypoperfusive lesions resulting from cardiac disease or circulatory failure (Roman, 2005).

Lewy body dementia: Dementia with Lewy bodies (DLB) accounts for 15 to 20 per cent of dementia cases. Lewy bodies are balloonlike clumps of protein. The disease seems to lie somewhere between Alzheimer's disease (AD) and Parkinson's disease. DLB has distinct microscopic features: patients present with Lewy bodies and amyloid plaques in the subcortical and cortical regions of the brain. Symptoms also include problems with focus and attention. Other signs include uncoordinated or slow movement, tremors, and stiffness, known as parkinsonism (Husband and Worsley, 2006).

Fronto temporal dementia: FTD, sometimes also referred to as fronto-temporal lobar degeneration (FTLD), is the second commonest cause of dementia in younger people (< 65 years) (Ratnavalli *et al*., 2002), and produces focal atrophy of the frontal and/ or anterior temporal lobes, with concomitant cognitive features. This is a group of diseases characterized by the breakdown of nerve cells and their connections in the frontal and temporal lobes of the brain. These areas are associated with personality, behavior and language (Neary *et al*., 2005).

Other disorders linked to dementia:

Huntington's disease: Huntington's disease (HD) is an autosomal dominant disorder with an average course of 15 to 20 years. It typically affects patients between 30 and 50 years of age and has a prevalence of between four and seven per 100,000 worldwide. The disease causes certain nerve cells in the brain and spinal cord to waste away. Symptoms include a decline in thinking skills, known as cognitive skills. Symptoms usually appear around age 30 or 40 (Roze *et al*., 2010).

Parkinson's disease: The one-third patients with Parkinson's disease are prone to subcortical and progressive dementia. The neurodegeneration is not only confined to substantia nigra but spread to other subcortical nuclei including the limbic system and the cerebral cortex. Furthermore, the underlying neurochemical deficits associated may be losses of cholinergic, dopaminergic and noradrenergic innervations (Kulisevsky and Pagonabarraga, 2009; Hindle, 2010).

Creutzfeldt-Jakob disease: It is a dementia with an extremely rapid course, caused by transmissible infectious agent, the prion. Cognitive deterioration is progressive, widespread and accompanied by pyramidal and extrapyramidal signs i.e myoclonic jerks, ataxia and muscle rigidity. Death generally occurs in 6-12 months. The pathological changes are widespread in the cortex and the subcortical structures. Spongiform change in neurons is characteristic and neuronal loss and astrocytic proliferation occur (Dupiereux *et al*., 2009).

Stages of dementia

Dementia has three progressive and successive stages from mild to moderate to

severe (Fymat, 2018). The features of each stage is given below (Three stage Model)

Early stage - (Mild degree): Symptoms (memory difficulties, anomia, executive function problems, personality change, social withdrawal, etc.) are more noticeable.

Middle stage - (Moderate degree): Symptoms (problem-solving difficulties, impaired social judgment, preclusion of outside-of-the-home functioning, needed assistance for personal care and hygiene) generally worsen.

Late stage - (Severe degree): Symptoms (required assistance for personal care and hygiene, needed supervision for personal safety, changes in diet and sleep patterns, etc.) change significantly.

Diagnosis

Symptoms are similar across dementia types and it is difficult to diagnose by symptoms alone. Diagnosis may be aided by brain scanning techniques. In many cases, the diagnosis requires a brain biopsy to become final, but this is rarely recommended (though it can be performed at autopsy) (Lin *et al*., 2013). Normally, symptoms must be present for at least six months to support a diagnosis. Cognitive dysfunction of shorter duration is called *delirium*. Delirium can be easily confused with dementia due to similar symptoms. Delirium is characterized by a sudden onset, fluctuating course, a short duration (often lasting from hours to weeks), and is primarily related to a somatic (or medical) disturbance. In comparison, dementia has typically a long, slow onset (except in the cases of a stroke or trauma), slow decline of mental functioning, as well as a longer trajectory (from months to years) (Caplan and Rabinowitz, 2010).

Some mental illnesses, including depression and psychosis, may produce symptoms that must be differentiated from both delirium and dementia (Rivera *et al*., 2022). These are differently diagnosed as pseudodementias, and any dementia evaluation needs to include a depression screening such as the Neuropsychiatric Inventory or the Geriatric Depression Scale (Lai, 2014).

Risk factors

Risk factor for dementia include high blood pressure, hearing loss, smoking, obesity, depression, inactivity, diabetes, lower levels of education and low social contact. Over-indulgence in alcohol, lack of sleep, anemia, traumatic brain injury, and air pollution can also increase the chance of developing dementia (Livingston *et al*., 2020).

