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Zebrafish Models in Pharmacological Research: Unraveling Mechanisms and Discovering New Drug Targets

Gowtham.K[1]*, Jothika.I[2], Mohankumar.S[3], Mohamed anas.S[4], Ranjith.T[5], Santhosh.M[6], Surendra kumar.M[7], E.Sindhu[8]

[1*] Assistant professor, Department of Pharmacology, Senghundhar college of pharmacy, Tiruchengode-637205.
[2,3,4,5,6]student, Department of Pharmacy, Senghundhar college of pharmacy, Tiruchengode-637205.
[7]Principal, Senghundhar college of pharmacy, Tiruchengode-637205.
[8]Student, M.Pharm., (Pharmaceutics) Department, Sri Vijay Vidyalaya College of Pharmacy-636807

***Corresponding Author:**Gowtham.K
*****Assistant professor, Department of Pharmacology, Senghundhar college of pharmacy, Tiruchengode-637205.
(ORCID ID: 0000-0003-2506-8338)

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ABSTRACT
The zebrafish, scientifically known as Danio rerio, stands out as a potent model organism in biological research due to its advantageous features such as genetic tractability, rapid development, and transparent embryos. Initially recognized for its role in vertebrate development studies, zebrafish has expanded its reach into diverse fields including pharmacology, clinical research as a disease model, and notably, drug development. With applications spanning lead compound screening, target identification, morpholino oligonucleotide screens, assay development, and drug toxicity studies, zebrafish has proven to be a practical and cost-effective alternative to traditional mammalian models. This review provides a concise overview of the key characteristics that position zebrafish as an invaluable research tool across various biological processes, particularly underscoring its significance in pharmaceutical research.

1. INTRODUCTION:

The zebrafish, native to South Asia, has gained prominence in various biological research fields, including pharmacology, developmental biology, genetics, neurology, and toxicology. Its significance as a model organism arises from specific attributes.[1,2]

Drug discovery involves identifying chemical entities with medicinal potential. The goal is to uncover novel molecules addressing unmet medical needs, focusing on life-threatening conditions lacking proven treatments. Existing medications predominantly target ion channels, nuclear receptors and G-protein coupled receptors, with enzymes as the primary focus.

Despite promising leads, compounds may face challenges in development due to factors such as unknown variables during lead discovery. Issues like intolerable toxicity, insufficient biopharmaceutical qualities and inadequate in vivo efficacy can contribute to failures. Development may also be hindered by poor potency, ambiguous toxicological results and synthetic complexity.[2,4]

The zebrafish (Danio rerio), a widely utilized freshwater teleost, has been a prominent model in research since the 1980s.[3] Initially focused on developmental biology, the discovery of millions of zebrafish mutant models with conserved disease genes expanded its applications. Zebrafish's translational research potential grew due to its relevance to hereditary and acquired human disorders, aided by their external embryo development.

With the 2013 genome sequencing revealing significant genomic homology with humans, the zebrafish's role in translational research has expanded. Over two decades, it evolved into a crucial tool in drug research and development.[4] Zebrafish's suitability for medium-to-high-throughput screening in pharmacology

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investigations, owing to their robustness and easy maintenance, has contributed to their rise in the industry.

Measuring 5 cm as adults and 5 mm as larvae, zebrafish's scale characteristics make them ideal for systems-level approaches in examining gene, biology and chemical space relationships. Their high fecundity allows large stocks and their optical transparency enables non-invasive observation of internal organ morphology and function.[3] The emphasis on phenotype over genetics or experimental instruments makes them unparalleled for high-throughput phenotyping. Recent applications, such as using fluorescence-labeled mauthner cells to study zebrafish neuron regeneration, showcase the model's versatility.[1, 4]

2. ADVANTAGES OF ZEBRAFISH AS A MODEL ORGANISM:[4, 5]

Zebrafish, with a remarkable 80% genetic overlap with humans, stand out as a versatile model for contemporary research. Their extensively characterized genes allow for precise manipulation, rendering them cost-effective for product development. The shared genomic features between zebrafish and mammals underscore their relevance in drug development methodologies.Figure No. 1 shows the basic concept of Zebrafish models and comparison with human and their advantages.

2.1 TRANSPARENCY AND IMAGING:

Zebrafish embryos and larvae's transparency enables real-time imaging of drug interactions, tissue development and disease progression. This unique feature provides valuable insights into pharmacological effects at the cellular and subcellular levels.

