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Utilizing Artificial Intelligence and Machine Learning for Early Detection of Adverse Drug Reactions and Drug-Induced Toxicities

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ABSTRACT

Adverse drug reactions (ADRs) and drug-induced toxicity represent critical barriers in drug discovery and development, posing substantial risks to patient safety and contributing significantly to healthcare costs. Unlike more overt health threats such as infectious diseases, ADRs often remain underrecognized until late-stage clinical trials or post-market surveillance, making their early prediction vitally important. The emergence of artificial intelligence (AI) and machine learning (ML) has transformed the landscape of pharmacovigilance, offering innovative and powerful tools for the early identification of ADRs and toxicological risks. These computational techniques enable rapid, accurate, and large-scale prediction of adverse effects—sometimes even prior to the physical synthesis of a drug—thus improving efficiency and minimizing the likelihood of costly late-stage failures or withdrawals. This review comprehensively examines the current and emerging applications of AI and ML in the early detection of ADRs and drug-induced toxicity. It explores a range of methodologies including data mining, quantitative structure-activity relationship (QSAR) modeling, and deep learning, alongside curated databases, algorithms, and specialized software platforms used for toxicity prediction. By providing an integrated overview of existing strategies and future directions, this review underscores the transformative potential of AI and ML in enhancing drug safety and accelerating the development of safer therapeutics.

Keywords: Adverse drug reactions, Drug-induced toxicity, Artificial intelligence, Machine learning, Deep learning, Toxicity prediction, Drug discovery, QSAR, Pharmacovigilance, Predictive modeling.

1. Introduction: AI for Predicting Adverse Drug Reactions and Toxicology

Adverse Drug Reactions (ADRs) represent a significant challenge in clinical medicine and drug development, often leading to patient morbidity, mortality, and the withdrawal of pharmaceutical products from the market. Traditional methods of toxicity assessment, such as in vivo animal studies and in vitro assays, though valuable, are often costly, time-consuming, ethically contentious, and may not always predict human-specific reactions accurately (1). As a result, there is a growing interest in the integration of Artificial Intelligence (AI) technologies in pharmacovigilance and predictive toxicology to enhance drug safety and efficacy profiles.

AI, particularly through machine learning (ML), deep learning (DL), and natural language processing (NLP), offers powerful data-driven approaches capable of uncovering complex, non-linear patterns in large-scale biological and chemical datasets. These tools have the potential to predict ADRs before clinical manifestation by analyzing a multitude of features including chemical structures, biological pathways, genomic interactions, and electronic health records (2). For instance, graph neural networks (GNNs) and ensemble learning models have shown superior accuracy in predicting off-target effects and potential toxicity based on structural-activity relationships and molecular descriptors (3).

Moreover, AI enables the synthesis of heterogeneous data sources—such as literature mining, real-world data, omics technologies, and clinical reports—to generate predictive models that can improve decision-making during drug

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discovery and development phases. These models can facilitate early-stage screening of drug candidates, guide dose optimization, and identify at-risk populations, thereby reducing late-stage drug failure and enhancing patient safety (4).

In this review, we explore the role of AI in predicting ADRs and toxicological outcomes, discuss current methodologies and their applications, and highlight future perspectives that aim to revolutionize pharmacovigilance and personalized medicine through intelligent, data-centric approaches.

2. Drug Withdrawals: The Reason for Early Detection of ADRs and Drug-Induced Toxicity

Adverse drug reactions (ADRs) and drug-induced toxicities have been major contributors to the post-marketing withdrawal of pharmaceutical products, underscoring the need for robust early detection systems during the drug development pipeline. Despite rigorous preclinical and clinical trials, unforeseen toxicities can still arise once drugs are exposed to larger, more heterogeneous patient populations in real-world settings (6). This highlights the limitations of conventional safety evaluation approaches and the critical importance of proactive pharmacovigilance strategies.

Several high-profile drug withdrawals have drawn attention to the serious implications of ADRs. For instance, **Rofecoxib (Vioxx)**, a COX-2 inhibitor, was withdrawn due to increased cardiovascular risks, while **Cisapride**, a gastrointestinal prokinetic agent, was removed from the market following reports of fatal cardiac arrhythmias (7). These examples illustrate how late-stage or post-marketing detection of ADRs can not only jeopardize patient health but also result in substantial financial and reputational losses for pharmaceutical companies.

