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Review paper

Systemic Review and Role of Zebrafish as a Pharmacological Model

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ABSTRACT

Zebrafish (*Danio rerio*) are transforming drug discovery and safety assessment. Their genetic similarity and transparent embryos enable real-time visualization of drug effects. This has led to breakthroughs in neuropharmacology, cardiology, and oncology, paving the way for personalized medicine. Zebrafish also provide a cost-effective and ethical alternative for toxicology testing. Their sensitivity to toxins and human-like development aid in identifying potential hazards. This has informed risk assessment and the development of safer, more efficacious therapeutics. Overall, this systematic review demonstrates the significant role of zebrafish as a pharmacological model and underscores its importance in advancing drug discovery and development. Future research utilizing zebrafish is expected to further enhance our understanding of pharmacology and lead to the development of new and effective therapeutics for various diseases.

1. Introduction

Zebrafish (*Danio rerio*) was first described by Francis Hamilton in 1822 and was found near river Kosi, Nathpur, India and named as *Cyprinus rerio*, the founding father of zebrafish research was George Streisinger. It is also known as *Brachydanio rerio*. Zebrafish is a freshwater vertebrate that is prominently used as a pharmacological model for drug discovery and medical research. These fish are ideal for abundant research because of their combination of genetic, physical and economic factors and these aspects provide a possibility to advance the process of drug delivery. A couple of adult zebrafish, due to their rapid weekly breeding cycles, can produce between 100 and 200 offspring through external fertilization[1]. Zebrafish are endemic in India, Pakistan, Bangladesh, Nepal and Myanmar where they multiply in stagnant standing water bodies like ditches, streams, ponds, rice fields and canals typically live at the bottom of natural habitat[2]. The temperature conditions required for maintenance of zebrafish larvae in a laboratory is around 28.5°C, which naturally hatches within 2.5-3 days post fertilization. They generally feed on a wide variety of benthic and planktonic cr-

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-ustaceans, including worms and insect larvae as they are omnivores. They also help in controlling mosquitoes as they feed on dipteran larvae. The average lifespan of laboratory zebrafish is expected to be above 5 years. These are batch spawners and asynchronous, after attaining sexual maturation they spawn continuously under favorable conditions. Their reproduction is mainly governed by photoperiod(night)[3]. Housing water temperature for maintenance of zebrafish varies from 24–29 °C [4]. It is widely for research and treatment of neurodegenerative disease and studying viral, genetic, fungal, bacterial, parasitic, metabolic diseases and veterinary research. Adult zebrafish are small with a length of 2.5 cm and have a short generation time i.e. 3-4 months. Their transparent egg wall gives a chance to observe the development of fish and use it for particular research. Many research techniques help to improve the diversity and quality of zebrafish research such as fluorescent tracer time-lapse lineage analysis, fate mapping and single-cell transplantation[5].

2. Zebrafish in comparison with other laboratory animals

The maintenance of zebrafish is much cheaper than other laboratory animals like rats and mice. It requires less space compared to the rainbow trout (a model organism popular in aquaculture). zebrafish share the same gene with vertebrates, has a full operational immunologic system and embryo transparency and can be used to observe the pathogenesis of fluorescent-labeled pathogen[5]. The maximum lifespan of a laboratory zebrafish is 2 -3 years. Zebrafish can be a valuable species to investigate the relationship between early growth rate and longevity. zebrafish and mouse show approaches for conventional transgenic overexpression but the cost and technical complications of generating transgenic zebrafish are lower. Pathological analysis is simpler and more cost efficient in zebrafish as we can place an entire adult fish on a single microscopic slide[6]. Medaka unravels is a fish model similar to zebrafish which has common ancestors. They have similar reference genomes and features to that of zebrafish such as size, diet, organ system, gross anatomy and living environment. They vary in regenerative capacity as medaka shows uneven regenerative capacity[7]. Unlike many vertebrates, cleavage is holoblastic whereas in zebrafish teleost cleavage is meroblastic[8]. Zebrafish are preferable for the study of vertebrate development and study than Rodent models. As laboratory animals easily get stressed certain human behaviors are not produced accurately, hence researchers prefer the zebrafish model[9].

3. Similarity between Zebrafish and humans

Zebrafish hold similar organs as that of humans such as blood, muscles, pancreatic adipose tissue, kidneys, eyes, skeletal muscle and hold high genetic similarities mainly in the central nervous system. It shares approximately 70% of its genes with humans and also shares 12,719 genes with mice and other animals[9].

