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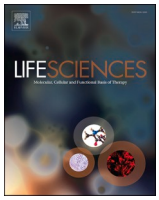

The role of machine learning in predictive toxicology: A review of current trends and future perspectives☆

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ABSTRACT

Adverse drug reactions (ADRs) are a major challenge in drug development, contributing to high attrition rates and significant financial losses. Due to species differences and limited scalability, traditional toxicity testing methods, such as in vitro assays and animal studies, often fail to predict human-specific toxicities accurately. The emergence of artificial intelligence (AI) and machine learning (ML) has introduced transformative approaches to predictive toxicology, leveraging large-scale datasets such as omics profiles, chemical properties, and electronic health records (EHRs). These AI-powered models provide early and accurate identification of toxicity risks, reducing reliance on animal testing and improving the efficiency of drug discovery. This review explores the role of AI models in predicting ADRs, emphasizing their ability to integrate diverse datasets and uncover complex toxicity mechanisms. Validation techniques, including cross-validation, external validation, and benchmarking against traditional methods, are discussed to ensure model robustness and generalizability. Furthermore, the ethical implications of AI, its alignment with the 3Rs principle (Replacement, Reduction, and Refinement), and its potential to address regulatory challenges are highlighted. By expediting the identification of safe drug candidates and minimizing late-stage failures, AI models significantly reduce costs and development timelines. However, challenges related to data quality, interpretability, and regulatory integration persist. Addressing these issues will enable AI to fully revolutionize predictive toxicology, ensuring safer and more effective drug development processes.

1. Introduction

The process of drug discovery is a challenging and resource-intensive endeavor, often spanning over a decade and costing billions of dollars [1]. Despite these investments, the attrition rate of drug candidates remains alarmingly high, with adverse drug reactions (ADRs) being a significant contributing factor. ADRs, which represent unintended and harmful effects of medications, account for a substantial proportion of drug development failures, particularly during clinical trials [2]. The inability to predict these toxic effects early in the drug development process not only results in wasted resources but also delays the introduction of life-saving therapies to patients [3].

Traditional toxicity testing methods, including in vitro assays and in vivo animal models, have been the cornerstone of drug safety assessments for decades [4]. However, these methods have inherent limitations that restrict their ability to predict human-specific ADRs accurately [5]. Animal models, for example, often fail to replicate the complexity of human biological systems, leading to discrepancies in toxicity profiles between preclinical and clinical stages [6]. Moreover, traditional methods are time-consuming, expensive, and fraught with ethical concerns, particularly regarding the extensive use of animals for testing purposes [7]. These limitations underscore the urgent need for

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innovative approaches to toxicity prediction.

The advent of artificial intelligence (AI) and machine learning (ML) has introduced a transformative paradigm in the field of predictive toxicology [8]. These technologies leverage vast datasets, including omics data, chemical properties, and real-world patient records, to predict potential toxicities with remarkable accuracy [9]. By identifying ADR risks at earlier stages of drug discovery, AI models have the potential to significantly reduce the time and cost associated with traditional toxicity testing [10]. Furthermore, the ability of AI to analyze complex datasets and uncover hidden patterns offers insights that traditional methods may overlook, enhancing the overall efficiency and precision of toxicity assessments [11].

In addition to improving predictive accuracy, AI-powered models also align with global efforts to minimize animal testing [12]. By providing human-relevant predictions and reducing dependency on animal studies, these technologies address ethical concerns while adhering to the principles of replacement, reduction, and refinement (3Rs) in research [13]. The 3Rs framework, first introduced by Russell and Burch in 1959, has become the foundation for more ethical and humane animal research globally. “Replacement” refers to methods that avoid or replace animal use; “Reduction” aims to minimize the number of animals used per experiment; and “Refinement” focuses on minimizing suffering and improving animal welfare. This framework has gained significant regulatory support worldwide, with organizations like the European Union's Directive 2010/63/EU and the US FDA Modernization Act 2.0 explicitly endorsing alternative methods to animal testing [14,15]. As regulatory agencies increasingly recognize the potential of AI in toxicology, its integration into the drug development pipeline is becoming more feasible and necessary [16].

The high attrition rates in drug development, largely driven by unforeseen adverse drug reactions, underscore the critical need for innovative approaches to toxicity prediction [17]. Traditional methods often fail to accurately predict human-specific toxicity, leading to costly late-stage failures and raising ethical concerns about the use of animals in research [18]. The advent of artificial intelligence offers a transformative solution, leveraging vast and diverse datasets to identify toxicity risks with greater precision and efficiency [8].

This narrative review aims to explore the application of AI-powered predictive models in drug toxicity screening, with a focus on their ability to utilize large-scale datasets, including omics data, chemical properties, and patient records, to predict ADRs and minimize toxicity risks. The review further seeks to examine validation techniques, compare AI approaches to traditional methods, and discuss the broader implications of AI adoption, such as reduced reliance on animal testing and accelerated identification of safe drug candidates. By synthesizing current evidence and emerging trends, this review provides insights into how AI can revolutionize the drug discovery process and address long-standing challenges in predictive toxicology.

2. AI vs. traditional toxicity testing methods

The evolution of predictive toxicology from traditional methods to AI-powered models represents a paradigm shift in drug development. While traditional methods such as animal studies and in vitro assays have been the foundation of toxicology, they face critical limitations such as ethical concerns, species differences, high costs, lack of systemic interactions, limited metabolic capability, and challenges in replicating human-relevant exposure and chronic effects, driving the need for alternative approaches [19].

2.1. Types of artificial intelligence in toxicology

Artificial intelligence encompasses various approaches with specific applications in toxicology. Machine learning represents the most widely used AI approach, where algorithms learn patterns from data without explicit programming [20]. This includes supervised learning methods that use labeled data to train models for toxicity classification or regression tasks such as predicting LD50 values. Unsupervised learning techniques identify patterns in unlabeled data through clustering or dimensionality reduction, proving useful for discovering novel toxicity mechanisms without prior assumptions [21]. Reinforcement learning optimizes decision-making processes through reward-based mechanisms, although its application in toxicology remains limited compared to other domains.

Deep learning, a subset of machine learning utilizing neural networks with multiple processing layers, has shown remarkable success in toxicity prediction [22]. Convolutional Neural Networks (CNNs) excel in analyzing visual data from high-content cell imaging, detecting morphological changes indicative of toxicity. Recurrent Neural Networks (RNNs) and their variants process sequential data, including temporal changes in biomarkers following drug exposure. Transformer models have revolutionized handling complex biological text and sequence data, extracting valuable toxicity information from scientific literature [23].

Natural Language Processing (NLP) represents another critical AI domain for toxicology, extracting information from scientific literature, clinical reports, and adverse event databases. Recent advancements in biomedical NLP have enabled the automated extraction of toxicity relationships from millions of publications, significantly enhancing the knowledge base available for predictive models [24]. Computer vision applications analyze high-content screening images to detect subtle cellular changes indicative of toxicity, often identifying effects invisible to human observers.

Knowledge-based systems integrate domain expertise with data-driven approaches through expert systems that encode toxicological rules and knowledge graphs representing relationships between compounds, targets, and biological pathways. These systems provide context and interpretability to pure data-driven approaches, addressing one of the key challenges in AI toxicology adoption [25]. Each AI approach offers unique advantages in toxicity prediction, with hybrid systems often providing the most comprehensive assessments by combining the strengths of multiple approaches.