The key challenges in traditional toxicological assessments lie in their limited ability to predict **idiosyncratic drug reactions**, **organ-specific toxicity**, and **inter-individual variability**. Many adverse effects, such as **hepatotoxicity**, **nephrotoxicity**, or **neurotoxicity**, are often dose-dependent or occur due to long-term use, making them difficult to detect in short-duration clinical trials (8). Additionally, rare genetic predispositions and drug–drug interactions often go unnoticed until post-approval.

As a result, **early prediction of ADRs using Artificial Intelligence (AI)** has gained significant momentum. AI can analyze large, diverse datasets—from chemical structures and target profiles to real-world adverse event reports—to forecast potential toxicity issues even before clinical testing. This proactive approach allows for early filtering of high-risk compounds and helps prioritize safer drug candidates, thereby **reducing the burden of late-stage failures and post-marketing withdrawals** (10).

Thus, the historical trend of drug withdrawals emphasizes the **urgent need for AI-driven predictive toxicology** to enhance safety surveillance and decision-making throughout the drug development lifecycle.

Table.1. List of Drugs Withdrawn Due to ADRs and Toxicity

Drug Name	Brand	Intended Use	Reason for Withdrawal	Year of Approval	Year of Withdrawal	Citation
Rofecoxib	Vioxx	Pain/Arthritis	Cardiovascular risks (MI, stroke)	1999	2004	(11)
Cisapride	Propulsid	Gastroesophageal reflux	QT prolongation, fatal arrhythmias	1993	2000	(12)
Terfenadine	Seldane	Antihistamine	Cardiotoxicity, torsades de pointes	1985	1998	(13)
Troglitazone	Rezulin	Type 2 Diabetes	Hepatotoxicity, liver failure	1997	2000	(14)
Phenylpropanolamine	Multiple OTC	Nasal decongestant,	Hemorrhagic stroke risk	1930s	2000	(15)

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		appetite suppressant				
Tegaserod	Zelnorm	Irritable Bowel Syndrome	Cardiovascular ischemic events	2002	2007	(16)
Pemoline	Cylert	ADHD	Hepatotoxicity	1975	2005	(17)
Benoxaprofen	Oraflex	Arthritis	Hepatotoxicity, photosensitivity	1982	1982	(18)
Thalidomide	Contergan	Morning sickness (later: cancer, leprosy)	Birth defects, teratogenic effects	1957	1961 (reintroduced under restrictions)	(19)
Mibefradil	Posicor	Hypertension, angina	Severe drug interactions via CYP3A4 inhibition	1997	1998	(20)

3. ADRs data resources

Adverse Drug Reactions (ADRs) are unintended, harmful reactions to medications. Reliable data on ADRs are essential for pharmacovigilance, drug safety assessment, and AI-based predictive modeling. Below is a categorized list of **key ADR data resources**, including databases, regulatory agencies, and specialized tools:

1. Regulatory & Public ADR Databases

Name	Organization	Description	References
FAERS (FDA Adverse Event Reporting System)	US FDA	Contains voluntary and mandatory reports of ADRs and medication errors submitted to the FDA	(21)
VigiBase	WHO (Uppsala Monitoring Centre)	The largest global database of individual case safety reports (ICSRs), used for global pharmacovigilance	(22)
EudraVigilance	European Medicines Agency (EMA)	European database of suspected adverse drug reactions	(23)
Canada Vigilance	Health Canada	National database of ADRs reported in Canada	(24)
Yellow Card Scheme	MHRA (UK)	ADR reporting system in the UK	(25)

2. Biomedical & Clinical Databases with ADR Info

Name	Type	Description	References
SIDER	Public dataset	Side Effect Resource linking drugs to ADRs using public documents and labels	(26)

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OFFSIDES / TWOSIDES	Public datasets	Derived from FAERS, lists significant drug-AE and drug-drug-AE associations	(26)
DrugBank	Bioinformatics	Contains detailed drug info including ADRs	(27)
PubMed / MEDLINE	Literature	Source of case reports, reviews, and clinical studies on ADRs	(28)
ClinicalTrials.gov	Clinical trials registry	Reports of ADRs in trial results	(29)

3. AI & Computational Resources for ADR Prediction

Tool / Dataset	Description	References
BioSNAP-Disease	Drug–ADR relationships for ML training	(31), (32)
ADE Corpus V2	Annotated biomedical texts with ADRs for NLP tasks	
PAERS	Pharmacovigilance AI model trained on FAERS	

4. Commercial & Clinical Tools (Restricted Access)

Database	Provider	References
Micromedex	IBM	(34),(35),(36)
Lexicomp	Wolters Kluwer	
UpToDate	Wolters Kluwer	