2.2 GENETIC TRACTABILITY:

Zebrafish possess a well-characterized genome and genetic manipulation techniques like CRISPR/Cas9 allow researchers to create precise genetic modifications. This facilitates the investigation of specific drug targets and pathways.

2.3 RAPID DEVELOPMENT:

Zebrafish embryos undergo swift development, with organs and systems forming within days. This rapid development allows researchers to study drug effects and toxicity at various developmental stages, providing a holistic understanding of drug actions.

2.4 REGENERATIVE ABILITIES:

Zebrafish exhibit impressive regenerative capabilities, especially in regrowing fins, the heart and the central nervous system. This regenerative potential positions them as an ideal model for investigating tissue repair and regeneration.

2.5 DEVELOPMENTAL BIOLOGY:

Zebrafish embryos undergo rapid embryogenesis, providing a comprehensive understanding of vertebrate development. The transparency of embryos enables the visualization of organogenesis, making it an excellent system for studying developmental biology.

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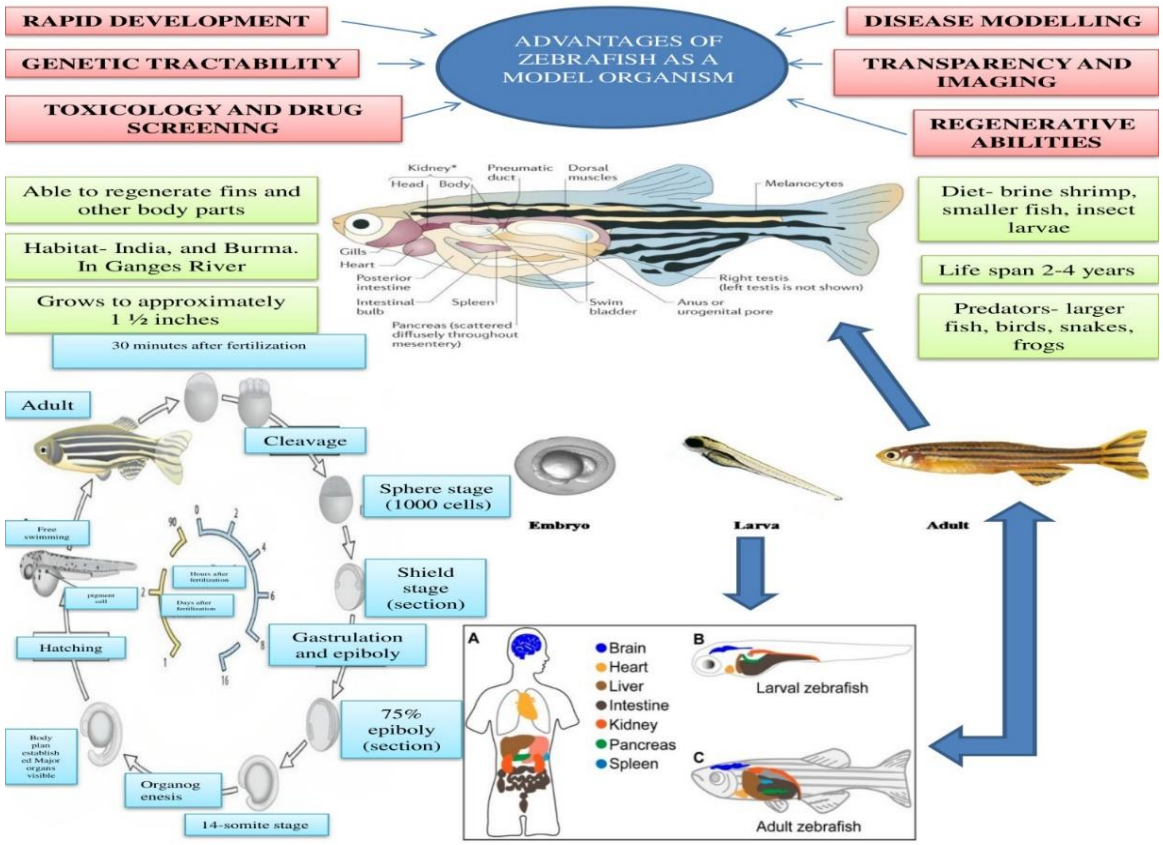

Figure No. 1: Basic concept of Zebrafish models and comparison with human and their advantages. [1, 12]

2.6 DISEASE MODELLING:

Zebrafish are successfully employed to model various human diseases, encompassing neurological disorders, cardiovascular diseases and cancer. Their physiological similarities to humans, combined with genetic manipulability, allow researchers to explore disease mechanisms and potential therapies.