In contrast to traditional approaches, AI models offer innovative solutions that address these challenges, enabling more accurate, efficient, and ethical approaches to toxicity prediction [26]. Table 1 compares AI models with traditional toxicity testing methods, highlighting the superior scalability, time efficiency, and ethical benefits of AI. Unlike conventional approaches, AI leverages human-specific data, such as electronic health records (EHRs) and omics datasets, enabling accurate, human-relevant toxicity predictions and reducing reliance on ethically contentious animal studies.

2.2. Limitations of traditional methods

Traditional toxicity testing methods, particularly animal studies and in vitro assays, have been central to preclinical drug development for decades. However, these methods are increasingly recognized as insufficient in predicting human-specific adverse drug reactions (ADRs) [5]. One of the primary issues with animal studies is the variability in species-specific responses. Biological differences between animals and humans often result in poor translation of findings [39]. For instance, drugs that are safe in animal models may later exhibit significant toxicities in human clinical trials, as observed with several high-profile drug withdrawals e.g., Corticosteroids for septic shock, a Tegenero immunomodulatory agent led to severe organ failure in healthy volunteers, even though earlier animal studies revealed no significant issues. Conversely, potentially beneficial drugs might be prematurely abandoned due to false-positive toxicity findings in animal models e.g., immunosuppressant drugs cyclosporine and tacrolimus [38].

In vitro assays, while useful for mechanistic studies, are limited in replicating the complexity of human physiological systems. These assays often fail to capture multi-organ interactions, immune system responses,

Table 1
Detailed comparison of AI models and traditional toxicity testing methods.

Aspect	AI Models	Traditional Methods
Data Sources	Leverage large-scale datasets such as omics (genomics, transcriptomics), chemical properties, and EHRs [27].	Animal models, in vitro assays, and limited clinical observations [28].
Predictive Accuracy	High predictive accuracy for human-specific ADRs due to the use of human data and advanced algorithms [10].	Limited by species-specific differences and simplified in vitro systems that do not mimic human complexity [29].
Ethical Considerations	Minimal ethical concerns; aligns with global initiatives to reduce animal testing [30].	High ethical concerns due to animal suffering and large-scale animal use.
Scalability	Capable of processing thousands of compounds in parallel with high throughput [31].	Low scalability; each compound requires separate experiments, increasing time and resource requirements [31].
Time Efficiency	Significantly faster; AI can analyze toxicity risks within hours to days [32].	Time-consuming, requiring weeks or months for preclinical toxicity studies [33].
Cost Efficiency	Cost-effective after initial implementation; suitable for large-scale screening [34].	High costs due to animal procurement, experimental setup, and labor-intensive protocols.
Integration Potential	Easily integrated with digital workflows, databases, and computational pipelines [35].	Requires dedicated laboratory infrastructure and extensive manual handling [36].
Regulatory Status	Limited current adoption but growing acceptance as validation and guidelines develop [36].	Long-established regulatory frameworks; widely used but increasingly scrutinized [37].

and metabolic processes that influence drug toxicity in vivo [40]. In vitro hepatocyte monocultures fail to capture the full extent of acetaminophen (APAP)-induced liver toxicity, as they lack multi-organ interactions and metabolic processes, it's been reported that APAP-induced nephrotoxicity, mediated by kidney involvement, is not replicated in these models [41]. However, while lung epithelial cell models exposed to diesel exhaust particles (DEP) successfully demonstrate enhanced expression of inflammatory genes and cellular transformation, capturing important immune responses, these in vitro models still lack the complexity of multi-organ interactions and systemic immune responses that occur in vivo [42]. Moreover, cyclophosphamide metabolism is poorly replicated in in vitro systems, as study demonstrated that liver microsomal enzymes, critical for its activation into toxic metabolites, are inadequately represented, leading to an underestimation of hematological toxicities seen in vivo [43]. Additionally, the scalability of traditional methods is constrained by resource-intensive experimental setups, making them impractical for high-throughput screening of large compound libraries [44].

Beyond scientific limitations, traditional methods are costly and time-consuming. Developing and testing a single compound can take years, with significant financial investments required for laboratory resources, skilled personnel, and compliance with regulatory standards. Fig. 1 provides a clear and concise overview of the limitations that drive the need for alternative approaches in toxicity testing, such as machine learning methods concerns regarding the use of animals in research further underscore the need for alternative approaches, aligning with global efforts to adopt the principles of Replacement, Reduction, and Refinement (3Rs) in research [45].

2.3. Advantages of AI models

AI-powered toxicity prediction models address the shortcomings of traditional methods by leveraging advanced computational techniques and diverse, human-specific datasets [46]. These models are transforming how drug safety is assessed, offering significant advantages in accuracy, scalability, and ethical considerations [47]. One key advantage of AI models is their ability to utilize human-specific data, such as electronic health records (EHRs) and omics datasets, to make personalized toxicity predictions [48]. By analyzing patient demographics, genetic profiles, and environmental factors, AI models can provide insights into individual variability in drug responses [49]. This capability is particularly valuable for predicting ADRs in diverse populations, ensuring broader safety assessments beyond standardized animal models.

AI models using EHR data were used to predict acetaminophen (APAP)-induced liver toxicity by analyzing genetic variations in CYP450 enzymes involved in APAP metabolism. The study demonstrated how integrating genetic data, such as variations in CYP2E1, could predict the risk of toxicity in individuals [50]. Another example is where AI models using genomic and proteomic datasets were employed to predict adverse

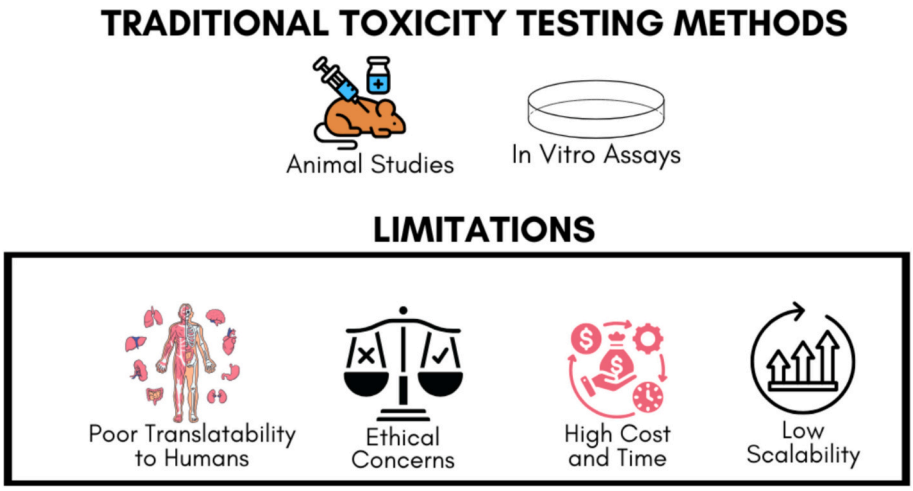

Fig. 1. Limitations of traditional toxicity testing methods. The figure provides a simplified representation of the major limitations associated with traditional toxicity testing approaches, including poor translation of animal studies to human outcomes, the inability of in vitro assays to replicate complex physiological systems, scalability constraints, high costs, and time requirements, and ethical concerns related to animal testing.

drug reactions (ADRs) for flutamide, based on its hepatic bioactivation by cytochrome P450 enzymes, which plays a crucial role in forming reactive metabolites that have been linked to fulminant hepatitis, an idiosyncratic and potentially fatal liver injury [51]. Also, AI models were applied to predict hepatotoxicity in acetaminophen using computational simulations of cytochrome P450 enzyme interactions and glutathione depletion pathways [52]. This mechanistic model not only helped reduce animal testing but also identified potential biomarkers for early detection of toxicity. In the case of cyclophosphamide, AI has been used to model the cytochrome P450-mediated activation of cyclophosphamide into toxic metabolites, demonstrating AI's ability to predict metabolism-related toxicity more efficiently than traditional methods [53].

