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# THERAPEUTIC SAFETY AND RATIONALITY IN CLINICAL PHARMACY: THE ROLE OF PRECLINICAL STUDIES AND THE ZEBRAFISH MODEL IN SUPPORTING CLINICAL DECISION-MAKING

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## ABSTRACT

**Background:** Clinical pharmacy practice requires the implementation of safe and rational therapies to optimize clinical outcomes and minimize the risk of adverse drug reactions. Limited availability of early clinical data, particularly for newly developed drugs and the increasing use of natural products, poses challenges in therapeutic decision-making. Under these conditions, preclinical studies serve as an essential source of early evidence for evaluating compound safety prior to human use. **Objective:** This review aims to examine the role of preclinical studies using the zebrafish (*Danio rerio*) model in supporting clinical decision-making in clinical pharmacy practice. **Methods:** This article was conducted using a narrative review approach of national and international scientific literature addressing therapeutic safety, clinical pharmacy, preclinical studies, and the application of the zebrafish model. **Result:** The literature indicates that zebrafish offer significant advantages as an efficient, sensitive, and translationally relevant preclinical model for toxicity testing and drug safety assessment, including natural product–based compounds. Integration of preclinical data with clinical considerations contributes to improved accuracy of therapeutic decisions and strengthens the role of clinical pharmacists in ensuring patient safety. **Conclusions:** Zebrafish-based preclinical studies represent a significant supportive component in evidence-based clinical pharmacy practice.

## ABSTRAK

**Latar belakang:** Praktik farmasi klinik menuntut penerapan terapi yang aman dan rasional guna mengoptimalkan luaran klinis serta menekan risiko efek merugikan obat. Keterbatasan data klinis awal, terutama pada obat baru dan meningkatnya penggunaan bahan alam, menimbulkan tantangan dalam pengambilan keputusan terapi. Kondisi ini menempatkan studi preklinik sebagai sumber bukti awal yang penting dalam evaluasi keamanan senyawa sebelum digunakan pada manusia. **Tujuan:** Tinjauan ini bertujuan mengkaji peran studi preklinik dengan model zebrafish (*Danio rerio*) sebagai pendukung pengambilan keputusan klinis dalam praktik farmasi klinik. **Metode:**

Penulisan artikel dilakukan menggunakan pendekatan *narrative review* terhadap literatur ilmiah nasional dan internasional yang membahas keamanan terapi, farmasi klinik, studi preklinik, dan pemanfaatan model zebrafish. **Hasil:** Tinjauan pustaka menunjukkan bahwa zebrafish memiliki keunggulan sebagai model preklinik yang efisien, sensitif, dan relevan secara translasi dalam uji toksisitas serta penilaian keamanan obat, termasuk senyawa berbasis bahan alam. Pemanfaatan data preklinik secara terintegrasi dengan pertimbangan klinis berkontribusi dalam meningkatkan akurasi keputusan terapi dan memperkuat peran farmasis klinik dalam menjamin keselamatan pasien. **Simpulan:** Studi preklinik berbasis model zebrafish berfungsi sebagai komponen pendukung yang signifikan dalam praktik farmasi klinik berbasis bukti.

## INTRODUCTION

### 1. Clinical Pharmacy and Challenges in Therapeutic Safety

Clinical pharmacy is a patient-oriented pharmaceutical discipline aimed at optimizing drug therapy through the application of rationality, effectiveness, and safety principles grounded in scientific evidence (Cipolle et al., 2023; Hepler & Strand, 1990). The role of the clinical pharmacist extends beyond medication dispensing to include therapeutic risk assessment, monitoring of clinical outcomes, and prevention of drug-related problems within modern healthcare systems (ASHP, 2025; Cappelletty et al., 2004). Therapeutic safety represents a central pillar of clinical pharmacy practice, as adverse drug reactions continue to contribute significantly to morbidity, hospital admissions, and increased healthcare costs globally (WHO, 2019).

Challenges in therapeutic safety have become increasingly complex due to the high proportion of preventable adverse drug reactions and the limited availability of long-term safety data, particularly for newly approved drugs and the expanding use of natural product–based therapies among the general population (EMA, 2024; Posadzki et al., 2013; WHO, 2021). These conditions necessitate more cautious clinical decision-making supported by additional evidence beyond early clinical trial data (Christine Maynié-François et al., 2020; Rawlins, 2008; Titler, 2008). The integration of preclinical data as an early source of information for assessing potential therapeutic risks has therefore become increasingly relevant in supporting evidence-based clinical pharmacy practice and strengthening patient safety (Clark & Steger-Hartmann, 2018; Olson et al., 2000).