In addition to the above risk factors, other psychological features, including certain personality traits (high neuroticism, and low conscientiousness), low purpose in life, and high loneliness, are risk factors for Alzheimer's disease and related dementias (Sutin *et al*., 2021). The two most modifiable risk factors for dementia are physical inactivity and lack of cognitive stimulation (Cheng, 2016).Sensory impairments of vision and hearing are modifiable risk factors for dementia (Dawes, 2019). These impairments may precede the cognitive symptoms of Alzheimer's disease for example, by many years (Panza, 2019). Hearing loss may lead to social isolation which negatively affects cognition (Thomson *et al*., 2017).

Management

There are limited options for treating dementia, with most approaches focused on managing or reducing individual symptoms. There are no treatment options available to

delay the onset of dementia (Hafdi *et al*., 2021). Acetylcholinesterase inhibitors are often used early in the disorder course; however, benefit is generally small (Schneider *et al*., 2014). Palliative care interventions may lead to improvements in comfort in dying, but the evidence is low (Walsh *et al*., 2021). Exercise programs are beneficial with respect to activities of daily living, and potentially improve dementia (Forbes *et al*., 2015).

Animal models to evaluate dementia and cognitive deficits

Various animal models of dementia:

Spontaneous models: Memory loss is a primary characteristic feature of old age therefore aged animals can serve as natural model of memory deficits and dementia.

Aged induced dementia: Aging animals are used routinely in drug development due to age related cognitive decline and behavioral alterations which mimic not only the neurochemical and morphological alterations (Erickson and Barnes, 2003) but also the cholinergic hypofunction (Sherman and Friedman, 1990) that is similar to pathophysiology of Alzheimer's disease. Reports indicate that dopaminergic and glutamatergic dysfunctions may also contribute to age related dementia (Collier *et al*., 1988).The advantage of this model is that it is non-invasive, natural and without any central neurochemical manipulations.

Sam models: Senescence-accelerated prone 8 (SAMP8) mice mimic many of the salient features of Alzheimer's disease (AD) (Chen *et al*., 2014). The SAM models were developed in early 1981 including nine major senes cence accelerated mouse-prone (SAMP) sub-strains that undergo accel erated aging and three senescence accelerated mouse-resistant (SAMR) sub-strains that undergo normal aging process (Okuma and Nomura, 1998).

Chemically induced models: Manipulations of central neuronal/neurotransmitters pathways by chemical means form the basis of these models.

Scopolamine induced memory deficits: It is well documented that cholinergic system plays a central role in the memory function (Roloff *et al*., 2007). Decrease in function of central cholinergic system may induce aspects of dementia like loss of memory and disorientation as seen in Alzheimer's disease (Dhingra *et al*., 2003).

Intracerebroventricular streptozotocin induced dementia: Streptozotocin (STZ) is a glucosamine nitrosourea compound (STZ, (C8H15N3O7, 2-deoxy-2- (3-ethyl-3-nitrosoureido)-D-glucopyranose)) present in a strain of the soil microbe Streptomyces achromogenes discovered in 1956 (Wiley, 1981). Streptozotocin is an alkylating agent which mimics some properties of nitrosoureas, a class of anticancer agents which is applicable in pancreatic carcinoma. STZ has been widely explored for its diabetogenic potential in animals (Haidara *et al*., 2008).

Alcohol induced memory deficits: High doses of ethanol have been reported to induce retrograde amnesia and impair memory, disruption of encoding, storage, consolidation, and retrieval capability (Spinetta *et al*., 2008). The advantage of this model is that it does not require any surgical procedures when used for assessment of various memory enhancers. The limitation of this model is that the procedure is very long and time-consuming because pregnant female rats are employed.

Amyloid B-peptide (Aβ) induced memory deficits: Amyloid beta plaques are characteristic feature of AD and administration of Aβ peptide has been noted to induce memory loss (Flood *et al*., 1994). This model is highly specific for screening of drugs used in AD.

Methionine induced dementia: Chronic hyperhomocysteinemia have been reported to cause endothelial dysfunction and cognitive impairment (Streck *et al*., 2004).

Okadaic acid (OKA) induced memory deficit: It is proposed that an imbalance between tau phosphorylation and dephosphorylation is critical to AD (Gong *et al*., 2006). Okadaic acid induced memory loss mimics many of the salient features of Alzheimer's disease (AD) (Bai *et al*., 2013).

Excitoxins, neurotoxins and cholinotoxins induced memory deficits: Excitotoxicity occurs due to overstimulation of glutamate receptors is a major cause of neuron death in several neurological diseases, including AD and epilepsy (Ramirez *et al*., 2011).

Miscellaneous animal models: It has been reported that bioactive phospholipid lysophosphatidic acid (LPA) causes neurite retraction in neuronal cells. It has been shown that there is a site specific increase in Alzheimer's disease like tau phosphorylation during LPA induced retraction in neuronal cells (Bhattacharya *et al*., 1995).