2.7 TOXICOLOGY AND DRUG SCREENING:

Zebrafish models are invaluable for toxicological studies and drug screening. They prove instrumental in assessing the toxicity of environmental pollutants and pharmaceutical compounds, contributing significantly to safety evaluations.

3. ZEBRAFISH MODELS IN DISEASE RESEARCH: [1, 6]

Zebrafish serve as an excellent model organism for disease and translational research, witnessing a surge in utilization over the last five years. Table No.1 shows Different types of zebrafish models and organ used in disease and activity research.

3.1 Nutritional Abnormalities in Zebrafish:

Zebrafish, with major organs mirroring human metabolic control, are pivotal for studying obesity and metabolic diseases. Experimental manipulation of zebrafish blood sugar levels, simulating diabetes, revealed insights into diabetes-related complications such as retinal inflammation. Osmoregulation studies unveiled connections to glucose uptake, offering a unique perspective for investigating retinopathy.

3.2 Frameworks of Inflammatory Pathology in Zebrafish:

Zebrafish models aid in understanding inflammation and regeneration through tail injury-induced acute inflammation. These models enable the study of

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glucocorticoid mechanisms, anti-inflammatory properties and the development of new medications. Pro-resolution pathways, including lipoxins, contribute to inflammation resolution. Mast cells in zebrafish share similarities with those in mammals, offering insights into inflammatory responses.

3.3 Cancer Research in Zebrafish:

Zebrafish prove valuable in cancer research, demonstrating spontaneous tumorigenesis and offering methods such as genetic engineering, transgenic models, allografts, xenografts and high-throughput genetic screening. The transparent nature of zebrafish embryos allows real-time monitoring of tumorous growth, providing a unique advantage for cancer biology investigations. Zebrafish models replicate various human cancers and facilitate screening for potential treatments.

3.4 Cardiovascular Study Using Zebrafish as a Genetic Model:

Zebrafish offer advantages in studying cardiovascular genetic processes, providing transparent embryos for phenotypic screens. The prominent embryonic heart location allows visual evaluation of cardiovascular development. Genetic screenings reveal heart-specific abnormalities, aiding in understanding circulatory disorders. Zebrafish models mimic human responses to cardiac medications, making them valuable for drug discovery. High-throughput assays enable efficient screening for cardiovascular effects.

3.5 Zebrafish in toxicology and safety assessment:

Zebrafish serve as a valuable model for assessing drug developmental and reproductive toxicity, helping identify potential hazards early in drug development. Organ-specific toxicity, particularly affecting the heart and liver, is a crucial consideration in preclinical testing. Zebrafish, as vertebrate models, contribute to *in vivo* drug toxicity screening, efficacy assessment and safety evaluation. Safety pharmacology investigates adverse effects on respiratory, neurological and cardiovascular systems, influenced by various factors, including compound class and mode of action.

3.6 Embryotoxicity and teratogenicity:

Zebrafish models aid in studying embryotoxicity and teratogenicity, providing insights into compound-induced dysmorphology and pathophysiology. The fully mapped zebrafish genome facilitates understanding signaling pathways linked to teratogenicity. Drug impact on development and reproduction is rigorously evaluated, following procedures developed since thalidomide's teratogenic effects were identified. Zebrafish embryos' rapid development allows efficient testing of viability, morphological flaws, and new endpoints, expanding beyond simple death assessment.

3.7 Cardiotoxicity and hepatotoxicity:

Zebrafish embryos prove instrumental in toxicology investigations, especially for environmental contaminants and developmental toxicants affecting the cardiovascular system. Studies on cigarette exposure and continuous alcohol exposure highlight zebrafish utility in cardiovascular toxicity assessments.[9] Zebrafish models also demonstrate efficacy in evaluating human cardiotoxic medications, showcasing their relevance in drug cardiotoxicity research. Assessing hepatotoxicity involves both in vitro and *in vivo* models, with zebrafish embryos displaying similar gene changes to human hepatotoxins. The zebrafish liver's unique organization in tubules enables real-time monitoring of specific cell types' responses, contributing to liver damage studies for pharmaceuticals and environmental pollutants.

Table No.1: Different types of zebrafish models and organ used in disease and activity research.