In a study by Zeish et al. [54], a machine learning model was developed that utilized genetic variants to predict the risk of severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), associated with carbamazepine and similar drugs. The model achieved a high predictive performance, with a median area under the receiver operating characteristic curve (AUC) of 0.9815, indicating its potential utility in clinical settings. This mechanistic prediction was further validated by genomic data analysis, showing how patient-specific genetic information influences drug metabolism and toxicity risks. Similarly, Al-Hammadi [55] used AI models to predict anticoagulant-related adverse events for warfarin, incorporating genetic data related to VKORC1 and CYP2C9 variants to personalize treatment plans and reduce adverse reactions.

AI models are also scalable, capable of simultaneously processing and analyzing thousands of compounds. Techniques such as high-throughput virtual screening allow for rapid assessment of chemical libraries, enabling the identification of promising candidates and the elimination of high-risk compounds early in the drug discovery process [56]. AI models are also scalable, capable of simultaneously processing and analyzing thousands of compounds, as demonstrated by Guttman and Kerem [57] where they developed a deep-learning model to classify compounds as CYP3A4 inhibitors or non-inhibitors. They virtually screened approximately 60,000 dietary compounds and identified 115 potential inhibitors, with 31 being previously suggested. Machine learning models have been successfully applied to predict hERG potassium channel inhibition, a critical factor in assessing cardiotoxicity. For example, Chuipu et al. [58] developed a deep learning model named deephERG to predict hERG channel blockers. They utilized a dataset of 7889 compounds, achieving an area under the receiver operating characteristic curve (AUC) of 0.967 on the validation set. Additionally, Ylipää et al. [59] benchmarked six machine learning techniques including support vector machine (SVM), random forest, XGBoost, deep neural networks, gated recurrent unit-based deep neural networks, and graph neural networks for hERG toxicity prediction. Using an integrated dataset of 291,219 compounds from ChEMBL, GOSTAR, PubChem, and hERGCentral, with 203,853 compounds for training and 87,366 for testing, their SVM model achieved an AUC ROC score of 0.95 on both validation and test sets, with balanced accuracy scores of 0.90 and 0.89 respectively. These machine learning approaches have significantly advanced the identification of cardiotoxic risks associated with compounds, including known hERG blockers like cisapride and terfenadine.

This efficiency significantly reduces the time and cost associated with traditional toxicity testing. Furthermore, AI models excel in capturing complex, non-linear relationships between chemical properties, biological pathways, and toxicological outcomes [60]. For instance, machine learning algorithms can identify patterns in multi-dimensional data that would be challenging or impossible for traditional methods to detect [61]. For instance, a study utilizing a Graph Neural Network (GNN) with bagging methods successfully predicted mitochondrial toxicity in compounds known to induce hepatotoxicity, demonstrating its potential in uncovering hidden toxicity mechanisms [62]. These studies highlight how machine learning algorithms can identify patterns in multi-dimensional datasets, revealing toxicity risks that might otherwise remain undetected using conventional approaches.

2.4. Model interpretability and explainable AI

While AI models offer powerful predictive capabilities, their "black box" nature can limit understanding of the underlying mechanisms and hinder regulatory acceptance. Addressing this challenge, explainable AI (XAI) approaches are being developed specifically for toxicity prediction [63]. Feature importance analysis techniques identify chemical features or molecular substructures most associated with toxicity predictions. Methods such as SHAP (SHapley Additive exPlanations) values quantify how each molecular feature contributes to toxicity predictions, while chemical fragment analysis highlights toxic structural alerts, providing medicinal chemists with actionable insights [64].

Attention-based mechanisms applied in deep learning models visualize which parts of a molecule receive most focus during prediction. These approaches generate heat maps identifying potentially problematic regions in molecular structures and demonstrate sequential attention showing which pathway steps are most implicated in toxicity [65]. Local Interpretable Model-Agnostic Explanations (LIME) approximate complex models with simpler, interpretable ones for specific instances. This technique generates simplified surrogate models to explain individual predictions and is particularly valuable when analyzing unexpected toxicity predictions [66].

Pathway analysis integration links predictions to known biological pathways and mechanisms, connecting statistical predictions to mechanistic understanding of toxicity and helping bridge computational predictions and biological plausibility [67]. Rule extraction techniques are used to derive human-readable rules from complex models such as neural networks and ensemble methods. These techniques help translate mathematical patterns into toxicological principles, aiding in the development of safety guidelines and improving the understanding of structure-activity relationships (SARs) [68]. The integration of these interpretability approaches strengthens the reliability of AI predictions and facilitates regulatory acceptance by providing transparency and mechanistic insights alongside predictions.

By integrating diverse datasets such as omics data, chemical descriptors, and patient records, AI models provide a more comprehensive understanding of drug-induced toxicities [48]. Ethically, AI-driven approaches align with global initiatives to reduce reliance on animal testing. By offering reliable alternatives that mimic human biology more closely, AI models contribute to the ethical advancement of research while adhering to regulatory standards [69]. Additionally, the use of AI reduces the need for repetitive and resource-intensive experiments, freeing up resources for other critical areas of drug development.

While traditional methods provide valuable baseline data and are deeply ingrained in regulatory frameworks, they are increasingly being complemented or replaced by AI-powered models [70]. Fig. 2. provides a visual summary of the main advantages of AI models in toxicity prediction. AI offers the precision and adaptability required for modern drug development, addressing long-standing challenges in toxicity prediction [71]. As AI technologies continue to evolve, their integration with traditional methods can create a hybrid approach, leveraging the strengths of both systems to optimize drug safety assessments [72].

2.5. Hybrid approaches: integrating ai with traditional methods

The integration of AI with traditional toxicity testing creates powerful hybrid approaches that enhance predictive accuracy while maintaining biological relevance [73]. These hybrid methods combine computational efficiency with mechanistic insights. Sequential testing strategies represent one important hybrid approach. Initial computational screening identifies high-risk compounds for focused traditional testing through AI-based prioritization. Tiered evaluation progressively applies more resource-intensive tests only to compounds that pass initial AI screening. This approach has been successfully applied in screening

Fig. 2. Flow diagram depicting the advantages of AI models in toxicity prediction. The figure visually emphasizes how these advantages address key challenges in traditional toxicity testing methods, such as limited scalability, ethical concerns, and the need for more personalized and accurate predictions.

large compound libraries, where AI has identified the most promising candidates for subsequent in vitro testing, significantly reducing resource requirements while maintaining predictive power [74].

Parallel validation systems simultaneously apply AI and traditional methods, analyzing agreement patterns through concordance analysis. This approach combines the statistical power of AI with the biological relevance of traditional assays. Recent implementations have integrated AI-driven predictions alongside experimental assay results to classify compounds with greater confidence, especially in borderline cases where either method alone might be inconclusive [75]. Model enhancement through experimental data represents another valuable hybrid strategy. Iterative refinement feeds experimental results back to improve AI model performance, while active learning strategically selects compounds for testing to maximize information gain for model improvement. This approach has been particularly effective in developing models for toxicity endpoints like hERG inhibition, where continuous improvement occurs as new experimental data becomes available [76].