Transgenic animal models: Alzheimer's disease (AD) is an ideal disease for modeling in the transgenic animals. Transgenic models are generated either by introducing genetic modification in existing genetic makeup or by altering the gene of interest in its normal chromosomal position called gene targeting (Elder *et al*., 2010).

Amyloid B peptide related models: The initial transgenic rat models of AD results in accumulation of in tracellular Aβ but no senile plaques.Reports suggest to develop animal models that express human amyloid precursor protein (APP), amyloid β (Aβ) and the amyloid precursor protein (APP) genes carrying familial AD mutations (Balducci and Forloni, 2010). A number of amyloid precursor protein (APP) transgenic (Tg) mice harboring APP mutations have been generated as animal models of AD (Umeda *et al*., 2014).

PDAPP mouse model: The first transgenic mouse (PDAPP) model was developed by Games *et al*., (1995) by using a platelet-derived growth factor-β promoter driving a human amyloid precursor protein (APP) minigene encoding APP V717F mutation associated with familial Alzheimer's disease (FAD). The advantage of this mouse is that it shows numerous extracellular thioflavin-S-positive Aβ deposits, neuritic plaques, synaptic loss, microgliosis and astrocytosis (Yamada and Nabeshima, 2000). Amyloid plaques develop at 6–9 months of age.

Tg2576 mouse model: Tg2576 mouse model of AD is one of the most widely used model expressing human APP695 containing the double mutation K670N/M671L, which shows neuronal loss in CA1 region of hippocampus and deficits in learning with similar effects as produced by PDAPP transgenic mouse such as prominent gliosis and neuritic dystrophy (Hsiao *et al*.,1996).

APP23 mouse model: APP23 model was developed by Sturchler-Pierrat and Staufenbiel (2000) on similar lines to Tg2576 mouse. It also carries a Swedish double mutation at positions 670/671. The APP23 mouse model carries an APP751 isoform and

the transgene is under the control of Thy-1 promoter (Richardson and Burns, 2002).

Neurofibrillary and tau related models: Transgenic mouse that express the mutated form of human tau has been generated to mimic the characteristics of neurofibrillary tangles (NFT) in Alzheimer's disease (AD) (Carmo and Cuello, 2013).

R406W mouse model: R406W tau mutations have also been used to generate transgenic mouse because it closely resembles to Alzheimer's disease (AD) (Lindquist *et al*., 2008).

ApoE mouse models: ApoE plays a pivotal role in the pathogenesis of Alzheimer's disease (AD) (Youmans *et al*., 2012).

Presenilin transgenic mouse models: It is well documented that mutation in presenilin 1 (PS1) is one of the major cause of familial Alzheimer's disease (AD) associated with locus on chromosome 14 (Ertekin-Taner, 2007). These transgenic mouse models result in plaque formation, synaptic dysfunction, and loss of memory which are the characteristic features of AD (Parent and Thinakaran, 2010).

Axonal transport models: Axonal transport deficits have been reported in tau and amyloid precursor protein (APP) and this deficit is implicated in the pathology of Alzheimer's disease (AD) (Higuchi *et al*., 2005).

Knock out animal models: In addition to transgenic mouse models that result in overproduction of amyloid beta and hyperphosphorylation of tau which are the characteristic features of AD, genetically modified mice that lack genes have been produced (LaFerla and Green, 2012).

Htau mouse model: Htau mouse model has been generated by crossing a mouse that expresses human tau transgene with tau knock out mouse (Tucker *et al*., 2001)

Insulin degrading enzyme knock out models: The gene for insulin degrading enzyme (IDE), which is located at chromosome 24, has been proposed as an important gene for late-onset Alzheimer's disease (AD) based on its ability to degrade amyloid beta-protein (APP) (Vepsalainen *et al*., 2007).

Mutated human A-synuclein mouse model: Transgenic mouse expressing wild type or mutant human α-synuclein has been successfully developed with similar pathological changes like motor neurodegeneration and effects on axonal integrity similar to that seen in AD (Putten *et al*., 2000).

Other models

Brain injury induced animal models: Reports showed that injury to specific areas of the brain such as diencephalons and medial temporal lobe produces memory impairment (Squire and Zola-Morgan, 1988). There are many advantages of such models since most of the procedures do not require surgical manipulations and injury to nucleus basalis magnocellularis (NBM) produces memory impairment similar to that of Alzheimer's disease (AD). The only limitation is that certain brain injury procedures are very tedious (Savage *et al*., 1997).

Concussion like brain injury induced animal model: This model has been developed in mice by Tang *et al*., (1997a).

