RESEARCH PAPER

Zebrafish as a Translational Model for Alzheimer's Disease

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ABSTRACT

Alzheimer's disease (AD) is the one of the most difficult neurodegenerative diseases in the world, AD is marked by progressive cognitive loss, synaptic dysfunction, and distinctive pathological hallmarks such neurofibrillary tau tangles and amyloid-β (Aβ) deposition. The necessity for alternate and supplementary model systems is highlighted by the low translational success in creating viable therapies despite substantial research. Because of their significant genetic similarity to humans, conserved neurotransmitter systems, optical transparency, quick development, and ease of genetic modification, zebrafish (Danio rerio) have become a significant vertebrate model for AD. This review shows the ability of contemporary zebrafish AD models, such as genetic, neurotoxin-induced, and Aβ/tau-based paradigms, to mimic important clinical, biochemical, and behavioural aspects of the disease. We also go over behavioural tests related to memory, anxiety, and cognition in zebrafish, as well as the neurobiological similarities between the brains of mammals and zebrafish. Zebrafish provide clear benefits for mechanistic research and high-throughput drug screening, despite several drawbacks, such as species-specific APP processing and inherent neuroregenerative potential. When taken as a whole, zebrafish offer a potent and complementary platform that improves preclinical AD research and has the potential to speed up the discovery of new treatment approaches.

Keywords: Alzheimer's disease; Zebrafish (Danio rerio); Amyloid-β; Tau pathology; Drug screening; Cognitive impairment; Neurodegeneration.

How to cite this article: Kumbhar P, Gaikwad V, Burli S, Dhole V, Shikalkar A, Kadam S, Karnale V, Netake M. Zebrafish as a Translational Model for Alzheimer's Disease. Int J Drug Deliv Technol. 2026;16(55s): 284-296. DOI: 10.25258/ijddt.16.55s.32

INTRODUCTION

The most common neurodegenerative illness and the primary cause of dementia in the global senior population is Alzheimer's disease (AD)[1]. By 2050, more than 100 million people worldwide are expected to have AD due to rising life expectancy, which presents a significant social and economic challenge[2,3]. Progressive cognitive decline, memory loss, behavioural abnormalities, and neuropsychiatric symptoms like anxiety and depression are the clinical characteristics of AD[4,5]. Neuropathologically, AD is characterised by neuronal loss and synaptic dysfunction, as well as extracellular amyloid-β (Aβ) plaque deposition and intracellular neurofibrillary tangles (NFTs) made of hyperphosphorylated tau protein[6].

Since acetylcholinesterase (AChE) inhibitors such donepezil, galantamine, tacrine, and huperzine are frequently recommended to improve cholinergic neurotransmission, the majority of current treatment approaches are symptomatic[7,8]. The need for new targets and better preclinical screening platforms is highlighted by the fact that current medicines do not stop the disease's development and that no disease-modifying drug has yet to achieve long-term success despite thorough clinical review[9-11].

Because of their genetic resemblance to humans, conserved neurotransmitter systems, quick development, optical transparency, and simplicity of genetic modification, Zebrafish (Danio rerio) have become a great vertebrate model for studying neurological diseases. Zebrafish allow for the real-time visualisation of pathogenic processes and display complex behaviours related to anxiety, memory, and cognition. They are an effective platform for examining AD processes and assessing treatment candidates due to their short life cycle and appropriateness for high-throughput drug screening[12,13].