5. National Pharmacovigilance Programs (India-specific)

Name	Organization	References
PvPI (Pharmacovigilance Programme of India)	Indian Pharmacopoeia Commission	(33)

4. ADRs and Drug-Induced Toxicity: The Determining Step in Drug Discovery

4.1. Preclinical Trials

Toxicology evaluation is a pivotal phase in the early development of pharmaceuticals, serving as a predictive tool for safety and dosing in humans. The process typically initiates with in vitro experiments involving genetically engineered cell lines and in vivo studies using transgenic or knockout animal models (37). These models are essential for assessing cytotoxicity, potential mutagenicity, and early carcinogenic signals that may disqualify a compound from further development.

Acute toxicity is assessed through high-dose studies in animal models to determine the lethal dose 50 (LD_{50}) and to observe any dose-limiting organ damage. Multi-species analysis (usually rodent and non-rodent models) ensures detection of species-specific responses (38). Subacute and chronic toxicity studies span several weeks to months, during which drugs are administered at sub-lethal doses. Pathologists then examine vital organs for signs of necrosis, inflammation, or carcinogenesis post-euthanasia (39).

Understanding drug metabolism in the preclinical stage is another cornerstone of safety assessment. The liver's cytochrome P450 enzymes, among others, can biotransform drugs into either pharmacologically active or toxic

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metabolites (40). The Absorption, Distribution, Metabolism, and Excretion (ADME) profile is studied using radiolabeled isotopes such as ^{14}C or ^{3}H to track metabolite formation in biofluids and tissues (41). These studies are crucial for bridging animal models with human metabolism and for forecasting appropriate starting doses in first-in-human (FIH) trials.

Advanced in vitro systems such as liver microsomes, S9 fractions, and hepatocyte cultures, along with in silico models, are used to identify reactive or potentially mutagenic intermediates (42). Furthermore, drug formulation and stability studies are carried out to ensure that the candidate compound maintains integrity under physiological and storage conditions. Formulation optimization addresses factors like solubility, bioavailability, and administration route (43).

4.2. Clinical Trials

4.2.1. Phase I Trials

Phase I clinical trials primarily assess safety, tolerability, pharmacokinetics, and pharmacodynamics in a small cohort of healthy volunteers (typically 20–80 participants). These trials determine the maximum tolerated dose (MTD) and detect early adverse reactions (44). For cytotoxic agents like anticancer drugs, patients may be enrolled directly due to ethical considerations (45).

Dose escalation protocols such as 3+3 designs or modified continual reassessment methods (mCRM) are implemented to incrementally increase the dose while monitoring for dose-limiting toxicities (DLTs) (46). The pharmacokinetic data obtained (e.g., half-life, Cmax, AUC) are foundational for designing later-phase trials.

4.2.2. Phase II Trials

Phase II trials, involving 100–300 patients, seek to evaluate the drug's therapeutic efficacy and refine the dose–response relationship. They are often divided into Phase IIa (pilot efficacy) and IIb (dose-ranging) studies (47). These are typically randomized, double-blind, and placebo-controlled to reduce bias.

Comparative studies may use standard-of-care or historical controls when placebo use is unethical—particularly in life-threatening conditions (48). Early signal detection of adverse events also continues in this phase, especially in terms of organ-specific toxicities, QT prolongation, or immunogenicity (49).

4.2.3. Phase III Trials

Phase III trials are the largest and most resource-intensive, involving thousands of patients across multiple centers and geographies. The primary aim is to confirm clinical efficacy, detect less frequent adverse effects, and establish the drug's risk-benefit ratio (50). Trials are generally randomized, double-blind, and include both active comparator and placebo arms.

In this phase, real-world factors such as polypharmacy, comorbidities, and demographic variations are captured, making it possible to detect rare but serious ADRs such as hepatotoxicity or cardiovascular events (51). Successful completion of Phase III leads to regulatory submission for market authorization with agencies like the FDA, EMA, or CDSCO.

4.2.4. Phase IV Trials

Phase IV or post-marketing surveillance focuses on long-term safety and effectiveness in the general population. Once approved, drugs continue to be monitored through pharmacovigilance systems such as the FDA Adverse Event Reporting System (FAERS) and VigiBase (WHO-UMC) to identify rare, delayed, or population-specific ADRs (52).

These observational studies also evaluate the drug's performance in broader populations, including pediatric, geriatric, and comorbid patients (53). Additionally, Phase IV data feed into treatment guidelines, cost-effectiveness analyses, and health technology assessments that influence formulary inclusion and insurance coverage (54).