Thiamine deficiency induced animal models: Experimental thiamine deficiency paradigm model induces Alzheimer's disease and neurodegeneration that typifies nutritional deficiencies associated with chronic alcohol-

induced Wernicke Korsakoff syndrome (WKS) (Savage *et al*., 2012).

Thiamine deficiency induced memory deficits: Thiamine deficiency can be induced in mice by exposing to thiamine deficient diet for an extended period of time (3–4 weeks) (Zhao *et al*., 2008; Nakagawasai *et al*., 2000).

CONCLUSION

Dementia is common, worldwide health and social care issue.Dementia can be caused by many different diseases. These diseases affect the brain in different ways, resulting in different types of dementia. Namely, new animal models that faithfully recapitulate dementia pathology and new technologies that accurately detect dementia symptoms are required.

DECLARATION OF INTEREST

The authors declare no conflicts of interests. The authors alone are responsible for the content and writing of this article.

Table 1: Animal models of dementia

S. No.	Model	Dementia disease	Reference
1	Spontaneous models	Alzheimer's disease	(Erickson and Barnes, 2003)
2	Miscellaneous chemically induced models	Alzheimer's disease	(Singh *et al*., 1997)
3	Hypoxia induced memory deficits	Vascular dementia, amnesia	(Santo-Yamada *et al*., 2001)
4	Chemically induced memory deficits	Alzheimer's disease	(Winslow and Camacho, 1995)
5	Transgenic animal models of dementia	Alzheimer's disease	(Bilkei-Gorzo, 2014)
6	Pyrithiamine induced thiamine deficiency dementia	Wernicke–Korsakoff syndrome	(Butterworth and Heroux, 1989)
7	Benzodiazepines induced dementia	Retrograde amnesia or anterograde amnesia	(Dhingra *et al*., 2004)
8	Colchicine induced dementia	sporadic dementia of AD	(Kumar *et al*., 2006)

REFERENCES

- Sutin, A.R., Aschwanden, D., Luchetti, M., Stephan, Y. & Terracciano, A. (2021) Sense of purpose in life is associated with lower risk of incident dementia: A meta-analysis. *Journal of Alzheimer's Disease*, 83, 249–258.
- Ashraf, A., Mehta, P. & Edison, P. (2013) Amyloid imaging in dementia. *Reviews in Clinical Gerontology*, 23, 43–60.
- Bai, P., Peng, X.M., Gao, L., Huo, S.X., Zhao, P.P. & Yan, M. (2013) Study on protective effect of acteoside on cellular model of Alzheimer's

disease induced by okadaic acid. *Zhongguo Zhong Yao Za Zhi*, 38, 1323–1326.

- Balducci, C. & Forloni, G. (2011) APP transgenic mice. Their use and limitations. *NeuroMolecular Medicine*, 13, 117–137.
- Bhattacharya, S.K., Kumar, A. & Jaiswal, A.K. (1995) Effect of mentat, a herbal formulation, on experimental models of Alzheimer's disease and central cholinergic markers in rats. *Fitoterapia*, 67, 216–219.
- Bilkei-Gorzo, A. (2014) Genetic mouse models of brain ageing and Alzheimer's disease. *Pharmacology and Therapeutics*, 142, 244–257.
- Black, K., LoGiudice, D., Ames, D., Barber, B. & Smith, R. (2001). *Diagnosing Dementia*. Alzheimer's Association Australia: Higgins, USA.
- Butterworth, R.F. & Héroux, M. (1989) Effect of pyrithiamine treatment and subsequent thiamine rehabilitation on regional cerebral amino acids and thiamine-dependent enzymes. *Journal of Neurochemistry*, 52, 1079–1084.
- Caplan, J.P. & Rabinowitz, T. (2010) An approach to the patient with cognitive impairment: Delirium and dementia. *Medical Clinics of North America*. Medical Clinics, 94, 1103–1116.
- Carmo, S.D. & Cuello, A.C. (2013) Modeling Alzheimer's disease in transgenic rats. *Molecular Neurodegeneration*, 8, 1–37.
- Chen, Y., Wei, G., Nie, H., Lin, Y., Tian, H., Liu, Y., Yu, X., Cheng, S., Yan, R., Wang, Q., Liu, D.H., Deng, W., Lai, Y., Zhou, J.H., Zhang, S.X., Lin, W.W. & Chen, D.F. (2014) β-asarone prevents autophagy and synaptic loss by reducing ROCK expression in asenescence-accelerated prone 8 mice. *Brain Research*, 1552, 41–54.
- Cheng, S.T. (2016) Cognitive reserve and the prevention of dementia: The role of physical and cognitive activities. *Current Psychiatry Reports*, 18, 85.
- Collier, T.J., Gash, D.M. & Sladek, J.R. (1988) Transplantation of norepinephrine neurons into aged rats improves performance of a learned task. *Brain Research*, 448, 77–87.
- da Silva, J., Gonçalves-Pereira, M., Xavier, M. & Mukaetova-Ladinska, E.B. (2013) Affective disorders and risk of developing dementia: Systematic review. *British Journal of Psychiatry*, 202, 177–186.
- Dawes, P. (2019) Hearing interventions to prevent dementia. *HNO*, 67, 165–171.
- Dhingra, D., Parle, M. & Kulkarni, S.K. (2003) Effect of combination of insulin with dextrose, D (−) fructose and diet on learning and memory in mice. *Indian Journal of Pharmacology*, 35, 151–156.
- Dhingra, D., Parle, M. & Kulkarni, S.K. (2004) Memory enhancing activity of Glycyrrhiza glabra in mice. 969 Ethnopharmacol, 91, 361–365.
- Dupiereux, I., Zorzi, W., Quadrio, I., Perret-Liaudet, A., Kovacs, G.G., Heinen, E. & Elmoualij, B. (2009)