AD Pathogenesis and Molecular Mechanism

The two main pathological features of Alzheimer's disease (AD) are intracellular neurofibrillary tangles (NFTs) made of modified microtubule-associated tau protein and extracellular deposition of amyloid-β (Aβ) plaques, both of which contribute to synaptic dysfunction and neuronal loss[14,15]. Clinically, AD is characterised by gradual cognitive impairment and neuropsychiatric symptoms; severe stages are characterised by significant brain shrinkage and neuronal degeneration[16-20]. There are two types of AD: familial (FAD) and sporadic (SAD). FAD makes up 1–5% of cases and is linked to autosomal dominant mutations in APP, PSEN1, and PSEN2, while SAD is caused by intricate interactions between genetic and environmental factors, with the ApoE ε4 allele being a significant risk factor and ε2 providing relative protection[21-26]. The amyloid hypothesis, which implicated Aβ as an upstream trigger of inflammation and oxidative stress, was developed as a result of the accumulation of Aβ. However, AD has since been accepted to be a multifactorial disorder involving additional mechanisms such as tau pathology, cholinergic dysfunction, calcium imbalance, and mitochondrial oxidative stress[27-35]. The association cortex and hippocampal regions are primarily affected by neuropathological alterations, where neuronal loss is correlated with extracellular Aβ deposition and intracellular tau accumulation, leading to neurotransmitter dysregulation and progressive cognitive impairment[36-44]. Limited translational success highlights the need for better disease models and reliable biomarkers to enhance treatment research, even though animal models replicating amyloid and tau pathology are available[45-47]. The major molecular mechanisms involved in alzheimer`s disease, including amyloid-β accumulation, tau hyperphosphorylation, neuroinflammation, and calcium dysregulation, are summarized in (Fig. 1).

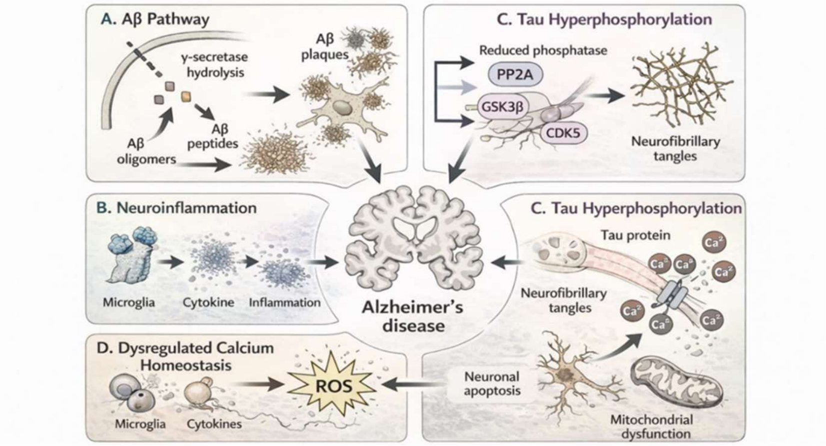


Fig 1. Schematic representation of major pathological pathways contributing to Alzheimer's disease.

Zebrafish as a Model Organism

In biomedical research, zebrafish (Danio rerio) are a well-known vertebrate model organism, especially in developmental biology, genetics, and neuroscience[48]. Direct in vivo visualisation of organ development and disease processes is made possible by their external fertilisation, quick embryogenesis, and optical transparency (Fig.2). high-scale genetic and pharmacological screening is made possible by zebrafish, which achieve sexual maturity in 12 weeks and produce a high number of offspring[49].

The entire zebrafish genome has been sequenced, and it exhibits strong conservation with the human genome, including orthologs of genes linked to neurological disorders. Human disease-associated mutations can be precisely modelled by genetic manipulation employing transgenic and gene-editing methods. Maintaining zebrafish embryos in micro-volumes allows for high-throughput, affordable drug screening while maintaining in vivo relevance[50].

Zebrafish are a vertebrate model that satisfies the replacement, reduction, and refinement (3Rs) principles in animal research and has a closer evolutionary relationship to humans than invertebrate models. In many places, larval zebrafish up to five days after fertilisation are not subject to regulations, which makes them a morally superior option for early-stage screening research[51]. Together, these characteristics make zebrafish an effective model for studying neurodegenerative diseases, such as Alzheimer's disease[52-54].