4. Zebrafish in toxicity screening

Zebrafish play an important role in environmental toxicity testing and preclinical drug discovery. Researchers have established the degree to which zebrafish assay can estimate toxicity in humans. Considering the limitations of in vitro approaches and traditional mammalian models. Researchers have increased their appeal towards zebrafish-based assay to evaluate toxicity endpoints. The zebrafish model is used to understand different toxicity studies like teratogenicity, cardiotoxicity, neurosensory organs toxicity and nanoparticle toxicity. Zebrafish larvae or embryos are the aspiring models for high throughput in vivo screening of organ systems[10]. They have a notably higher susceptibility to toxins than adult zebrafish. Zebrafish as a toxicological model can reveal developmental mechanisms as they are similar to mammals. The zebrafish model gives perception into the mechanism of toxicity of herbal medicinal plants, it also helps to recognize and discover new medications for the treatment of human disease. This model can be used as a substitute model for higher vertebrate animals to study the toxicity of medicinal plants[11]. Different toxicity techniques are automated zebrafish egg sorting, automated removal of chorions, automated imaging systems, automated microinjection, Dechorionated Zebrafish Embryo Developmental toxicity assay or culture assay, Cystic kidney disease model, FISH inspector, Multiparametric renal function assay, Computer aided automation in imaging analyses, automatic feature recognition, Next-gen CRISPR/ Cas9, single nucleotide editing, RNA-Seg, scRNA-seg[12].

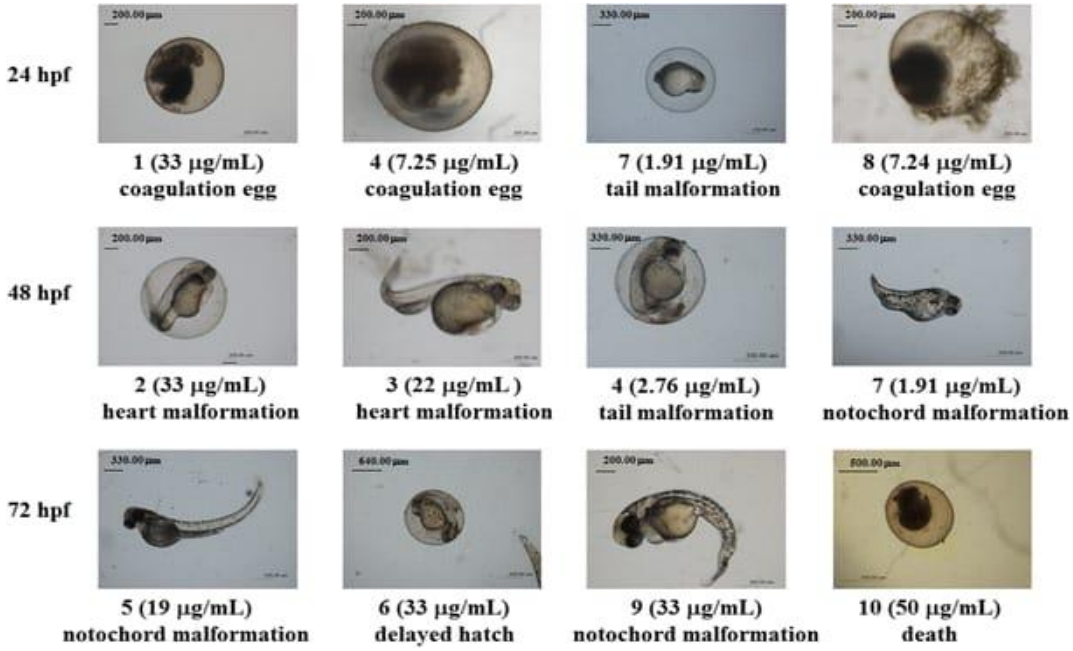

Fig. 1 Representative toxicological endpoints in zebrafish embryo toxicity test of compounds 1–10 at different concentrations