Creutzfeldt–Jakob, Parkinson, Lewy body dementia and Alzheimer diseases: From diagnosis to therapy. Central nervous system agents in medicinal chemistry (formerly current medicinal chemistry-central nervous system agents), 9, 2–11.

- Elder, G.A., Gama Sosa, M.A. & De Gasperi, R.D. (2010) Transgenic mouse models of Alzheimer's disease. *Mount Sinai Journal of Medicine, New York*, 77, 69–81
- Erickson, C.A. & Barnes, C.A. (2003) The neurobiology of memory changes in normal aging. *Experimental Gerontology*, 38, 61–69.
- Erickson CA, Barnes CA.The neurobiology of memory changes in normal aging. Exp 976 Gerontol 2003;38:61–9.
- Ertekin-Taner, N. (2007) Genetics of Alzheimer's disease: A centennial review. *Neurologic Clinics*, 25, 611–667.
- Ferri, C.P., Prince, M., Brayne, C., Brodaty, H., Fratiglioni, L., Ganguli, M., Hall, K., Hasegawa, K., Hendrie, H., Huang, Y., Jorm, A., Mathers, C., Menezes, P.R., Rimmer, E., Scazufca, M. & Alzheimer's Disease Int. (2005) Global prevalence of dementia: A Delphi consensus study. *Lancet*, 366, 2112–2117.
- Flood, J.F., Roberts, E., Sherman, M.A., Kaplan, B.E. & Morley, J.E. (1994) Topography of a binding site for small amnestic peptides deduced from structure–activity studies: Relation to amnestic effect of amyloid β protein. *Proceedings of the National Academy of Sciences of the United States of America*, 91, 380–384.
- Forbes, D., Forbes, S.C., Blake, C.M., Thiessen, E.J. & Forbes, S. Exercise programs for people with dementia. *Cochrane Database of Systematic Reviews*, 2015, 78.
- Fratiglioni, L., Winblad, B. & von Strauss, E. (2007) Prevention of Alzheimer's disease and dementia. Major findings from the Kungsholmen Project. *Physiology and Behavior*, 92, 98–104.
- Fymat, A.L. (2018) Dementia: A review. *J. Clin. Psychiatr. Neurosci.*, 1, 27–34.
- Games, D., Adams, D., Alessandrini, R., Barbour, R., Berthelette, P., Blackwell, C., Carr, T., Clemens, J., Donaldson, T. & Gillespie, F. et al (1995) Alzheimer-type neuropathology in transgenic mice overexpressing V717F b-amyloid precursor protein. *Nature*, 373, 523–527.
- Gong, C.X., Liu, F., Grundke-Iqbal, I. et al (2006) Dysregulation of protein phosphorylation/dephos phorylation in Alzheimer's disease: A therapeutic target. *Journal of Biomedicine and Biotechnology*, 318–325.
- Hachinski, V., Iadecola, C., Petersen, R.C., Breteler, M.M., Nyenhuis, D.L., Black, S.E., Powers, W.J., DeCarli, C., Merino, J.G., Kalaria, R.N., Vinters, H.V., Holtzman, D.M., Rosenberg, G.A., Wallin, A., Dichgans, M., Marler, J.R. & Leblanc, G.G. (2006) National Institute of Neurological Disorders and Stroke–Canadian stroke

network vascular cognitive impairment harmonization standards. *Stroke*, 37, 2220–2241.