Organ-on-chip integration combines microfluidic systems that replicate human organ functionality with AI-driven analysis of complex cellular responses. This physiologically relevant approach has shown particular promise in combining liver-on-chip systems with deep learning for hepatotoxicity prediction, offering a more human-relevant testing platform while minimizing animal use [77]. In silico clinical trials represent an advanced hybrid approach that simulates drug effects across diverse populations through virtual patient cohorts. These systems integrate physiologically-based pharmacokinetic (PBPK) models with AI predictions to model population variability in drug responses before human testing begins [78].

These hybrid approaches represent the future of toxicity testing - offering reduced animal use, lower costs, and improved prediction of human outcomes through strategic integration of complementary methods. By leveraging the strengths of both computational and experimental approaches, these integrated systems address the limitations of each individual approach while maximizing their collective potential [79].

3. Large-scale datasets in AI-powered toxicity prediction

The foundation of AI-powered toxicity prediction lies in the ability of machine learning algorithms to process and analyze large-scale datasets [80]. These datasets encompass diverse and complex information, including omics data, chemical properties, and patient-specific records, which together provide a comprehensive view of drug-induced toxicological effects [81]. By integrating these data types, AI models can uncover intricate relationships and patterns, enabling more accurate predictions of adverse drug reactions (ADRs) [82]. Table 2 categorizes the diverse datasets utilized by AI models, including omics data (e.g., genomics, transcriptomics, proteomics), chemical descriptors, and real-

Table 2
Types of large-scale datasets used in AI-powered toxicity prediction.

Dataset Type	Key Features	AI Applications	Examples of Use
Genomics Data	Variations in DNA sequences, such as SNPs and gene mutations [83].	Identification of genetic biomarkers for susceptibility to ADRs [5].	Prediction of drug-induced hepatotoxicity linked to CYP450 genetic polymorphisms [84].
Transcriptomics Data	Gene expression profiles under drug exposure [85].	Analysis of toxicity pathways and prediction of organ-specific toxicities [86].	Detecting hepatotoxic gene signatures from human liver cell transcriptomes [87].
Proteomics Data	Protein expression, interactions, and modifications in response to drugs [88].	Prediction of disruptions in protein networks associated with toxic effects [20].	Identification of cardiac toxicity through changes in cardiac-specific proteins [89,90].
Metabolomics Data	Biochemical changes and metabolic profiles induced by drug exposure [91].	Biomarker discovery for early toxicity detection [92].	Prediction of renal toxicity using urine metabolomics data [93].
Chemical Descriptors	Molecular weight, solubility, lipophilicity, and structural motifs [94].	Structure-toxicity relationship modeling using QSAR and deep learning models [95].	Screening for mutagenic properties in chemical libraries [96].
Patient Records (EHRs)	Real-world clinical data, including demographics, drug history, and ADRs [97].	Personalized toxicity prediction and identification of population-specific risks [98].	Prediction of drug-induced arrhythmia using longitudinal patient ECG data [99].
Pharmacovigilance Data	Adverse event reports from surveillance databases [100].	Mining for rare or delayed ADRs using NLP and machine learning [101].	Identifying patterns of drug hypersensitivity reactions from the FDA Adverse Event Reporting System [102].
Multi-Omics Integration	Combination of genomics, transcriptomics, proteomics, and metabolomics data [103].	Holistic toxicity prediction by analyzing cross-level biological interactions [104].	Understanding multi-organ toxicities from simultaneous analysis of liver, kidney, and cardiac datasets [86].

world patient records. These datasets provide a multi-dimensional view of toxicity mechanisms, facilitating the integration of molecular, chemical, and clinical insights for predictive modeling.

3.1. Data acquisition and preprocessing techniques

The quality and preparation of datasets are critical factors in developing reliable AI models for toxicity prediction. Data acquisition and preprocessing techniques ensure data integrity and model performance [105]. Public repositories and databases serve as primary sources for toxicology datasets. Resources like Tox21, ToxCast, and DrugMatrix provide standardized toxicity data for thousands of compounds, while omics databases such as Gene Expression Omnibus (GEO) and ArrayExpress offer transcriptomic and proteomic datasets from toxicology experiments [106]. The LINCS (Library of Integrated Network-Based Cellular Signatures) project provides extensive molecular response data to drug exposure across multiple cell types. Electronic health record repositories and systems have become increasingly valuable for real-world toxicity assessment, while pharmaceutical industry internal databases often contain proprietary toxicity data from preclinical and clinical studies that complement public resources [107].

High-throughput screening platforms generate large toxicity datasets through automated testing of thousands of compounds across multiple endpoints. These technologies include high-content imaging systems that capture cellular morphological changes and microfluidic organs-on-chips that model human tissue responses to toxic exposures [108]. Collaborative research initiatives play a crucial role in data pooling and standardization efforts. Consortia like the Innovative Medicines Initiative (IMI) eTOX project have established data-sharing frameworks for pharmaceutical toxicity data, while initiatives like the Toxicology in the 21st Century (Tox21) program represent collaborations between regulatory agencies and research institutions to generate standardized toxicity datasets [109].

Data preprocessing and standardization techniques are essential for ensuring AI model performance. Quality control procedures identify and address issues like experimental artifacts, outliers, missing values, and batch effects that could compromise model reliability. Data normalization and standardization procedures ensure consistent scales across different datasets, particularly important when integrating heterogeneous data sources like omics and clinical measurements [110]. Feature engineering and selection techniques identify the most informative variables for toxicity prediction, reducing dimensionality and improving model performance. Imputation strategies address missing data problems through statistical or ML-based approaches, while data augmentation techniques generate synthetic samples to address class imbalance issues common in toxicity datasets [111]. Ontology mapping and harmonization ensure consistent terminology across datasets, particularly important when integrating data from different sources, while annotating datasets with relevant metadata enhances interpretability and enables more sophisticated analyses [112].

Advanced preprocessing techniques include trajectory-based analyses for time-series toxicity data that capture dynamic responses to compounds and cross-platform data integration methods that harmonize data from different experimental platforms. Text mining of literature extracts toxicity information from published studies, while data debiasing techniques identify and mitigate biases in historical toxicity data that could lead to unfair or inaccurate predictions for certain chemical classes or populations [113].

3.2. Omics data

Omics datasets—genomics, transcriptomics, proteomics, and metabolomics—play a pivotal role in understanding the biological mechanisms underlying drug toxicity. Each omics layer provides distinct insights into cellular and molecular responses to chemical exposures, and their integration amplifies the predictive power of AI models [114]. Genomics data examines genetic variations that influence individual susceptibility to ADRs. AI models can analyze genomic patterns, such as mutations or single nucleotide polymorphisms (SNPs), to identify populations at higher risk of toxicity. Machine learning models can be designed to predict the reported irinotecan-induced neutropenia based on variations in the UGT1A1*28 allele, allowing for risk stratification in different patient groups [114,115]. Genetic polymorphisms in drug-metabolizing enzymes like CYP450 are well-documented contributors to inter-individual variability in drug responses; for instance, the analysis of TPMT (thiopurine *S*-methyltransferase) and NUDT15 genetic variants accurately predicted severe thiopurine-induced myelosuppression, guiding safer chemotherapy dosing in leukemia patients [116], while CYP2C19 polymorphisms, successfully predict poor metabolism of clopidogrel in patients carrying the CYP2C192 and 3 alleles, which are linked to reduced drug activation and increased cardiovascular risks [117].