### 2. The Role of Preclinical Data in Clinical Decision-Making

Safety assessment of compounds prior to human clinical trials relies on preclinical studies involving both *in vitro* and *in vivo* approaches, including the use of animal models with translational relevance to human physiology and pathology (Mahalmani et al., 2022). *In vitro* studies play a critical role in efficiently identifying early toxicity signals and molecular mechanisms of action, whereas *in vivo* studies provide insights into systemic responses, drug distribution, and metabolism that cannot be fully represented by cellular models alone (Almeida et al., 2017; Turner et al., 2023).

Preclinical data enable early identification of potential toxicities as well as pharmacokinetic and pharmacodynamic characteristics that form the basis for determining initial dosing and designing early-phase clinical trials (ICH, 2009; Mahalmani et al., 2022). The integration of preclinical findings with evidence-based clinical considerations contributes to rational therapeutic decision-making and enhances patient safety in the development and clinical use of new drugs (EMA, 2024; Kimmelman et al., 2024).

**3. Advantages and Emerging Trends in the Use of the Zebrafish Model**

The zebrafish (*Danio rerio*) has emerged as an important model organism in preclinical research due to its advantages in rapid pharmacological and toxicological assessment, relatively low maintenance costs, and high translational relevance to humans (Cassar et al., 2019; MacRae & Peterson, 2015; Siddiqui et al., 2025). As a vertebrate organism, zebrafish share substantial homology in organ structure and physiological function with humans, enabling large-scale toxicity screening, including evaluation of toxicokinetics, morphological alterations, and biochemical responses to a wide range of compounds (Bonan & Siebel, 2022; Siddiqui et al., 2025).

The zebrafish model is also widely applied in drug response evaluation and environmental toxicology, including exposure to complex substances such as per- and polyfluoroalkyl substances (PFAS), which require advanced hazard assessment prior to clinical decision-making (Bonan & Siebel, 2022; de Souza Anselmo et al., 2018).

**4. Technological Advances and Innovations in Preclinical Studies**

Technological innovations in preclinical research have significantly enhanced the capabilities of the zebrafish model through the implementation of automated high-throughput *in vivo* screening systems. These approaches enable multi-organ evaluation of pharmacological and toxicological effects with high accuracy and without invasive procedures, thereby improving both the efficiency and quality of preclinical data (Cassar et al., 2019; Li & Xia, 2019; Yozzo et al., 2013).

Advances in genetic engineering techniques, *omics* approaches, and high-resolution imaging technologies have further strengthened the utility of zebrafish in elucidating mechanisms of toxicity and pharmacological responses at molecular and systemic levels. These developments facilitate the translation of early biological findings into clinically relevant contexts, effectively bridging the gap between laboratory research and human clinical applications (MacRae & Peterson, 2015; Siddiqui et al., 2025).

**5. Relevance of Preclinical Models to Clinical Pharmacy Practice**

The utilization of robust preclinical data, particularly those generated from the zebrafish (*Danio rerio*) model, demonstrates high relevance in supporting evidence-based clinical pharmacy practice, especially in situations where early clinical data are limited. The zebrafish model enables early assessment of drug effectiveness, toxicity, and mechanisms of action in a systemic manner within a relatively short timeframe,

thereby providing preliminary information on safety profiles and potential therapeutic risks prior to human application (Cassar et al., 2019; MacRae & Peterson, 2015).

The incorporation of preclinical findings into clinical decision-making processes contributes to the development of safer and more rational therapeutic strategies by clinical pharmacists, including determination of initial dosing, identification of potential drug–drug interactions, and anticipation of adverse drug reactions (Siddiqui et al., 2025). The use of translationally relevant preclinical data also plays a critical role in reducing the risk of adverse drug events and improving overall clinical outcomes and patient safety.

## METHOD

This article was prepared using a narrative review approach to examine the role of preclinical studies, particularly the zebrafish (*Danio rerio*) model, in supporting clinical decision-making within clinical pharmacy practice. A narrative and targeted literature search was conducted across international scientific databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy employed combinations of keywords such as *clinical pharmacy*, *drug safety*, *preclinical studies*, *zebrafish model*, *toxicity assessment*, and *natural products*.