- Hafdi, M., Hoevenaar-Blom, M.P. & Richard, E. (2021) Multi-domain interventions for the prevention of dementia and cognitive decline. *Cochrane Database of Systematic Reviews*, 11, CD013572.
- Haidara, M.A., Mikhailidisc, D.P. & Rateba, M.A. (2008) Evaluation of the effect of oxidative stress and vitamin E supplementation on renal function in rats with streptozotocin-induced type 1 diabetes. *J. Diabetes Complicat*, 521, 231–235.
- Higuchi, M., Zhang, B., Forman, M.S., Yoshiyama, Y., Trojanowski, J.Q. & Lee, V.M.Y. (2005) Axonal degeneration induced by targeted expression of mutant human tau in oligodendrocytes of transgenic mice that model glial tauopathies. *Journal of Neuroscience*, 25, 9434–9443.
- Hindle, J.V. (2010) Ageing, neurodegeneration and Parkinson's disease. *Age and Ageing*, 39, 156–161.
- Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., Yang, F. & Cole, G. (1996) Correlative memory deficits, Ab elevation, and amyloid plaques in transgenic mice. *Science*, 274, 99–102.
- Husband, A. & Worsley, A. (2006) Different types of dementia. *Pharmaceutical Journal*, 277.
- Jorm, A.F. (2001) History of depression as a risk factor for dementia: An updated review. *Australian and New Zealand Journal of Psychiatry*, 35, 776–781.
- Kalaria, R.N., Maestre, G.E., Arizaga, R., Friedland, R.P., Galasko, D., Hall, K., Luchsinger, J.A., Ogunniyi, A., Perry, E.K., Potocnik, F., Prince, M., Stewart, R., Wimo, A., Zhang, Z.X., Antuono, P. & World Federation of Neurology Dementia Research Group (2008) Alzheimer's disease and vascular dementia in developing countries: Prevalence, management, and risk factors. *Lancet. Neurology*, 7, 812–826.
- Komal, D.R., Kannor, E.J., Pranjali, D.P. & Kishor, D.N. (2024) A updated review in the dementia is major disease. *International Journal of Research* Publication and Reviews, 5, 4949–4959.
- Kulisevsky, J. & Pagonabarraga, J. (2009) Cognitive impairment in Parkinson's disease: Tools for diagnosis and assessment. *Movement Disorders*, 24, 1103–1110.
- Kumar, A., Seghal, N., Padi, S.V. & Naidu, P.S. (2006) Differential effects of cyclooxygenase inhibitors on intracerebroventricular colchicine-induced dysfunction and oxidative stress in rats. *European Journal of Pharmacology*, 551, 58–66.
- LaFerla, F.M. & Green, K.N. (2012) Animal models of Alzheimer disease. *Cold Spring Harbor Perspectives in Medicine*, 2.
- Lai, C.K.Y. (2014) The merits and problems of Neuropsychiatric Inventory as an assessment tool in people with dementia and other

neurological disorders. *Clinical Interventions in Aging*, 9, 1051–1061.

- Lin, J.S., O'Connor, E., Rossom, R.C., Perdue, L.A. & Eckstrom, E. (2013) Screening for cognitive impairment in older adults: A systematic review for the US Preventive Services Task Force. *Annals of Internal Medicine*, 159, 601–612.
- Lindquist, S.G., Holm, I.E., Schwartz, M., Law, I., Stokholm, J., Batbayli, M., Waldemar, G. & Nielsen, J.E. (2008) Alzheimer disease-like clinical phenotype in a family with FTDP-17 caused by a MAPT R406W mutation. *European Journal of Neurology*, 15, 377–385.
- Livingston, G., Huntley, J., Sommerlad, A., Ames, D., Ballard, C., Banerjee, S., Brayne, C., Burns, A., Cohen-Mansfield, J., Cooper, C., Costafreda, S.G., Dias, A., Fox, N., Gitlin, L.N., Howard, R., Kales, H.C., Kivimäki, M., Larson, E.B., Ogunniyi, A., Orgeta, V., Ritchie, K., Rockwood, K., Sampson, E.L., Samus, Q., Schneider, L.S., Selbæk, G., Teri, L. & Mukadam, N. (2020) Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *Lancet*, 396, 413–446.
- Nakagawasai, O., Tadano, T., Hozumi, S., Tan-No, K., Niijima, F. & Kisara, K. (2000) Immunohistochemical estimation of brain choline acetyltransferase and somatostatin related to the impairment of avoidance learning induced by thiamine deficiency. *Brain Research Bulletin*, 52, 189–196.
- Neary, D., Snowden, J. & Mann, D. (2005) Frontotemporal dementia. *Lancet. Neurology*, 4, 771–780.
- Okuma, Y. & Nomura, Y. (1998) Senescence-accelerated mouse (SAM) as an animal model of senile dementia: Pharmacological, neurochemical and molecular biological approach. *Japanese Journal of Pharmacology*, 78, 399–404.
- Ownby, R.L., Crocco, E., Acevedo, A., John, V. & Loewenstein, D. (2006) Depression and risk for Alzheimer disease: Systematic review, meta-analysis, and metaregression analysis. *Archives of General Psychiatry*, 63, 530–538.
- Paelecke-Habermann, Y., Pohl, J. & Leplow, B. (2005) Attention and executive functions in remitted major depression patients. *Journal of Affective Disorders*, 89, 125–135.
- Panza, F., Lozupone, M., Sardone, R., Battista, P., Piccininni, M., Dibello, V., La Montagna, M., Stallone, R., Venezia, P., Liguori, A., Giannelli, G., Bellomo, A., Greco, A., Daniele, A., Seripa, D., Quaranta, N. & Logroscino, G. (2019) Sensorial frailty: Age-related hearing loss and the risk of cognitive impairment and dementia in later life. *Therapeutic Advances in Chronic Disease*, 10, 2040622318811000.
- Parent, A.T. & Thinakaran, G. (2010) Modeling presenilin-dependent familial Alzheimer's disease: Emphasis on presenilin substrate-mediated signaling and synaptic