5. Drug Redesign and Structural Optimization

Drug redesign and structural optimization are integral aspects of modern drug development, aimed at enhancing therapeutic performance while minimizing toxicity and side effects (55). These strategies typically involve deliberate alterations to a drug's molecular framework to refine its pharmacological attributes—such as receptor affinity, metabolic stability, solubility, or target specificity (56). A well-known example of this approach is the transformation

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of doxorubicin into its pegylated liposomal form, known as Doxil, which markedly improved drug solubility, pharmacokinetics, and safety profile by minimizing cardiac toxicity (57).

Structural derivatization of existing drugs is also a common method used to generate analogs with enhanced therapeutic index. This can include the modification of functional groups to improve target interaction or to resist metabolic degradation. For instance, structural refinements to the original penicillin molecule led to semi-synthetic derivatives such as ampicillin and amoxicillin, which possess broader antimicrobial spectra and increased stability against β-lactamases (58). More recently, rational design methods have been employed to engineer novel siderophore–antibiotic conjugates, termed "sideromycins," which exploit bacterial iron transport pathways to enhance intracellular delivery of antimicrobial agents (59).

Target specificity and receptor selectivity are crucial in minimizing adverse reactions. This was a key principle behind the design of selective serotonin reuptake inhibitors (SSRIs), including fluoxetine and sertraline. These were developed to selectively block serotonin reuptake, thereby reducing off-target receptor interactions commonly seen with older tricyclic antidepressants (60) In addition, the use of prodrug strategies has become increasingly valuable. A notable case is capecitabine, a prodrug converted enzymatically in the body to 5-fluorouracil, offering improved tumor targeting and reduced gastrointestinal toxicity compared to direct 5-FU administration (61).

Advanced drug delivery systems also contribute to structural re-engineering efforts. Technologies like nanoparticles, microspheres, and liposomes are employed to optimize pharmacokinetics and drug targeting. For instance, paclitaxel was reformulated into albumin-bound nanoparticles (Abraxane), which increased its aqueous solubility and allowed for safer administration without toxic solvents (62). These innovations enhance not only therapeutic efficacy but also patient compliance and quality of life.

Structure–activity relationship (SAR) studies further support drug restructuring by identifying key pharmacophores and molecular motifs essential for biological activity (63). SAR-guided design enables the systematic tuning of a compound's structure to maximize activity while reducing off-target effects. This rational approach to drug design plays a pivotal role in optimizing lead compounds and accelerating the drug discovery process (64).

6. Types of ADRs and Toxicity Considerations in Drug Development

6.1. Mechanistic Insights into Drug-Induced Toxicity

Understanding the underlying biological mechanisms of drug toxicity is pivotal in pharmaceutical development, as it helps anticipate potential adverse drug reactions (ADRs) and ensures patient safety (65). Drug toxicity is commonly defined as the extent to which a substance can cause harm to a living organism, often quantified by parameters like the Lethal Dose 50 (LD_{50})—the dose at which 50% of the test population succumbs (66). This section delves into key mechanisms contributing to drug-induced toxicity and their relevance to preclinical and clinical drug assessment.

6.1.1. Cytotoxicity and Structural Cellular Injury

A primary mechanism through which drugs exert toxic effects involves direct interaction with cellular structures or disruption of vital biochemical processes (67). Such cytotoxic effects can damage membranes, proteins, organelles, or even genetic material. For example, Amphotericin B is known to bind to ergosterol in fungal cell membranes, but it can also disrupt human cell membranes, leading to ion imbalance and cellular lysis (68). Similarly, anthracycline-based chemotherapeutics like doxorubicin can impair mitochondrial function and induce oxidative stress, culminating in apoptosis (69).

Hepatotoxicity from acetaminophen exemplifies the danger of reactive metabolites. Its toxic metabolite, NAPQI, binds covalently to cellular proteins when glutathione is depleted, resulting in severe liver injury (70). DNA alkylation by chemotherapy drugs such as cyclophosphamide can lead to mutations and increased cancer risk (71). These direct mechanisms of toxicity are critical to understand for mitigating risk and refining lead compounds during drug development.