S.No.	Activity or Disease Activity	Organ or Models of zebrafish
1.	Antibacterial Activity	Embryos And Tissue[13]
2.	CNS Effect Of Antimicrobial Drugs	Brain[14]
3.	Seizures Induced(Behavioral Characterization)	Adult Zebra fish[15]
4.	Epigenetics In Renal Disease	Kidney[16]
5.	Neurotoxic Effects And Neurodegeneration (Behavioral Assessment)	Brain[17]
6.	Senescence Independent Anti-Inflammatory activity	Zebra fishLarvae[18]
7.	Inflammatory bowel Disease	Intestine[19]
8.	Lipid-Lowering drug Induced Myopathies	Muscle[20]

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9.	Cancer therapy Induced Cardiovascular Toxicity.	Heart[21]
10.	Glioblastoma Cellular And Molecular Mechanisms	Glial Cells[22]
11.	Toxicity	Embryo[23]
12.	Drug- Induced Liver Injury	Liver[24]
13.	Neuropsychopharmacology & CNS Drug Discovery	Brain[25]
14.	Locomotor Activity	Brain[26]
15.	Optical Mapping Of Neuronal Activity During Seizures	Brain[27]
16.	Alzheimer's Disease.	Brain[28]
17.	Neutrophilic Inflammation	Larvae Neutrophils[29]
18.	Embryo Toxicity	Zebrafish Blood[30]
19.	Autism Spectrum Disorder (ASD)	Brain[31]
20.	Analysis Of The Retina	Eye (Retina)[32]
21.	Thyroid Gland Development And Function	Thyroid gland[33]
22.	Dual Oxidase - Anti- Bacterial Properties	Larvae[34]
23.	A Model Of Superinfection of: Increased Susceptibility To Bacteria Associated With Neutrophil Death.	Virus-Infected Zebrafish Larvae[35]
24.	Antibiotic Chlortetracycline Causes Transgenerational Immunosuppressant Ianf-Kb:	Larvae[36]
25.	Anticarcinogenic And Antioxidant Action Of An Edible Aquatic Flora Jussiaea Repens L.	Larvae[37]
26.	Mucosal Inflammation At The Repository Interface	Zebrafish gills[38]
27.	Quantitative analysis of Protein Turnover And Tissue Regeneration	Tissues[39]
28.	Screening Of Antimycobacterial Compounds	Naturally Infected Zebrafish Larvae Model[40]
29.	Antifungal Activity Of 2′- Hydroxychalcone Loaded In Nanoemulsion Against Paracoccidioides Spp.	Whole Zebrafish[41]
30.	Influenza A And Exacerbate Disease -Duchenne Muscular Dystrophy	Virus Infection Damage Zebrafish Skeletal Muscle[42]
31.	Spermatogonial Stem Cell Niche Spermatogonial Stem Cell Transplantation	Spermatogonial Stem Cells (SSCS)[43]
32.	Estrogen Signaling Influences Nephron Segmentation	Zebrafish Embryonic Kidney.[44]
33.	Exocrine Pancreas Development	Pancreas[45]
34.	Ocular Tuberculosis.	Eyes[46]
35.	Bacterial Meningitis In Streptococcus Agalactiae Infection.	Adult Zebrafish.[47]
36.	Visual Of Von-Hippel Lindau Disease	Eye[48]
37.	Attention Deficit Hyperactivity Disorder (ADHD).	Zebrafish[49]

4. CHALLENGES AND LIMITATIONS: [7, 11]

The zebrafish model presents challenges despite its advantages in balancing conservation efforts and experimental tractability. While generating numerous embryos at a low cost, key challenges include difficulties in linking toxic in-water dosing levels to mammalian plasma levels and the need for further research on absorption, distribution, metabolism, and excretion (ADME) data. Limitations include partial genome duplication affecting gene redundancy and moderate-length generation time. Although zebrafish are convenient for lab work, challenges arise in investigating toxicology aspects, raising concerns about translatability.

5. FUTURE DIRECTION:

The zebrafish model, serving as a preclinical tool, requires more research to identify molecular targets of tested chemicals related to cardiac genes and proteins. Comprehensive evaluation of chemical effects on pathways disrupting similar traits is crucial. [10] The investigation should explore known molecular targets and pathways, with a contingency plan for identifying novel targets if necessary. Advancing zebrafish research involves addressing these aspects to enhance understanding and applications in drug safety assessment.[8]

6. CONCLUSION:

The zebrafish, with its genetic advantages, rapid development and regenerative capabilities, plays a pivotal role in diverse biological research areas. From unraveling fundamental processes to disease modeling and drug evaluation, the zebrafish remains indispensable. While appreciating its value, there is a need for continuous improvement in welfare considerations, disease studies and drug screening techniques. Ongoing efforts will contribute to furthering the field of Danio rerio study, leading to enhanced insights into biomedical research applications.

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