function. *International Journal of Alzheimer's Disease*, 2010, 1–11.

- Ramirez, C., Tercero, I., Pineda, A. & Burgos, J.S. (2011) Simvastatin is the statin that most efficiently protects against kainate-induced excitotoxicity and memory impairment. *Journal of Alzheimer's Disease*, 24, 161–174.
- Ratnavalli, E., Brayne, C., Dawson, K. & Hodges, J.R. (2002) The prevalence of frontotemporal dementia. *Neurology*, 58, 1615–1621.
- Richardson, J.A. & Burns, D.K. (2002) Mouse models of Alzheimer's disease: A quest for plaques and tangles. *ILAR Journal*, 43, 89–99.
- Rivera, C., Sarah Shi, D.O., Parinda Patel, D.O. & Choudhry, H. (2022) John Dedousis. A rare case of delirium after Johnson & Johnson's Janssen's vaccination. *Medical Case Reports*, 3, 223–225. Sch. J.
- Roman, G.C. (2002) Vascular dementia may be the most common form of dementia in the elderly. *Journal of the Neurological Sciences*, 203–204, 7–10.
- Roman, G.C. (2005) Vascular dementia prevention: A risk factor analysis. *Cerebrovascular Diseases*, 20 (Supplement 2), 91–100.
- Rosen, H.J., Hartikainen, K.M., Jagust, W., Kramer, J.H., Reed, B.R., Cummings, J.L., Boone, K., Ellis, W., Miller, C. & Miller, B.L. (2002) Utility of clinical criteria in differentiating frontotemporal lobar degeneration (FTLD) from AD. *Neurology*, 58, 1608–1615.
- Roze, E., Bonnet, C., Betuing, S. & Caboche, J. (2010) Huntington's disease. *Advances in Experimental Medicine and Biology*, 685, 45–63.
- Santo-Yamada, Y., Yamada, K. & Wada, K. (2001) Posttraining administration of gastrin-releasing peptide improves memory loss in scopolamine- and hypoxia-induced amnesic mice. *Physiology and Behavior*, 74, 139–143.
- Savage, L.M., Hall, J.M. & Resende, L.S. (2012) Translational rodent models of Korsakoff syndrome reveal the critical neuroanatomical substrates of memory dysfunction and recovery. *Neuropsychology Review*, 22, 195–209.
- Savage, L.M., Sweet, A.J., Castillo, R. & Langlais, P.J. (1997) The effect of lesions to thalamic lateral internal Med ullary lamine and posterior nuclei on learning, memory and habituation in the rat. *Behavioural Brain Research*, 82, 133–147.
- Schneider, L.S., Mangialasche, F., Andreasen, N., Feldman, H., Giacobini, E., Jones, R., Mantua, V., Mecocci, P., Pani, L., Winblad, B. & Kivipelto, M. (2014) Clinical trials and late-stage drug development for A lzheimer's disease: An appraisal from 1984 to 2014. *Journal of Internal Medicine*, 275, 251–283.
- Sherman, K.A. & Friedman, E. (1990) Pre- and postsynaptic cholinergic dysfunction in aged rodents brain regions: New findings and an interpretative review. *International*

Journal of Developmental Neuroscience, 8, 689–708.