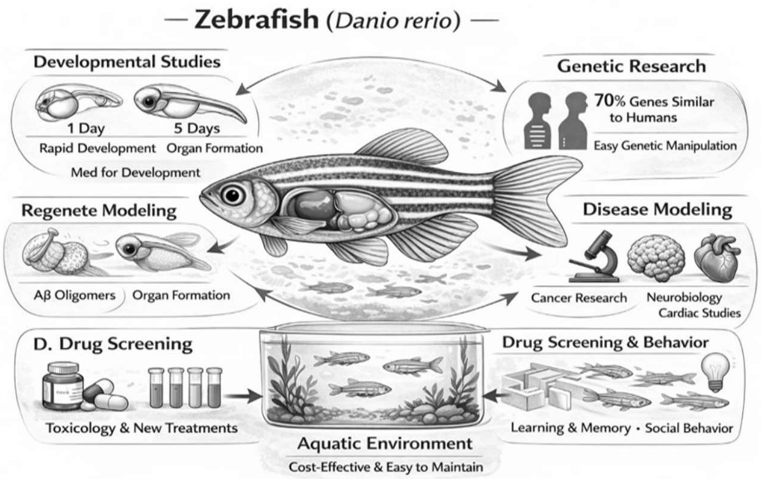
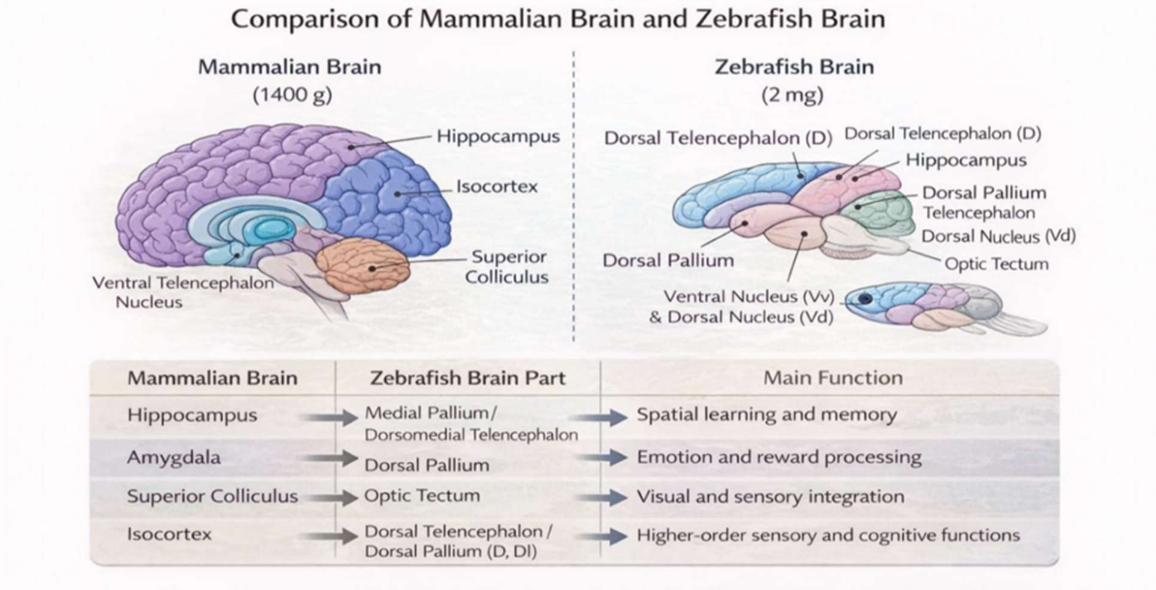


Fig 2. Major research applications of Danio rerio in disease modeling, genetic studies, and drug screening.