Included articles comprised preclinical studies, review articles, international guidelines, and policy reports relevant to therapeutic safety and rational drug use. Literature selection and synthesis were based on topic relevance, methodological quality, and alignment with the objectives of the review. Data analysis was performed descriptively and integratively. Although this review did not adopt a systematic review methodology, the reporting and organization of the article were guided by the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), particularly during the stages of literature identification, selection, and synthesis, to enhance transparency and clarity of reporting (Page et al., 2021). This approach aimed to improve credibility and traceability of sources while maintaining the analytical flexibility characteristic of narrative reviews.

## RESULT

The findings of this literature review indicate that the zebrafish (*Danio rerio*) model is consistently utilized in preclinical studies for drug safety evaluation, toxicity screening, and early pharmacological response assessment, involving both synthetic compounds and natural product–based substances. Numerous studies report that zebrafish exhibit high sensitivity in detecting cardiovascular toxicity, neurotoxicity, hepatotoxicity, and developmental disturbances, with relatively short observation periods and high cost efficiency (Bonan & Siebel, 2022; Cassar et al., 2019; Siddiqui et al., 2025). The similarity of molecular pathways and physiological processes between zebrafish and humans supports the translational relevance of preclinical findings to clinical contexts.

Table 1 presents a summary and comparison of the main findings from zebrafish-based preclinical studies, including the types of tested compounds, evaluated toxicity parameters, methodological strengths, and potential implications for clinical pharmacy practice. This tabulated presentation provides a systematic comparative overview and facilitates identification of patterns across studies. Overall, the comparison demonstrates the advantages of zebrafish in early toxicity screening and safety risk identification prior to clinical trial stages.

**Table 1.** Summary of Studies Related to Therapeutic Safety, Preclinical Studies, and the Zebrafish Model

| Author (Year) | Study Design | Object/ Model | Main Findings | Relevance to Clinical Pharmacy |
|---|---|---|---|---|
| **Lee et al. (2021)** | Narrative review | Zebrafish model | Reviewed the use of zebrafish as an *in vivo* platform for drug and protein screening in biomedical applications; demonstrated the model's ability to detect pharmacological responses relevant to candidate drug selection | Demonstrates the potential of zebrafish as an early model for drug safety and efficacy assessment, strengthening evidence-based clinical therapeutic decisions |
| **Lei et al. (2023)** | Narrative review | Zebrafish for toxicity assessment | Described high-throughput toxicity screening mechanisms (oxidative stress, ER stress, inflammation) and emerging technologies (gene editing, 3D imaging) in zebrafish models | Provides insights into advanced toxicity mechanisms and techniques that enhance prediction of drug-related risks prior to clinical trials |
| **Chakraborty et al. (2020)** | Narrative review | Zebrafish (*Danio rerio*) | Highlighted zebrafish as a vertebrate model with high genetic similarity to humans (≈70% of human disease-related genes have functional homologs), embryo transparency, rapid organ development, and suitability for high-throughput drug and toxicity screening | Establishes a scientific basis for the use of zebrafish as an early preclinical model to evaluate safety, toxicity, and pharmacological effects of candidate drugs prior to mammalian and human studies |

| Author (Year) | Study Design | Object/ Model | Main Findings | Relevance to Clinical Pharmacy |
|---|---|---|---|---|
| **Miyawaki (2020)** | Review | Zebrafish in neurotoxicity studies | Demonstrated the application of zebrafish in assessing neurotoxicity and its relevance to central nervous system disorders | Relevant for predicting complex adverse drug effects prior to clinical trials |
| **Li et al. (2025)** | Experimental study | Zebrafish embryos | Lurasidone exposure induced neurodevelopmental toxicity, including neurotransmitter dysfunction | Serves as an example of clinically relevant drug toxicity testing using a preclinical zebrafish model |
| **Agus W et al. (2021)** | Experimental study | Zebrafish; *Tacca leontopetaloides*, *Tacca palmata* extracts | All extracts exhibited acute toxicity to zebrafish embryos with varying $LC_{50}$ values. Leaf extracts of *jalawure* and *gadung tikus*, as well as *gadung tikus* tuber, showed moderate toxicity, while other extracts showed low toxicity. Embryo coagulation was the most dominant lethal endpoint | Confirms the utility of zebrafish as an early screening model for the safety evaluation of natural products. $LC_{50}$ data provide a basis for risk–benefit assessment in herbal drug development and help prevent translation of potentially toxic compounds into clinical use |

## DISCUSSION

The findings of this review demonstrate that preclinical models are not merely experimental validation tools but strategic contributors to evidence-informed clinical decision-making. The zebrafish (*Danio rerio*) model has emerged as a biologically relevant vertebrate platform capable of detecting early toxicity signals and pharmacodynamic responses in both synthetic compounds and natural products. Genetic homology with humans, conserved molecular pathways, rapid organogenesis, and embryonic transparency allow real-time visualization of organ-specific toxic effects, positioning zebrafish as a sensitive early-stage screening system.