- Singh, N., Sharma, A. & Singh, M. (1997) Effects of BN-50730 (PAF receptor antagonist) and physostigmine (AChE inhibitor) on learning and memory in mice. *Methods and Findings in Experimental and Clinical Pharmacology*, 19, 585–588.
- Spinetta, M.J., Woodlee, M.T., Feinberg, L.M., Stroud, C., Schallert, K., Cormack, L.K. & Schallert, T. (2008) Alcohol-induced retrograde memory im pairment in rats: Prevention by caffeine. *Psychopharmacology*, 201, 361–371.
- Squire, L.R. (1988) Zola-Morgan S. Memory: Brain systems and behaviour. *Trends in Neurosciences*, 11, 170–175.
- Streck, E.L., Bavaresco, C.S., Netto, C.A. & Wyse, A.T.S. (2004) Chronic hyperhomocysteinemia provokes a memory deficit in rats in the Morris water maze task. *Behavioural Brain Research*, 153, 377–381.
- Sturchler-Pierrat, C. & Staufenbiel, M. (2000) Pathogenic mechanisms of Alzheimer's disease analyzed in the APP23 transgenic mouse model. *Annals of the New York Academy of Sciences*, 920, 134–139.
- Tang, Y.P., Noda, Y., Hasegawa, T. et al (1997a) A concussive like brain injury model in mice impairment in learning and memory. *Journal of Neurotrauma*, 82, 851–862.
- Thomson, R.S., Auduong, P., Miller, A.T. & Gurgel, R.K. (2017) Hearing loss as a risk factor for dementia: A systematic review. *Laryngoscope Investigative Otolaryngology*, 2, 69–79.
- Tucker, K.L., Meyer, M. & Barde, Y.A. (2001) Neurotrophins are required for nerve growth during development. *Nature Neuroscience*, 4, 29–37.
- Umeda, T., Maekawa, S., Kimura, T., Takashima, A., Tomiyama, T. & Mori, H. (2014) Neurofibrillary tangle formation by introducing wild-type human tau into APP transgenic mice. *Acta Neuropathologica*, 127, 685–698.
- Van der Flier, W.M. & Scheltens, P. (2005) Epidemiology and risk factors of dementia. *Journal of Neurology, Neurosurgery, and Psychiatry*, 76 (Supplement 5), v2–v7.
- van der Putten, H.V.D., Wiederhold, K.H., Probst, A., Barbieri, S., Mistl, C., Danner, S., Kauffmann, S., Hofele, K., Spooren, W.P., Ruegg, M.A., Lin, S., Caroni, P., Sommer, B., Tolnay, M. & Bilbe, G. (2000) Neuropathology in mice expressing human α-synuclein. *Journal of Neuroscience*, 20, 6021–6029.
- Vepsäläinen, S., Parkinson, M., Helisalmi, S., Mannermaa, A., Soininen, H., Tanzi, R.E., Bertram, L. & Hiltunen, M. (2007) Insulin-degrading enzyme is genetically associated with Alzheimer's disease in the Finnish population. *Journal of Medical Genetics*, 44, 606–608.
- von Linstow Roloff, E., Harbaran, D., Micheau, J., Platt, B. & Riedel, G. (2007) Dissociation of cholinergic

function in spatial and procedural learning in rats. *Neuroscience*, 146, 875–889.

- Walsh, S.C., Murphy, E., Devane, D., Sampson, E.L., Connolly, S., Carney, P. & O'Shea, E. (2021) Palliative care interventions in advanced dementia. *Cochrane Database of Systematic Reviews*, 9, CD011513.
- Wild, R., Pettit, T.A., Burns, A. & Cochrane Dementia and Cognitive Improvement Group (1996) Cholinesterase inhibitors for dementia with Lewy bodies. *Cochrane Database of Systematic Reviews*, 2010.
- Wiley, P.F. Isolation and chemistry of streptozotocin. *Streptozotocin: Fundamental and Therapy. Amsterdam, The Netherlands: Elsevier North-Holland Biomedical Press* (1981), p. 3–18.
- Winslow, J.T. & Camacho, F. (1995) Cholinergic modulation of a decrement in social investigation following repeated contacts between mice. *Psychopharmacology*, 121, 164–172.
- Yamada, K. & Nabeshima, T. (2000) Animal models of Alzheimer's disease and evaluation of anti-dementia drugs. *Pharmacology and Therapeutics*, 88, 93–113.
- Youmans, K.L., Tai, L.M., Nwabuisi-Heath, E., Jungbauer, L., Kanekiyo, T., Gan, M., Kim, J., Eimer, W.A., Estus, S., Rebeck, G.W., Weeber, E.J., Bu, G., Yu, C. & Ladu, M.J. (2012) APOE4-specific changes in Aβ accumulation in a new transgenic mouse model of Alzheimer disease. *Journal of Biological Chemistry*, 287, 41774–41786.
- Zekry, D., Hauw, J.J. & Gold, G. (2002) Mixed dementia: Epidemiology, diagnosis, and treatment. *Journal of the American Geriatrics Society*, 50, 1431–1438.
- Zhao, N., Zhong, C., Wang, Y., Zhao, Y., Gong, N., Zhou, G., Xu, T. & Hong, Z. (2008) Impaired hippocampal neurogenesis is involved in cognitive dysfunction induced by thiamine deficiency at early pre-pathological lesion stage. *Neurobiology of Disease*, 29, 176–185.