Comparative Neurobiological Insights of Zebrafish and Mammalian Model

Despite obvious evolutionary differences in brain shape, comparative neurobiological investigations show a high degree of conservation between zebrafish and mammalian brain organisation and neurochemical pathways[55-59]. Zebrafish have functionally similar brain areas that facilitate learning, memory, emotion, and sensory processing even though they lack a laminated cortex and hippocampus[60]. Because the zebrafish brain develops by eversion rather than inversion and is divided into forebrain, midbrain, and hindbrain divisions, classical mammalian structures like the hippocampus and amygdala are not anatomically present but are represented by homologous pallial regions with similar functions[61-63]. Conserved cognitive, emotional, sensory, and motor functions are supported by functional correlation between zebrafish and human brain regions, such as pallial, subpallial, tectal, and hindbrain structures (Fig.3). The use of zebrafish as a pertinent vertebrate model for researching cognition and neurodegenerative diseases like Alzheimer's disease is supported by this preserved neuroanatomical and functional organisation, despite structural changes[64,65]. (Fig. 3)



Mammalian Brain	Zebrafish Brain Part	Main Function
Hippocampus	Medial Pallium/ Dorsomedial Telencephalon	Spatial learning and memory
Amygdala	Dorsal Pallium	Emotion and reward processing
Superior Colliculus	Optic Tectum	Visual and sensory integration
Isocortex	Dorsal Telencephalon / Dorsal Pallium (D, Dl)	Higher-order sensory and cognitive functions

Fig 3. Comparison of major brain regions in mammals and zebrafish with their corresponding functions.

Zebrafish as a Genetic and Pathophysiological Model for Alzheimer Disease

Since many human genes and pathways are conserved, zebrafish are useful for studying Alzheimer's disease. The hallmarks of AD, such as β-amyloid buildup, neuronal loss, microglial activation, synaptic degradation, and behavioural impairments, are triggered by injection of $A\beta_{42}$ or expression of human Swedish mutant APP[66-71]. Two APP genes (appa, appb) and two tau genes (mapta, maptb) that produce isoforms like human 3R/4R tau are present in zebrafish. Hyperphosphorylation, aggregation, neurodegeneration, and poor protein clearance result from the expression of human MAPT mutations (P301L, A152T) or tau overexpression[72-73,81-84].

Zebrafish have been used to imitate the familial AD genes PSEN1 and PSEN2, which cause cognitive impairments, Aβ buildup, synaptic decrease, loss of histaminergic neurones, altered Notch signalling, and, in PSEN2 K115fs, early brain ageing and immunological activation[74-77]. According to pathophysiology, high $A\beta_{40/42}$ causes vascular abnormalities and cell death, while moderate Aβ stimulates cerebrovascular expansion[78-80]. All of these models show zebrafish as a quick and affordable platform for researching tauopathy, AD pathways, and cerebrovascular pathology.

Congentive and Behavioral Correlates

Strong behavioural parallels between zebrafish and humans are shown by a number of anthropomorphic behavioural tests, suggesting conserved brain circuitry and behavioural mechanisms. Numerous physiological and cognitive processes, involving feeding, learning, sensory processing, and emotional behaviours including fear, anxiety, social interaction, and decision-making, have been studied in zebrafish[85-103]. Significantly, axonal projections and hypocretin/orexin neurone expression patterns are preserved in humans and zebrafish, indicating functional similarities in arousal and sleep control[104].

Additionally, zebrafish have been widely used to study circadian rhythm-regulated locomotor activity and sleep-like states[104]. The pathophysiology of Alzheimer's disease is intimately linked to circadian rhythm disruptions[105-110], while the exact molecular connections are still unknown. Zebrafish and mammals have several molecular components that control circadian rhythms[111-113]. Zebrafish can be used as a vertebrate model to research complicated behaviours connected to neurodegenerative illnesses because of their conserved cholinergic neurotransmitter system, which also controls reward-related behaviour[114].

Parallel Neurotransmitter Systems in Zebrafish and Mammalian Models

Alzheimer's disease (AD) pathology is largely caused by neurotransmitter dysregulation; loss of cholinergic, glutamatergic, GABAergic, dopaminergic, and serotonergic signalling contributes to behavioural abnormalities and cognitive decline[115-119]. Mammals and zebrafish have similar neurotransmitter systems, such as glutamatergic NMDA receptor signalling, cholinergic circuits in the telencephalon that promote memory, and extensive GABAergic inhibitory regulation[120-135]. Zebrafish are a translational system for researching neurotransmitter-mediated processes of AD and assessing possible treatments since these pathways can be pharmacologically altered to simulate AD-like impairments[136,137].