5. Zebrafish as a model in Alzheimer's disease

Alzheimer's disease is the most prevailing form of dementia. The clinical sign of AD is accelerating memory loss, it can also be depicted by impairment of speech, motor ability, and aggressive behavior. Zebrafish is quickly becoming an appealing model for alzheimer's research. The researchers so far analyzed that the zebrafish brain has an acceptable level of resemblance of basic brain structure with mammals, they also have similar neuroanatomical and neurochemical pathway which has an important role in human disease[13]. The dorsal, medial and lateral pallium of zebrafish are identical to isocortex, amygdala and hippocampus in other vertebrates respectively. Several anthropomorphic assays have been rendered to show identical behavioral patterns between zebrafish and humans. Sleep behavior patterns are similar to humans[14]. The conservation of the Aβ domain and secretases between zebrafish and humans suggests that zebrafish may possess similar molecular machinery for APP processing[15]. Different pharmacological models of AD in zebrafish are cholinergic neurotoxins, glutamatergic neurotoxins, GABAergic neurotoxins and AD neurotoxins. Comparative study of zebrafish with other animals will assist in comprehending the molecular basis of AD and establish a peculiar approach to avert neurodegenerative diseases[16]. The beneficial characteristic of zebrafish is the optical clarity of the embryo which helps in phenotypic visualization of gene effects in the development process and helps in understanding transient genetic manipulations and chemical manipulations. These characteristics with orthologous genes in humans make zebrafish a viable model to study AD in contrast to rodents. When AD inducing drug is given to zebrafish it shows cognitive and memory impairments. Zebrafish can be grouped based on basic motor responses which include observed sensorimotor response which shows enhanced learning and memory related reactions of fish. The different behavioral model of adult zebrafish is Y-maze test, T-maze test and Hole board test[17]. Metals like lead, aluminum, copper and manganese help to induce memory loss and Amyloid-β42 (Aβ42), the microtubule-associated protein tau (MAPT) and Okadaic acid (OA) help to induce neurodegeneration in zebrafish [18].

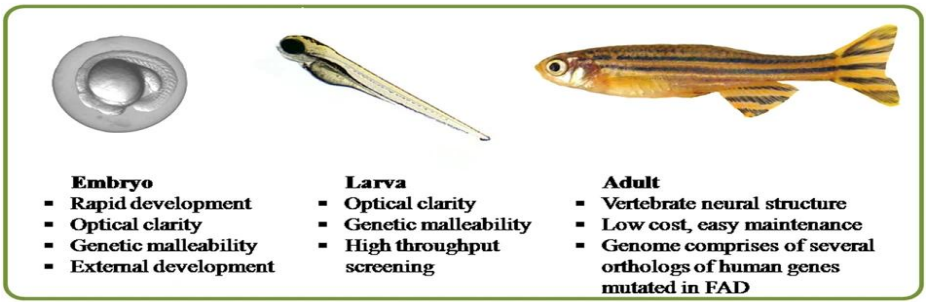

Fig. 2 Advantages of zebrafish

6. Zebrafish as a model in Parkinson's disease

Parkinson's disease also called as Hypokinetic rigid syndrome or Paralysis agitans is a part of the complex set of neurological disorders. These disorders are characterized by a lack of ability to initiate or regulate movements. Parkinson's is the most common movement disorder, impacting 100 to 200 per 100,000 individuals[19].

A critical analysis should be taken while selecting a model organism to determine the value of findings concerning human diseases. A high level of replicability must be possessed by studies of a model. A meta-analysis of transgenic mouse models of alzheimer's disease found that these models were not always the same within their own group, between groups or in human alzheimer's disease models, showing poor replicability. Many of the therapies developed with animal models did not show good human trials for various reasons. We should look into these obstacles when developing animal models of human diseases. When considering invertebrates the clear disadvantages of them are lack of brain structures and organ systems that are similar to humans, making them inaccurate as models for human diseases. The brain of a zebrafish is similar to that of mammals in sections like the forebrain, midbrain, and hindbrain, accompanied by a diencephalon and telencephalon, having their primary neurotransmitter functions identical to that of humans. One of the significant advantage of zebrafish is their adaption to genetic manipulation creating thousands of genetically altered strains. Another advantage of zebrafish is having a blood-brain barrier resembling that of mammals. Creating genetically modified zebrafish that display a specific genotype or phenotype is less labor-intensive than it is with rodents. Reason is the ability to inject DNA and RNA in a single cell with ease which is facilitated by the external fertilization and development process of fish[20].

7. Zebrafish as a model in Diabetes Mellitus

Zebrafish serve as an emerging disease model organism in diabetes research. Their glucose metabolism and reactive metabolite pathways closely resemble those of humans. Here are some established protocols for altering blood glucose levels in zebrafish.