Evidence summarized in Table 1 indicates that zebrafish models consistently identify cardiovascular toxicity, neurotoxicity, hepatotoxicity, and developmental abnormalities at early exposure stages. Detection of such toxic signals before mammalian testing introduces an additional safety layer in the translational pipeline. Reviews by Lee et al. (2021), Lei et al. (2023), and Chakraborty et al. (2020) highlight

the predictive validity, cost-efficiency, and scalability of zebrafish models in preclinical safety evaluation.

Relevance to clinical pharmacy practice becomes evident when preclinical safety signals are interpreted within therapeutic risk management frameworks. Early identification of organ-specific toxicity profiles may guide pharmacists in anticipating adverse drug reactions, strengthening medication surveillance, and refining patient counseling strategies. Neurodevelopmental toxicity observed in zebrafish embryos exposed to lurasidone (Li et al., 2025) provides an example of how preclinical findings may raise caution in prescribing decisions for pregnant women or pediatric populations. Such safety data can support pharmacists in recommending closer monitoring, reassessing therapeutic alternatives, or reinforcing informed consent discussions.

Preclinical toxicity patterns derived from zebrafish studies may also inform dose-related risk considerations. Although direct dose extrapolation to humans requires caution, identification of concentration-dependent toxicity trends can support awareness of therapeutic windows and potential overdose risks. These findings may guide monitoring parameters in clinical practice, particularly for drugs with narrow safety margins. Integration of early toxicity signals into hospital formulary discussions and pharmacotherapeutic evaluations further strengthens the role of pharmacists in institutional decision-making processes.

Evaluation of natural products represents another critical domain. Herbal medicines are widely consumed yet frequently lack comprehensive toxicological characterization. Findings reported by Agus W et al. (2021) demonstrate measurable embryotoxic and acute toxicity endpoints in plant-derived compounds. Such data challenge assumptions of inherent safety associated with herbal therapies. Zebrafish-based assessments provide quantifiable safety indicators, including $LC_{50}$ values and developmental endpoints, which can support pharmacists in advising patients, identifying potential herb–drug interactions, and discouraging unsupervised high-dose consumption. Incorporation of this evidence enhances rational integration of complementary therapies into clinical care.

The translational value of zebrafish models lies in their capacity to function as an intermediate safety checkpoint between in vitro assays and mammalian or human studies. Preclinical signals generated at this stage do not replace clinical trials but contribute to a cumulative safety evidence framework. Clinical pharmacists, positioned at the interface between research evidence and patient care, may utilize such information to contextualize emerging therapies, interpret post-marketing safety alerts, and contribute to pharmacovigilance reporting systems.

Despite these advantages, limitations of the zebrafish model must be acknowledged. Physiological differences in drug metabolism, immune response, and long-term disease modeling may restrict direct extrapolation of quantitative findings to humans. Variability in experimental design, exposure duration, and endpoint selection across laboratories can affect reproducibility. Complex chronic toxicities and

idiosyncratic immune-mediated reactions may not be fully represented in zebrafish systems. Interpretation of zebrafish-derived data therefore requires cautious translational judgment and should complement, rather than substitute, mammalian studies and clinical investigations.

The narrative review approach employed in this article enables integrative synthesis of heterogeneous yet conceptually aligned evidence relevant to therapeutic safety. Application of PRISMA-guided identification and selection processes enhances transparency while preserving analytical flexibility.

Collectively, the reviewed evidence supports the positioning of zebrafish-based preclinical data as a translational resource for clinical pharmacy practice. Strategic interpretation of early toxicity findings may strengthen pharmacovigilance, inform monitoring strategies, support formulary evaluation, and enhance patient-centered risk communication. Such integration reinforces the evolving role of clinical pharmacists in bridging laboratory evidence and safe therapeutic implementation.

## CONCLUSION

Preclinical evidence, particularly from the zebrafish (*Danio rerio*) model, provides meaningful early safety signals that support evidence-based clinical decision-making in pharmacy practice. Detection of organ-specific and dose-related toxicities contributes to pharmacovigilance, therapeutic monitoring, formulary evaluation, and patient counselling, including in the use of natural products. Although translational interpretation requires caution, integration of zebrafish-derived data strengthens rational drug use and enhances medication safety.

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