Neurotoxin-Induced Zebrafish Models of Alzheimer's Disease

In zebrafish, neurotoxin-induced models are frequently employed to facilitate pharmacological screening and replicate specific clinical and cognitive aspects of Alzheimer's disease. Compounds that target the cholinergic system are often used since cholinergic dysfunction is a major characteristic of AD. Acetylcholinesterase inhibitors can correct the learning and memory deficits that scopolamine, a muscarinic acetylcholine receptor antagonist, consistently causes in zebrafish, demonstrating its usefulness as a model of cholinergic cognitive impairment[138,139].Okadaic acid (OKA), a protein phosphatase 2A inhibitor that causes tau hyperphosphorylation, synaptic dysfunction, and memory impairment in zebrafish, has been used to imitate tau-related disease in addition to cholinergic disruption[140]. This model is frequently used in mechanistic and drug discovery research because it replicates a number of neuropathological characteristics pertinent to AD. Heavy metals and other environmental neurotoxins have also been studied; exposure to aluminium causes cholinergic dysfunction and locomotor impairments[141-143], while lead has been demonstrated to modify APP-related pathways, although its direct connection to AD pathophysiology is yet unknown[144].

Zebrafish Behavioral Models for Alzheimer's Research

Alzheimer's disease (AD) can cause a variety of symptoms in humans, including motor dysfunction, behavioural and emotional disorders including anxiety, agitation, depression, and hallucinations, and cognitive deficiencies like poor memory, spatial recognition, problem solving, and language[145,146]. Behavioural outcomes are trustworthy indications of disease modelling and therapy efficacy at the organism level since exposure of zebrafish to AD-inducing drugs similarly causes cognitive and memory deficits. Because they are diurnal and have sophisticated visual, hearing, and olfactory capabilities, behavioural evaluation is made easier. While adult zebrafish have more sophisticated behavioural repertoires associated with greater cognitive function, larval zebrafish are especially well-suited for large-scale high-throughput behavioural screening[147]. It is simple to administer drugs to zebrafish through water exposure, which enables assessment of toxicity, bioavailability, and efficacy at various stages[148]. Table 1 summarises commonly used zebrafish behavioural assays related to AD research.

Table 1: Zebrafish behavioral assays used in Alzheimer's disease research

Behavioral assay	AD-related domain assessed	Life stage	Key behavioral readouts	Relevance to AD pathology	References
Locomotor activity	Motor function, anxiety	Larvae / Adult	Distance traveled, swimming velocity,	Detects neurotoxicity, motor impairment, and	149 – 151

			turning angle	general neural dysfunction	
Novel tank diving test	Anxiety, exploration	Adult	Time spent in bottom/top zones, freezing, erratic movement	Models anxiety-like behavior and stress responses observed in AD	152 – 156
Y-maze test	Spatial memory, novelty recognition	Adult	Time spent in novel arm, spontaneous alternation (%)	Assesses short-term memory and cognitive flexibility	157 – 160
T-maze test	Learning and associative memory	Adult	Correct arm choice, latency, time spent in target arm	Evaluates long-term learning and memory deficits	161– 163
Inhibitory avoidance test	Aversive learning, long-term memory	Adult	Latency to enter dark compartment	Measures memory retention and cognitive decline	164
Light–dark test	Anxiety, locomotion	Larvae /Adult	Time spent in light zone, transitions, activity levels	Suitable for Anxiety; HT drug screening	165 – 168