AI models can be developed using those studies as templates and by incorporating genomic datasets, AI models can provide personalized toxicity predictions, aiding precision medicine. A recent study introduced the TransTox approach, which integrates organ-specific transcriptomic data with AI models to predict multi-organ toxicity [86]. This method enhances the precision of toxicological evaluations by analyzing gene expression patterns across different tissues. Researchers have combined drug-induced gene expression profiles from the Open TG-GATEs database with adverse drug reaction data from the FDA Adverse Events Reporting System (FAERS). By applying deep neural networks, they successfully predicted adverse drug reactions, demonstrating the potential of integrating AI with toxicogenomic datasets [118].

Transcriptomics focuses on gene expression profiles under drug exposure, and AI algorithms trained on transcriptomic datasets can identify patterns associated with toxicological outcomes, such as hepatotoxicity or nephrotoxicity. Researchers have developed models like ToxMPNN, a deep learning framework based on the message passing neural network (MPNN) architecture, to predict the toxicity of small molecules [119]. ToxMPNN has demonstrated high accuracy in predicting the acute oral toxicity of various compounds, aiding in the assessment of chemical safety.

Proteomics explores protein interactions and expression changes caused by drugs, and machine learning models leveraging proteomic data can predict toxicity by identifying disruptions in protein networks or pathways. For instance, a study utilized label-free mass spectrometry to identify approximately 2800 proteins in induced pluripotent stem cell-derived sensory neurons (iSNs) exposed to bortezomib [120]. The analysis revealed alterations in proteins affecting microtubule dynamics, cytoskeletal organization, and molecular transport, suggesting a multifaceted relationship between bortezomib-induced proteotoxicity and microtubule cytoskeletal architecture. Integrating AI with proteomic analyses could potentially provide deeper insights into the molecular mechanisms underlying neurotoxicity and improve the predictive accuracy of such models.

3.3. Chemical properties

The chemical structure and physicochemical properties of drug candidates are fundamental to understanding their toxicological potential. AI models utilize chemical descriptors such as molecular weight, lipophilicity, hydrophobicity, and structural motifs as key inputs to predict toxicity [121]. Machine learning techniques, including enhanced quantitative structure-activity relationship (QSAR) models, play a critical role in this domain. QSAR models assess the relationships between chemical structures and biological activity, providing valuable predictions about a compound's potential toxicity. For example, AI models trained on datasets of previously tested compounds can predict the toxicity of novel molecules by identifying structural similarities linked to known toxic effects. For instance, a study developed a deep

neural network (DNN) model using extended connectivity fingerprints of diameter 4 (ECFP4) to predict DILI (drug-induced liver injury) risk. This model demonstrated an accuracy of 73.1 % on the validation dataset, suggesting its potential utility in evaluating drug safety [122]. Another study introduced an ensemble model combining multiple machine learning classifiers to assess hepatotoxicity risk based on molecular fingerprints. This approach achieved a prediction accuracy of 80.26 % and was validated through external test sets and cross-validation, indicating its reliability in predicting liver toxicity [123].

Recent studies have explored integrating chemical structure data with biological datasets to assess nephrotoxicity. For example, researchers have identified 87 structural alerts for chemical nephrotoxicity by analyzing molecular substructures, which can aid in predicting nephrotoxic potential in drug candidates [124]. Additionally, transcriptomic analyses have been employed to understand the differential nephrotoxicity of various compounds, revealing that molecular mechanisms of nephrotoxicity can be species- and chemical-dependent [125]. An AI/ML model that combines physicochemical properties with off-target interaction data to enhance the prediction of drug-induced kidney injury (DIKI) was introduced. The model was trained on a dataset of 360 FDA-classified compounds, achieving an accuracy of 79 % and an area under the curve (AUC) of 0.87. [126]. Key predictive features included off-target interactions and physicochemical properties such as the number of metabolites and polar surface area. A machine-learning model was developed, that utilizes transcriptomic profiles from human cell lines to predict kidney dysfunction in rats, serving as a proxy for drug-induced renal toxicity [127]. By combining gene expression data with compound chemical structure information, the model aims to reduce reliance on animal testing by accurately forecasting toxicological outcomes based on in vitro analyses.

3.4. Patient data

Real-world patient data, including electronic health records (EHRs) and pharmacovigilance databases, are invaluable for developing personalized toxicity prediction models. These datasets capture individual variability in drug responses, encompassing genetic, environmental, and lifestyle factors [78]. EHRs provide longitudinal health data, including medication histories, laboratory results, and clinical outcomes, which AI models can analyze to identify correlations between specific drugs and ADRs. For instance, a developed model was trained on EHR data to predict drug-induced liver injury (DILI) by detecting patterns in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations across patients taking amiodarone and methotrexate, both known to cause hepatotoxicity [128]. Similarly, applied AI models to warfarin-treated patient records, indicates previously unrecognized risk factors for bleeding complications, such as specific drug interactions and genetic polymorphisms in CYP2C9 and VKORC1 [129]. These examples demonstrate how AI-powered analysis of longitudinal patient data can improve ADR detection and enhance drug safety monitoring in real-world clinical settings.

Pharmacovigilance databases, such as the FDA Adverse Event Reporting System (FAERS), offer large-scale records of ADR reports from post-marketing surveillance and are particularly useful for identifying rare or delayed toxicity events. Studies have employed machine learning models on FAERS data to detect signals for QT interval prolongation caused by medications [130]. The study highlighted the role of AI in identifying drug safety signals faster than traditional methods, including previously underreported drugs linked to this serious heart condition. These cases demonstrate how AI-powered systems can mine pharmacovigilance databases to uncover hidden patterns and predict potential ADRs for new drugs, improving post-marketing safety monitoring. The combination of patient-specific data with omics and chemical datasets would enable the development of highly personalized toxicity prediction models.

4. Validation techniques for AI models

The validation of AI models is a critical step in ensuring their reliability, robustness, and generalizability in predictive toxicology. Proper validation builds confidence among researchers, regulatory bodies, and the pharmaceutical industry, paving the way for the integration of AI models into drug development pipelines.

4.1. Cross-validation

Cross-validation is a foundational technique for evaluating the performance of AI models, ensuring their predictions are not overly dependent on the specific characteristics of the training data. Cross-validation involves systematically partitioning the dataset into training and validation subsets to evaluate model performance across different data splits. This approach helps assess whether a model has learned generalizable patterns rather than simply memorizing the training data. Several cross-validation strategies exist, with k-fold cross-validation being among the most common in toxicity prediction studies. In this approach, the dataset is divided into k equal-sized folds, with the model trained on k-1 folds and tested on the remaining fold, repeating this process until each fold has served as the test set once [131].

For example, researchers developed machine learning models, including random forest (RF) and multilayer perceptron (MLP), to predict drug-induced liver injury (DILI) using a large human dataset. Their performance was evaluated through 10-fold cross-validation and external testing. Notably, both models successfully identified drug candidates previously withdrawn from development due to hepatotoxicity, demonstrating the potential of in silico approaches for early DILI risk assessment [132]. Similarly, Kyro et al. [133] utilized a pre-trained AI-based framework for predicting and minimizing hERG channel inhibition while preserving drug efficacy, applied it to an FDA-approved compound, pimozide. The model successfully generated analogs with significantly reduced hERG activity, most notably identifying fluspirilene, which retained pharmacological similarity but showed over 700-fold weaker hERG binding—demonstrating its potential to mitigate cardiotoxicity early in development.