7.1 Simple and Effective Techniques

7.1.1 High-fat diet

This straightforward approach involves raising the glucose concentration in the water where zebrafish reside. Exposing zebrafish to high-glucose environments (up to 4% for two months) effectively induces hyperglycemia in both young and adult stages, replicating a key feature of diabetes[21]. The elevated blood glucose levels could be maintained by alternating incubation such as water containing 2% glucose and glucose free water for over a long period. This experimental setup allows researchers to study the effects of elevated glucose levels on zebrafish physiology and potentially model conditions such as hyperglycemia or diabetes in these organisms[22].

7.1.2 Alloxan Injection

Alloxan, a specific chemical, can be directly introduced into zebrafish through a single intraperitoneal injection (300mg/kg). This method has proven successful in elevating fasting blood glucose levels, mimicking another hallmark of diabetes[23].

7.1.3 Monitoring Blood Glucose Levels

The blood glucose levels in adult zebrafish are reported in a range of 50-75 mg/dl which is around human physiological levels of 100mg/dl. Moreover, blood glucose is dynamically regulated either by fasting or feeding of zebrafish[24]. The glucose levels in zebrafish reach a maximum level at 24 hpf and decrease when start developing embryos. The production of insulin lowers glucose during later embryonic development stages[25].

8. Zebrafish as a model in cancer research

Zebrafish is a non-mammalian vertebrate that emerged as a popular model for cancer research mainly pre-clinical cancer models other than laboratory mice, as zebrafish is cost-effective maintenance, rapid fertilization and is capable of producing a large number of fertilized eggs. zebrafish is a main resource in human cancer

xenotransplantation studies. since zebrafish lack certain organs for study of human tumors, scientists insert cancer cells into zebrafish by microinjection of transgenic and mutant lines or by xenotransplantation. zebrafish has a unique feature that is body transparency, useful for researchers to observe the cancer cell's growth, tumor invading into other cells and helps in better understanding regarding cancer cells. Zebrafish is preferred as a model for the study of various cancers such as melanoma, carcinoma of breast, leukemia, hepatocellular carcinoma, prostate cancer, tumor induced non angiogenesis and vascularization and recently for the study of colorectal carcinoma [26]. Zebrafish xenografts show gene profiling features similar to human tumors and also share 70-80% of orthologous with human genes. Laboratory mice require longer duration, not suitable for high output screening and toxicity testing of anticancer drugs. Scientists make use of epifluorescence and confocal microscopes for identifying cancer progression[27]. There are various methods for establishing a human cancer model in zebrafish which have both advantages and disadvantages including the insertion of mutant lines which decides the upcoming tumorigenesis, in transgenic lines transgenic are injected into zebrafish by micro injecting exogenous DNA into zebrafish embryos at one-cell stage and, another method is by transplantation of mammalian tumor cells for understanding the progress of ontogenesis and invasion of tumors into other cells. Zebrafish embryos are mainly preferred for visualizing progress in cancer cells because of their transparent body and tumor cells grow vigorously in embryos when compared to adults. Adults are used as in-vivo model and assay models. It requires only 10-14 days for the formation of tumors in zebrafish but in the murine model, it needs at least 4 months to notice tumor growth. Tumor cells are injected into extensive organs in zebrafish including liver, pancreas, intestinal canal, skin, muscle and testis[28]. Due to their small size zebrafish require only few fractions of cancer stem cells and metastasis is visible within two days after injecting stem cells[29].

Table 1 Chemicals used to induce diseases in different stages of zebrafish

Disease	Model animal	Chemical used to induce	Stage of zebrafish	Reference
Alzheimer	Zebrafish	Valproate	Adults	30
		Carbachol	Adults	30
		Pilocarpine	Adults and larvae	30
		Ketamine	Adults	30
Parkinson	Zebrafish	1-Methyl-4-Phenyl-1,2,3,6-tetrahydropyridine	Adults and larvae	20
		Rotenone	Adults	20
		Titanium dioxide nanoparticles	larvae	20
Diabetic mellitus	Zebrafish	Bisphenol S induced model of hyperglycemia	Adults	31
		Bisphenol F induced model of hyperglycemia	Larvae or embryonic stage	32
Cancer	Zebrafish	N-ethyl-N-nitrosourea [ENU]	Embryo	33
		N-methyl-N-nitroguanidine [MNNG]	Embryo	33
		Dimethylbenzanthracene [DMBA]	Embryo	33
		N-nitro diethyl-amine [DEN]	Embryo	33