Advantages of the zebrafish model for AD

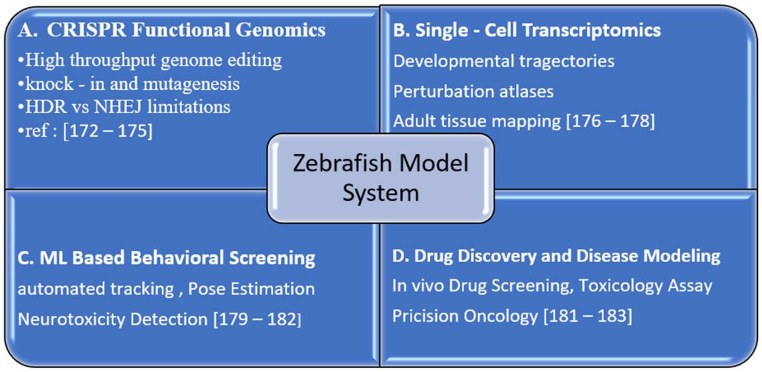
Due to their excellent genetic tractability, zebrafish (Danio rerio) are an effective model for studying Alzheimer's disease because they make it possible to efficiently create transgenic and gene knockout lines for AD-associated genes such APP, PSEN1, PSEN2, and APOE4. Large-scale genetic screens and real-time imaging of early AD-related clinical alterations, like as tau pathology and Aβ aggregation, are made possible by their quick development, high fecundity, and optical transparency. Furthermore, zebrafish exhibit quantifiable behavioural traits related to memory, learning, and movement, and they are ideal for high-throughput drug screening, which speeds up the search for new treatments[13].

Limitations of zebrafish as an AD model

Zebrafish have limits in translational AD research, despite these benefits. Pharmacological measurement is made more difficult by the unexpected chemical absorption that results from drug delivery via aquatic exposure[169]. Moreover, post-translational processing of APP and characterisation of zebrafish-specific Aβ peptides are still poorly understood[170]. Although it offers important insights into neuroinflammation and regenerative mechanisms, a significant biological limitation is their lifetime neuroregenerative capacity, including microglia-mediated neurogenesis after Aβ exposure, which differs from mammalian AD pathology and may limit direct disease modelling[171].

Recent Advances and Applications

Zebrafish (*Danio rerio*) offer an effective vertebrate model system due to their genetic tractability, transparent embryogenesis, and high fecundity. Recent developments in technology, such as single-cell transcriptomics, CRISPR-based functional genomics, and machine learning-driven behavioural phenotyping, have increased the use of zebrafish in fundamental and applied research. A detailed overview of these advances is presented in Table 2.



DISCUSSION

Zebrafish are increasingly recognized as a useful vertebrate model for Alzheimer's disease due to their genetic tractability, conserved neurochemical pathways, and ability to replicate core AD hallmarks such as amyloid-β deposition, tau hyperphosphorylation, synaptic loss, and cognitive decline. High-throughput screening techniques that are challenging in mammalian systems are made possible by genetic and pharmacological alterations, and their transparent embryos and quick life cycle allow direct visualisation of disease processes. Well-established behavioral assays provide sensitive readouts of memory, learning, anxiety, and locomotor function relevant to AD pathology.

Despite these advantages, there are a few drawbacks. Pharmacokinetic comparisons with humans are complicated by the fact that drug uptake mostly happens through water exposure. Strong adult neurogenesis and regenerative responses may reduce neurodegeneration, and results must be interpreted carefully because to species-specific variations in APP processing. These characteristics, however, also present chances to identify endogenous neuroprotective and regenerative pathways that may guide the development of new treatment approaches.

CONCLUSION

Zebrafish provide a powerful complementary platform for Alzheimer's disease research. They enable preclinical drug discovery through high-throughput screening, reproduce important AD characteristics, and facilitate effective mechanistic investigations. Direct translation is limited by species-specific variations in regenerative ability, but combining zebrafish with mammalian and human-derived models speeds up the creation of possible treatments and the understanding of disease causes.

ACKNOWLEDGEMENTS

I would like to express my heartfelt gratitude to my guide for constant support, guidance and encouragement me during preparation of this review article. I am also thankful to the department of pharmacology, Ashokrao Mane College of Pharmacy, Pethvadgaon for providing the necessary facilities and literature support.

CONFLICT OF INTREST

The authors declare that there is no conflict of intrest.

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