The selection of appropriate performance metrics is crucial in cross-validation. For binary classification tasks (toxic vs. non-toxic), metrics such as accuracy, precision, recall, and F1-score provide insights into different aspects of model performance. The Area Under the Receiver Operating Characteristic curve (AUC-ROC) is particularly valuable as it assesses model performance across different classification thresholds. For regression tasks predicting continuous toxicity values (e.g., LD50), mean squared error (MSE), root mean squared error (RMSE), and coefficient of determination (R^2) are commonly used [134].

Stratified cross-validation ensures that each fold maintains the same class distribution as the original dataset, which is particularly important for imbalanced toxicity datasets where toxic compounds might be significantly less common than non-toxic ones. Time-series cross-validation is essential when evaluating models trained on temporal data, such as longitudinal patient records or sequential drug exposure experiments, ensuring that future predictions are not made using data from later time points [135].

A toxicity prediction model was validated using the Area Under the Receiver Operating Characteristic Curve (AUC-ROC) metric, demonstrating high sensitivity in distinguishing aflatoxin B1 (AFB1) as a potent carcinogen. This validation approach not only aids in identifying potential overfitting but also offers insights into the model's stability and reliability across diverse datasets, enhancing its applicability in real-world toxicity assessments [136].

4.2. External validation

External validation involves evaluating AI models on entirely independent datasets that were not used during training or internal

validation. This process assesses the model's generalizability, ensuring it performs reliably across diverse datasets, conditions, and environments. Such validation helps detect overfitting and provides insights into the model's stability and applicability in real-world scenarios [137]. External validation represents the gold standard for assessing model robustness, as it evaluates performance on truly independent data that the model has never encountered during development. This approach is particularly critical in toxicity prediction, where models must eventually be applied to novel compounds with unknown toxicity profiles.

External validation datasets may come from different sources, including new experimental data, data from different laboratories or institutions, or data collected using different experimental protocols or measurement techniques. The chemical and biological diversity of these external datasets is crucial, as it challenges the model with new chemical structures, mechanisms of action, or patient populations that may not have been represented in the training data [138].

External validation is particularly important for regulatory and industry acceptance, as it demonstrates the model's applicability to real-world scenarios. For example, Wang et al. [139] reported an AI model on toxicity data specific to pesticides and were tested on a broader Tox21 dataset, confirming the model's ability to accurately predict the toxicity of non-pesticide compounds, such as dioxins and polychlorinated biphenyls (PCBs). Similarly, an external dataset from pharmaceutical industry databases has been used to validate a predictive model for genotoxicity, highlighting the model's ability to identify mutagenic compounds that had been missed in earlier screenings [140].

The domain of applicability represents a critical concept in external validation, defining the chemical, biological, or clinical space within which model predictions can be considered reliable. Compounds or scenarios falling outside this domain may result in less accurate predictions. Techniques for defining and visualizing the domain of applicability include principal component analysis of chemical descriptors, similarity measures to training compounds, or confidence estimates provided by the model itself [141].

For AI models intended for regulatory submission or clinical application, prospective validation represents the highest level of external validation. In this approach, the finalized model is used to predict the toxicity of entirely new compounds before experimental testing, with the predictions later compared to actual outcomes. This prospective approach provides the strongest evidence of model validity and practical utility [142].

The outcomes of external validation can highlight potential limitations or biases in the training data, as reported by studies that pointed out a model trained predominantly on data from preclinical animal studies had difficulty generalizing to human-specific toxicities, particularly those related to idiosyncratic drug reactions (IDRs) [143]. Models that perform well on external datasets are more likely to be trusted for high-stakes applications, such as clinical toxicity prediction or regulatory decision-making, ensuring that they are robust and reliable in diverse real-world contexts.

4.3. Benchmarking against traditional methods

Benchmarking AI models against traditional toxicity assessment methods is essential for establishing their advantages in terms of accuracy, speed, and cost-efficiency. This comparative validation approach directly evaluates AI predictions against conventional toxicity testing methods, assessing where AI offers improvements and identifying areas where traditional approaches might still retain advantages. Such benchmarking serves as a crucial bridge between innovative computational approaches and established regulatory frameworks.

The selection of appropriate comparison metrics is critical for meaningful benchmarking. These may include predictive performance metrics (sensitivity, specificity, accuracy), efficiency metrics (time and cost per compound), and practical utility assessments (scalability, resource requirements). Ideally, benchmarking should consider multiple dimensions of performance rather than focusing solely on prediction accuracy [144].

For example, AI predictions compared with in vitro assays and animal studies for hepatotoxicity prediction, demonstrating that AI models trained on large-scale adverse drug reactions (ADR) data outperformed traditional methods, such as rat liver assays, in predicting hepatotoxicity for drugs like acetaminophen and trovafloxacin [68]. Similarly, research has highlighted the superiority of AI-based quantitative structure-activity relationship (QSAR) models over traditional in vivo testing for identifying potential genotoxic compounds, which were correctly flagged by AI models but missed in animal trials [145].

Tiered benchmark testing represents a structured approach where AI models and traditional methods are evaluated on progressively more challenging toxicity prediction tasks. Beginning with well-characterized compounds having clear toxicity profiles, the evaluation moves to compounds with more subtle or complex toxicities, and finally to compounds representing edge cases or rare toxicity mechanisms. This progressive approach helps identify the specific conditions under which AI models outperform or underperform compared to traditional methods [146].

Mechanistic validation compares not only the predictions but also the biological insights generated by different approaches. While traditional testing may provide direct observations of biological effects, advanced AI models with explainability features can generate mechanistic hypotheses about toxicity pathways. Comparing these insights helps evaluate whether AI models capture biologically relevant mechanisms rather than merely statistical correlations [147].

AI models trained on extensive ADR datasets predicted drug-induced liver injury (DILI) with greater accuracy than traditional liver cell-based assays, offering improved scalability and rapid results for drugs like flutamide and valproic acid [148]. Furthermore, it is evident that AI models could process millions of chemical compounds much faster than conventional methods, enabling quicker screening of chemical libraries. Benchmarking would also facilitate discussions with regulatory authorities, as suggested that agencies like the FDA and EMA can now make it a requirement for comparative validation of AI models to traditional methods before product approval [149]. Successful benchmarking can expedite the adoption of AI models into regulatory frameworks, offering a more efficient and reliable pathway for toxicity testing.

When designing a benchmarking study, several considerations are critical. First, the selection of test compounds should represent diversity in chemical structures, mechanisms of action, and toxicity profiles. Second, the benchmark should include both positive controls (known toxic compounds) and negative controls (known safe compounds) to assess both sensitivity and specificity. Third, the evaluation should ideally be conducted by independent laboratories or researchers not involved in developing the AI model to minimize bias [150].

The outcomes of benchmarking studies should clearly articulate where AI models excel (e.g., high-throughput screening of large chemical libraries), where they complement traditional methods (e.g., prioritizing compounds for more extensive testing), and where traditional approaches may still offer advantages (e.g., detecting novel toxicity mechanisms not represented in training data). This balanced assessment supports the development of integrated approaches that leverage the strengths of both AI and traditional methods [151].