9. Disscusion

Zebrafish hailed as a versatile model organism, have revolutionized scientific research across various fields notably pharmacology, drug discovery and medical studies due to their genetics, ease of breeding, and cost-effectiveness. Zebrafish initially named Cyprinus rerio, were discovered in India in 1822. George Streisinger pioneered zebrafish research. Found in South Asian countries, they inhabit stagnant water bodies. Zebrafish in comparison with other laboratory animals is advantageous. Maintenance of zebrafish is cheaper than that of rats, mice and other laboratory animals. Zebrafish genes are similar to vertebrates, they have a fully functioned immune system. Zebrafish embryo transparency helps in drug discovery and toxicity screening. Pathological analysis is simpler and more cost effective in zebrafish. Zebrafish have striking similarities with humans in physiological processes and organ structure. Zebrafish have high genetic similarities with humans i.e. approximately 70%. Zebrafish serves as a comparative model in toxicity screening of new drug discovery,

treatment of human diseases, evaluating drug safety, estimating and understanding different toxicity studies. Due to higher sensitivity to toxins, early larval and embryo models of zebrafish are selected for in-vivo toxicity screening compared to adult zebrafish. Different toxicity techniques are used for assessing toxicity screening. Zebrafish is preferred as a model in translation research in human neurodegenerative diseases like alzheimer's and parkinson disease. Zebrafish model is selected in contrast to rodents and laboratory mice due to their similar brain physiology and anatomy resembling human brain structure; neurotransmitter function and their high level of replicability encourage genetic manipulation. Various toxins of parkinson disease are exposed to zebrafish resulting in loss of dopaminergic neurons whereas in alzheimer research drugs are induced causing memory impairment in zebrafish, both help in better understanding of the mechanism underlying neuronal loss in zebrafish. 3D imaging techniques are rapidly used in the zebrafish model for alzheimer research. Genetic manipulation and microscopic imaging techniques help in researching Parkinson disease for in-vivo visualization of cells and tissues. The Major drawback of zebrafish model in parkinson research is parkinson disease typically occurs in adults or older individuals but in the case of zebrafish, most of the research is carried out in larval, juvenile/ young adult stages. Zebrafish model resembles glucose metabolism and metabolic pathways with humans. Variations in blood glucose levels are seen in zebrafish that is before 24 hours of post fertilization and when the embryo starts developing and insulin production gradually decreases further development of the embryo. Various techniques and protocols are selected for altering and inducing hyperglycemia in zebrafish such as feeding of high fat diet or through alloxan injection, in turn it elevates glucose levels in zebrafish which helps researchers to study detailed effects of alterations in blood glucose levels. Zebrafish has been an alternative model for the study of tumor metastasis, mechanism, pathophysiology and treatment of cancer. Zebrafish emerge as a wide scope of cancer and development of tumors in distinct organ sites analogous to human malignancies both patho-histologically and genetically. Transplant of mutant cells and transgenic cancer cells, xenotransplantation into zebrafish gives a better understanding of human cancer, evaluating cancer cell growth, drug toxicity, in vivo research and clinical translation. Body transparency of zebrafish allows researchers for easy visualization of cancer progression.

10. Conclusion

Zebrafish are cost effective in maintenance; they have longer lifespans when compared to other laboratory animals and share similar genes with other vertebrates. Their transparent embryos and fully functioning immune system allow researchers to observe development and pathogenesis. Additionally, zebrafish are easier and cheaper to analyze than other models like rodents. While medaka fish share the same ancestors but differ in regenerative capacity. Overall, zebrafish are a preferred choice for studying vertebrate development and behavior due to their unique features and lower stress response. Zebrafish are a remarkably valuable model organism for studying human biology and disease due to their genetic and physiological similarities. They share a high percentage of genes with humans, particularly in the central nervous system, and possess similar organs relevant to human organs. This genetic similarity makes them a powerful tool for researchers to investigate human diseases and development. Zebrafish is effectively used as a toxicity model to examine new drug/chemical toxicity in different target tissues and for estimation of toxicity in humans. Using different concentrations of drugs, toxicity tests are evaluated in zebrafish embryos, mainly toxicity tests of herbal medicinal plants. Zebrafish mimic human diseases mainly in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease. Their sleep behavior pattern, disease-relevant behavior and brain structure resemble humans and they possess similar neuroanatomical and neurochemical pathways that are prominent in human diseases. The optical clarity of zebrafish embryos helps in a better understanding of the pathology of alzheimer and parkinson disease, especially gene effects. Since genetic manipulation is effectively achieved in zebrafish, various strains are created in zebrafish for parkinson research and various pharmacological model of alzheimer disease are employed in zebrafish. Diabetes mellitus leads to increased blood glucose levels due to a decrease in the production of insulin hormone. While comparing blood glucose levels, adult zebrafish constitute about 50-70 mg/dl which is close to human glucose levels which is 100 mg/dl. Inducing hyperglycemia and monitoring glucose levels in zebrafish allows researchers to examine the mechanism and test treatment. For the last few years, zebrafish have been certified as an authentic model for recapitulating and visualizing human