5. Challenges and future directions in AI-powered toxicity prediction

Table 3 outlines the challenges and future directions for AI in predictive toxicology, emphasizing the need for standardized data, model interpretability, regulatory acceptance, and ethical considerations.

Table 3
Challenges and future directions in AI-powered toxicity prediction.

Challenge	Description	Future Direction	Potential Outcomes
Data Quality and Scarcity	Inconsistent, biased, or incomplete datasets hinder model training and validation [111].	Standardizing toxicology datasets and promoting data-sharing across research institutions [106]	Improved model accuracy and generalizability across diverse compound classes.
Model Interpretability	Difficulty in understanding how AI models make predictions (black-box nature) [152].	Developing explainable AI (XAI) tools to clarify feature importance and decision pathways [153].	Increased trust among researchers, regulators, and stakeholders.
Regulatory Acceptance	Lack of clear guidelines for AI adoption in toxicity prediction [154].	Establishing collaborative frameworks between AI developers and regulatory agencies [155].	Faster integration of AI models into regulatory workflows.
Computational Demands	High resource requirements for training complex AI models [156].	Optimizing algorithms and leveraging cloud-based computing for scalability [157].	Reduced costs and enhanced accessibility for smaller research institutions.
Ethical Considerations	Risk of bias in datasets leading to inequitable predictions [158].	Implementing bias mitigation techniques and promoting diverse dataset inclusion [159].	Fair and equitable predictions across all populations.

5.1. Reducing reliance on animal testing

The reliance on animal testing for toxicity assessment has been a standard practice in drug development for decades. However, ethical concerns, scientific limitations, and the need for human-relevant testing methods have spurred the exploration of alternatives [6]. AI-powered predictive models have emerged as a transformative solution, addressing these challenges while aligning with the principles of Replacement, Reduction, and Refinement (3Rs) in animal research [160]. Animal testing, while historically valuable, is increasingly viewed as ethically contentious. The suffering inflicted on animals during toxicity studies has drawn significant public criticism, with advocacy groups and regulatory bodies demanding alternative methods [161]. Moreover, the scientific limitations of animal testing have become evident. Biological differences between animals and humans often result in poor translation of findings, where drugs deemed safe in animal studies may cause severe adverse reactions in humans [162]. Conversely, potentially effective compounds might be prematurely discarded due to false-positive toxicity results in animals. These discrepancies underscore the need for testing methods that more accurately predict human responses.

The integration of AI-powered models into toxicity prediction offers a scientifically robust and ethically sound alternative. By utilizing human-specific data such as genomics, chemical properties, and patient records, AI models replace the need for animal studies in many instances [163]. These models can analyze complex biological interactions and predict toxicities with greater accuracy, reducing the reliance on animal experiments. Furthermore, AI models help prioritize compounds with favorable safety profiles, allowing researchers to focus limited resources on the most promising candidates and reducing the number of animals required for testing [38]. AI technologies also refine the experimental process by providing more precise and targeted predictions of toxicity risks. This refinement enables researchers to design more focused in vivo studies, avoiding unnecessary experiments and minimizing animal use [148]. By improving the relevance and efficiency of toxicity assessments, AI not only reduces animal testing but also enhances the overall quality of preclinical research.

Cutting-edge research in alternatives to animal experimentation has accelerated in recent years, driven by both ethical imperatives and scientific advancements. Organ-on-chip technologies represent one of the most promising developments, with microfluidic devices containing living human cells arranged to mimic organ functionality. Multi-organ platforms now enable the study of complex inter-organ interactions critical for toxicity manifestation. For example, liver-heart-kidney connected systems have successfully modeled drug-induced toxicity cascades that would be impossible to observe in isolated cell cultures [164].

Advanced in vitro spheroid and organoid models have evolved dramatically, moving beyond simple cell monolayers to three-dimensional structures that better replicate tissue architecture and function. Human induced pluripotent stem cell (hiPSC) derived organoids for liver, kidney, brain, and cardiac tissues now demonstrate key physiological responses to toxic insults. When combined with AI analysis of high-content imaging data, these systems can detect subtle cellular changes indicative of toxicity mechanisms earlier than conventional endpoints [165].

In silico toxicology has expanded beyond traditional QSAR approaches to include sophisticated physiologically-based pharmacokinetic (PBPK) modeling integrated with systems biology. These approaches simulate the absorption, distribution, metabolism, and excretion of compounds alongside their effects on biological pathways. When coupled with machine learning algorithms trained on human biomarker data, these models can predict patient-specific adverse reactions with increasing accuracy [166].

Human tissue biobanking initiatives have created extensive repositories of diverse human samples for toxicity testing, allowing researchers to capture population variability in drug responses. Advanced "exposure systems" can now maintain these tissues in functional states while exposing them to test compounds under physiologically relevant conditions, generating human-specific toxicity data for AI model training [167].

Text mining and automated literature analysis tools scan millions of published studies to extract toxicity information and build knowledge graphs of compound-effect relationships. These systems facilitate evidence integration across multiple studies and are particularly valuable for identifying rare toxicities that might be missed in individual investigations. When these knowledge bases are coupled with machine learning, they can identify patterns and mechanisms that inform safer drug design [168].

In addition to addressing ethical concerns, AI-driven approaches meet the growing demand for high-throughput toxicity screening in modern drug discovery [169]. Unlike animal testing, which is time-consuming and resource-intensive, AI models can process large-scale datasets rapidly, offering scalable solutions for screening extensive chemical libraries. This efficiency makes AI an indispensable tool for reducing reliance on traditional methods, aligning with both scientific and ethical imperatives [170].

6. Accelerating the identification of safe drug candidates

The drug discovery process is notoriously time-consuming and resource-intensive, with high attrition rates that often stem from unforeseen toxicity issues. AI-powered predictive models are revolutionizing this process by enabling the early identification of safety risks, thereby prioritizing compounds with favorable toxicity profiles for further development. This capability significantly reduces the likelihood of late-stage failures, streamlining research and development timelines while cutting costs. Table 4 illustrates the key applications of AI models, such as high-throughput screening, hepatotoxicity prediction, and personalized medicine, demonstrating their transformative impact on the drug discovery process by accelerating the identification of safe drug candidates.

6.1. Early identification of toxicity risks

AI models excel in detecting potential toxicity risks during the initial

Table 4
Key applications of AI in predictive toxicology.