tumors and cancer cell biology, especially in the embryonic stage. Zebrafish generate virtually all cancer types known from humans with similar morphology. Zebrafish develop cancer impulsively after mutagen exposure and xenotransplantation through transgenesis. Zebrafish are advantageous over other models in the speed of development of tumors, genetic manipulation, inexpensive and unique feature transparency. The Zebrafish cancer model generates a peculiar perception of the elemental mechanism of cancer thus useful for drug discovery.

Abbreviations

CRISPR	Clustered regularly interspaced palindromic repeats
AD	Alzheimer disease
APP processing	Amyloid Precursor Protein processing
Aβ	Amyloid beta
GABA	Gamma aminobutyric acid
RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
HPF	Hours post fertilization
mg/dl	milligram/deciliter
mg/kg	milligram/kilogram

References

1. Goldsmith P. Zebrafish as a pharmacological tool: the how, why and when. Current opinion in pharmacology. 2004 Oct 1;4(5):504-12.
2. Vargesson, Neil. (2007). Zebrafish in 'Manual of Animal Technology'.
3. Lawrence C. The husbandry of zebrafish (Danio rerio): A review. Aquaculture. 2007 Sep 14;269(1-4):1-20.
4. Aleström P, D'Angelo L, Midtlyng PJ, Schorderet DF, Schulte-Merker S, Sohm F, Warner S. Zebrafish: Housing and husbandry recommendations. Laboratory animals. 2020 Jun;54(3):213-24.
5. Nowik N, Podlasz P, Jakimiuk A, Kasica N, Sienkiewicz W, Kaleczyc J. Zebrafish: an animal model for research in veterinary medicine. Polish journal of veterinary sciences. 2015;18(3).
6. Gerhard GS. Comparative aspects of zebrafish (Danio rerio) as a model for aging research. Experimental Gerontology. 2003 Nov 1;38(11-12):1333-41.
7. Chowdhury K, Lin S, Lai SL. Comparative study in zebrafish and medaka unravels the mechanisms of tissue regeneration. Frontiers in Ecology and Evolution. 2022 Feb 1; 10:783818.
8. Schilling TF, Webb J. Considering the zebrafish in a comparative context. Journal of Experimental Zoology Part B: Molecular and Developmental Evolution. 2007 Sep 15;308(5):515-22.
9. Kandasamy T, Chandrasekar S, Pichaivel M, Pachaiappan S, Muthusamy G, Sumathi L. A review of zebrafish as an alternative animal model and its benefits over other animal models in various disease conditions. Saudi J. Biomed. Res. 2022; 7:355-9.
10. Eimon PM, Rubinstein AL. The use of in vivo zebrafish assays in drug toxicity screening. Expert opinion on drug metabolism & toxicology. 2009 Apr 1;5(4):393-401.
11. Modarresi Chahardehi A, Arsad H, Lim V. Zebrafish as a successful animal model for screening toxicity of medicinal plants. Plants. 2020 Oct 12;9(10):1345.
12. Bauer B, Mally A, Liedtke D. Zebrafish embryos and larvae as alternative animal models for toxicity testing. International journal of molecular sciences. 2021 Dec 14;22(24):13417.
13. Newman M, Ebrahimie E, Lardelli M. Using the zebrafish model for Alzheimer's disease research. Frontiers in genetics. 2014 Jun 30; 5:89269.
14. Saleem S, Kannan RR. Zebrafish: an emerging real-time model system to study Alzheimer's disease and neurospecific drug discovery. Cell death discovery. 2018 Oct 3;4(1):45.
15. Saraceno C, Musardo S, Marcello E, Pelucchi S, Di Luca M. Modeling Alzheimer's disease: from past to future. Frontiers in pharmacology. 2013 Jun 19; 4:77.
16. Santana S, Rico EP, Burgos JS. Can zebrafish be used as animal model to study Alzheimer's disease? American journal of neurodegenerative disease. 2012;1(1):32.
17. Shenoy A, Banerjee M, Upadhya A, Bagwe-Parab S, Kaur G. The Brilliance of the Zebrafish Model: Perception on Behavior and Alzheimer's Disease. Frontiers in behavioral neuroscience. 2022 Jun 13; 16:861155.