Application Area	Specific Use	Benefits to Drug Discovery	Examples
High-Throughput Screening	Rapid screening of large chemical libraries for toxicity risks [171].	Saves time and resources; allows prioritization of safer candidates early in the pipeline [172].	Screening 100,000+ compounds for cardiac toxicity using deep learning models [173].
Hepatotoxicity Prediction	Identifying drugs likely to cause liver damage [174].	Reduces risk of late-stage failures; enables safer drug designs [26].	Predicting DILI using transcriptomic biomarkers from treated liver cell lines [175].
Cardiotoxicity Prediction	Assessing drugs for QT interval prolongation or other cardiac risks [71].	Improves cardiovascular safety profiles during preclinical stages [176].	Predicting arrhythmogenic risk using patient ECG and EHR datasets [177].
Dose-Response Modeling	Simulating toxicity thresholds based on exposure levels [178].	Provides precise dose optimization for therapeutic and safety margins [179]	Modeling nephrotoxicity at different exposure levels using metabolomics data [148].
Personalized Medicine	Tailoring drug safety profiles to individual genetic and environmental factors [180].	Enhances patient outcomes and reduces ADRs in diverse populations [181].	Predicting ADR risk for oncology drugs using patient-specific multi-omics data [182].
Environmental Toxicology	Assessing impact of drugs on ecosystems and non-human organisms [183].	Promotes sustainability and compliance with environmental regulations [183].	Predicting aquatic toxicity of pharmaceuticals using QSAR-based AI models [184].

phases of drug discovery by analyzing large datasets such as chemical properties, omics profiles, and patient-specific information to predict adverse drug reactions (ADRs) before significant resources are invested in preclinical and clinical studies. For instance, a developed AI model predicted hepatotoxicity in early-stage drug candidates like troglitazone, using chemical structure and gene expression data, identifying potential risks before moving into costly animal studies [5]. This early identification is particularly crucial, as late-stage failures due to toxicity not only incur substantial financial losses but also delay the introduction of potentially life-saving therapies to patients, as seen in the situation of the thalidomide recall, which resulted from severe teratogenicity discovered only after clinical trials [185]. This predictive power allows researchers to deprioritize compounds with unfavorable safety profiles, and focus on those with a higher probability of success, improving the efficiency of the discovery pipeline.

6.2. Reducing late-stage failures

Late-stage failures in drug development particularly during clinical trials are among the costliest setbacks for pharmaceutical companies, as noted in the toxicological issues not detected during preclinical testing but later resulted in the withdrawal of darapladib due to unforeseen hepatotoxicity [186]. AI models mitigate this risk by providing more accurate and human-relevant predictions than traditional animal-based methods. By incorporating various datasets, such as patient electronic health records (EHRs) and pharmacovigilance reports, AI models can simulate human-specific responses, reducing the likelihood of unexpected toxicities in clinical trials. For instance, Organ on Chips has demonstrated that AI models incorporating EHR data and genomic information would successfully predict drug-induced liver injury (DILI) with higher accuracy than traditional rat hepatocyte assays, successfully flagging some candidates as high-risk drugs [187]. Moreover, the ability of AI to uncover complex, non-linear relationships between chemical properties and biological responses enhances its predictive accuracy. AI models have identified a correlation between molecular size and cardiovascular toxicity in compounds like sotalol and quinine, which had not been recognized through conventional testing [188]. For example, machine learning algorithms can identify patterns in multi-omics data that indicate potential organ-specific toxicity, such as hepatotoxicity or cardiotoxicity, which might not be evident in conventional in vitro or in vivo studies, further underscoring the value of AI in reducing late-stage clinical trial failures.

6.3. Enhancing efficiency and cost savings

The integration of AI models into drug discovery accelerates the identification of safe drug candidates by automating the evaluation process. Unlike traditional methods, AI-powered systems can process and analyze vast chemical libraries in a fraction of the time. This high-throughput capability enables researchers to screen thousands of compounds simultaneously, rapidly narrowing down the pool of viable candidates [189]. The cost savings associated with AI-driven toxicity prediction are substantial. By reducing the need for extensive preclinical testing and minimizing late-stage failures, pharmaceutical companies can allocate resources more effectively, ultimately reducing the overall cost of bringing a drug to market. Additionally, the scalability of AI models makes them ideal for evaluating the safety profiles of drug candidates in emerging areas such as personalized medicine and targeted therapies [190].

6.4. Transforming the drug discovery landscape

AI's ability to prioritize safe drug candidates is transforming the drug discovery landscape, fostering a more targeted and efficient approach to pharmaceutical research [8]. By integrating predictive models into early-stage decision-making processes, researchers can streamline development timelines, reduce costs, and increase the likelihood of successful outcomes [191]. As AI technologies continue to evolve, their role in accelerating the identification of safe drug candidates is expected to expand, paving the way for a more innovative and effective drug development paradigm [192].

7. Conclusion

AI-powered predictive models are revolutionizing the field of drug toxicity screening, offering unparalleled advancements in accuracy, scalability, and efficiency. By leveraging diverse, large-scale datasets—including omics profiles, chemical properties, and patient-specific records—these models provide a comprehensive approach to predicting adverse drug reactions. The integration of advanced machine learning algorithms and rigorous validation techniques ensures their robustness, enabling more reliable and human-relevant toxicity assessments.

This review has highlighted several key advancements and benefits of AI in predictive toxicology. The ability to integrate and analyze heterogeneous data sources from molecular structures to patient records enables a more holistic understanding of toxicity mechanisms than previously possible with conventional methods. Machine learning and deep learning algorithms have demonstrated superior predictive performance across multiple toxicity endpoints, including hepatotoxicity, cardiotoxicity, nephrotoxicity, and genotoxicity. The emergence of explainable AI addresses critical transparency issues, making these powerful models more interpretable for researchers and regulators alike.

The comparative analysis between AI and traditional toxicity testing methods reveals complementary strengths that can be optimized through hybrid approaches. The convergence of computational models with advanced in vitro systems like organoids and organs-on-chips represents a particularly promising direction, offering human-relevant insights while reducing animal testing. Moreover, the application of AI

throughout the drug development pipeline—from early candidate screening to clinical trial monitoring creates multiple opportunities to identify and mitigate toxicity risks before they result in costly failures.

Looking toward the future, several research priorities emerge. First, the development of standardized, high-quality datasets specifically designed for toxicity prediction will be crucial for improving model performance and generalizability. Initiatives like the Innovative Medicines Initiative (IMI) and Toxicology in the 21st Century (Tox21) programs are making important contributions in this area, but more coordinated efforts are needed. Second, continued advancement in model interpretability will be essential for regulatory acceptance and scientific credibility. Third, establishing clear frameworks for validating AI predictions against gold-standard toxicity assessments will help build confidence in these novel approaches.

The implications of these advances extend beyond pharmaceutical development. Environmental toxicology, consumer product safety, and chemical risk assessment all stand to benefit from AI-powered toxicity prediction. Additionally, the potential for personalized toxicity assessments based on individual genetic profiles could transform clinical practice, enabling safer medication regimens tailored to patient-specific risks.

While challenges remain in data quality, model interpretability, and regulatory integration, the trajectory of advancement in AI-powered toxicity prediction is clear. Through collaborative efforts between computational scientists, toxicologists, clinicians, and regulatory bodies, these challenges can be systematically addressed. The result will be a more efficient, ethical, and accurate approach to toxicity assessment that ultimately benefits patients through safer medications developed in less time and at lower cost.

Despite these advancements, challenges remain in data quality, model interpretability, and regulatory integration. Ensuring access to high-quality, standardized datasets and enhancing transparency in AI model decision-making will be crucial for gaining broader acceptance. Collaboration among researchers, developers, and regulatory bodies will also be key to establishing guidelines and standards that facilitate the adoption of AI in predictive toxicology. As these challenges are addressed, AI is poised to become an indispensable tool in drug development. By enabling safer, faster, and more effective toxicity screening, AI-powered models are paving the way for a new era in pharmaceutical innovation, ultimately improving patient safety and accelerating the delivery of life-saving therapies to market.

CRediT authorship contribution statement

Olawale M. Ajisafe: Writing – review & editing, Writing – original draft, Methodology, Investigation, Data curation, Conceptualization. **Yemi A. Adekunle:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Eghosasere Egbon:** Writing – review & editing, Writing – original draft, Visualization, Investigation. **Covenant Ebubechi Ogbonna:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **David B. Olawade:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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