18. Thawkar BS, Kaur G. Zebrafish as a promising tool for modeling neurotoxin-induced Alzheimer's disease. Neurotoxicity research. 2021 Jun; 39:949-65.
19. Vaz RL, Outeiro TF, Ferreira JJ. Zebrafish as an animal model for drug discovery in Parkinson's disease and other movement disorders: a systematic review. Frontiers in neurology. 2018 Jun 1; 9:357994.
20. Doyle JM, Croll RP. A critical review of zebrafish models of Parkinson's disease. Frontiers in Pharmacology. 2022 Mar 15; 13:835827.
21. Connaughton, V.P.; Baker, C.; Fonde, L.; Gerardi, E.; Slack, C. Alternate immersion in an external glucose solution differentially affects blood sugar values in older versus younger zebrafish adults. Zebrafish 2016, 13, 87–94.
22. Gleeson M, Connaughton V, Arneson LS. Induction of hyperglycemia in zebrafish (Danio rerio) leads to morphological changes in the retina. Acta Diabetol 2007; 44: 157 – 163.
23. Mostafavinia, A.; Amini, A.; Ghorishi, S.K.; Pouriran, R.; Bayat, M. The effects of dosage and the routes of administrations of streptozotocin and alloxan on induction rate of type1 diabetes mellitus and mortality rate in rats. Lab. Anim. Res. 2016, 32, 160–165.
24. Eames SC, Philipson LH, Prince VE et al. Blood sugar measurement in zebrafish reveals dynamics of glucose homeostasis. Zebrafish 2010; 7: 205 – 213.
25. Jurczyk A, Roy N, Bajwa R et al. Dynamic glucoregulation and mammalian-like responses to metabolic and developmental disruption in zebrafish. Gen Comp Endocrinol 2011; 170: 334 – 345.
26. Hason M, Bartůněk P. Zebrafish models of cancer—new insights on modelling human cancer in a non-mammalian vertebrate. Genes. 2019 Nov 15;10(11):935.
27. Gamble JT, Elson DJ, Greenwood JA, Tanguay RL, Kolluri SK. The zebrafish xenograft models for investigating cancer and cancer therapeutics. Biology. 2021 Mar 24;10(4):252.
28. Letrado P, de Miguel I, Lamberto I, Díez-Martínez R, Oyarzabal J. Zebrafish: speeding up the cancer drug discovery process. Cancer research. 2018 Nov 1;78(21):6048-58.
29. Zhao S, Huang J, Ye J. A fresh look at zebrafish from the perspective of cancer research. Journal of Experimental & Clinical Cancer Research. 2015 Dec;34
30. Newman, M., Ebrahimie, E., & Lardelli, M. (2014). Using the zebrafish model for Alzheimer's disease research. *Frontiers in genetics*, *5*, 189.
31. Zhao, F., Jiang, G., Wei, P., Wang, H., and Ru, S. (2018b). Bisphenol S exposure impairs glucose homeostasis in male zebrafish (Danio rerio). Ecotoxicol. Environ. Saf. 147, 794–802. doi: 10.1016/j.ecoenv.2017.09.048.
32. Zhao, F., Wang, H., Wei, P., Jiang, G., Wang, W., Zhang, X., et al. (2018a). Impairment of bisphenol F on the glucose metabolism of zebrafish larvae. Ecotoxicol. Environ. Saf. 165, 386–392. doi: 10.1016/j.ecoenv.2018.09.017.
33. Al-Thani HF, Shurbaji S, Yalcin HC. Zebrafish as a model for anticancer nanomedicine studies. Pharmaceuticals. 2021 Jun 28;14(7):625.