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6.1.2. Immunologically Mediated Adverse Reactions

Certain ADRs originate not from direct toxicity, but from unintended immune system activation. Drugs or their reactive metabolites may act as haptens, triggering immune recognition and hypersensitivity responses (72). Immunological ADRs can be categorized into four types:

- **Type I reactions** (IgE-mediated) are immediate and can cause urticaria or anaphylaxis, as observed with penicillin (73).
- **Type II reactions** involve antibody-mediated cytotoxicity, where drugs like methyldopa may induce hemolytic anemia.
- **Type III responses**, seen with drugs like hydralazine, involve immune complex deposition and inflammation.
- **Type IV (T-cell mediated)** hypersensitivity can lead to delayed skin eruptions or organ toxicity, as observed with carbamazepine (74).

Increasingly, researchers use *in vitro*, *in silico*, and animal models to explore the immunotoxicity potential of drug candidates early in development, which helps in minimizing the risk of late-stage failure (75).

6.1.3. Toxicity from Reactive Metabolites

A major concern in pharmacology is bioactivation, where drugs are metabolized into reactive intermediates capable of inflicting harm (76). Liver enzymes such as cytochrome P450 are often involved in this transformation. When detoxification mechanisms (e.g., conjugation with glutathione) are overwhelmed, these metabolites may bind to macromolecules like proteins or DNA, leading to cellular dysfunction or immunological reactions.

Acetaminophen remains a classical example—non-toxic at low doses but capable of causing fulminant liver failure at high doses due to excessive NAPQI formation (77). Predicting these events involves the use of hepatic cell models, microsomal assays, and computational tools to forecast metabolic hotspots and reactive intermediate formation (78). These predictions are later validated in vivo before clinical translation.

6.1.4. Off-Target Interactions

Drugs designed for one molecular target may inadvertently interact with other proteins, resulting in off-target effects that manifest as toxicity (79). For instance, several antipsychotics block cardiac hERG potassium channels, increasing the risk of arrhythmias (80). Such adverse effects can emerge unexpectedly due to structural similarity between intended and unintended targets or due to unanticipated distribution in non-target tissues.

Off-target effects often go unnoticed in early testing but may lead to post-market drug withdrawals. Drug developers now routinely apply *in silico* docking simulations, broad-spectrum receptor binding assays, and systems biology tools to anticipate these interactions (81). Reducing polypharmacological liability without compromising efficacy is a fine balance crucial in lead optimization.

6.2. Toxicological Assessment Methods

Toxicity evaluation is a cornerstone of drug safety studies. Traditional methods like the LD_{50} test—though still used—are increasingly supplemented or replaced by more humane and informative alternatives (82). LD_{50} determines the dose at which half of the test population dies, but it offers limited insight into the nature of toxicity or long-term effects.

Modern toxicological profiling involves several key parameters:

- **ED_{50}** (effective dose for 50% of the population)
- **NOAEL** (No Observed Adverse Effect Level)
- **LOAEL** (Lowest Observed Adverse Effect Level)
- **Genotoxicity**, **carcinogenicity**, and **teratogenicity** tests for evaluating potential DNA damage, cancer risk, and fetal harm respectively (83).

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- **Neurotoxicity studies**, assessing impact on brain or nerve functions (84).

High-throughput screening platforms and predictive toxicology using *in silico* modeling are advancing rapidly, enabling faster, more ethical, and cost-effective safety profiling (85). These models often correlate with human data better than traditional animal-only models.

6.3. Classification Frameworks for ADRs

Accurate classification of ADRs is essential to guide clinical decisions, regulatory strategies, and pharmacovigilance. Two widely recognized frameworks are the **Rawlins and Thompson classification** and the **DoTS model**.

6.3.1. Rawlins and Thompson System

Established in 1977, this binary system categorizes ADRs into:

- **Type A (Augmented)**: predictable, dose-related, and often preventable events based on the drug's known pharmacological action (e.g., bleeding from warfarin).
- **Type B (Bizarre)**: idiosyncratic, dose-independent, and unpredictable reactions such as drug-induced lupus or Stevens–Johnson syndrome (86).

While simple and useful for routine clinical application, it lacks depth in explaining patient-specific responses like those driven by genetics. For example, hypersensitivity to abacavir in patients with the HLA-B*57:01 allele is not easily classified under this model (87).

6.3.2. DoTS Model

Proposed by Aronson and Ferner in 2003, the **DoTS (Dose–Time–Susceptibility)** classification offers a more nuanced approach. It considers:

- **Dose-related factors** (toxic, collateral, or hypersusceptibility effects)
- **Timing of ADR onset** (e.g., immediate vs. delayed)
- **Patient-specific susceptibility** (e.g., age, sex, genetic markers, comorbidities) (88)

This model is particularly useful in precision medicine, as it accounts for interindividual variability. However, its complexity may pose challenges in day-to-day clinical use or resource-limited settings.

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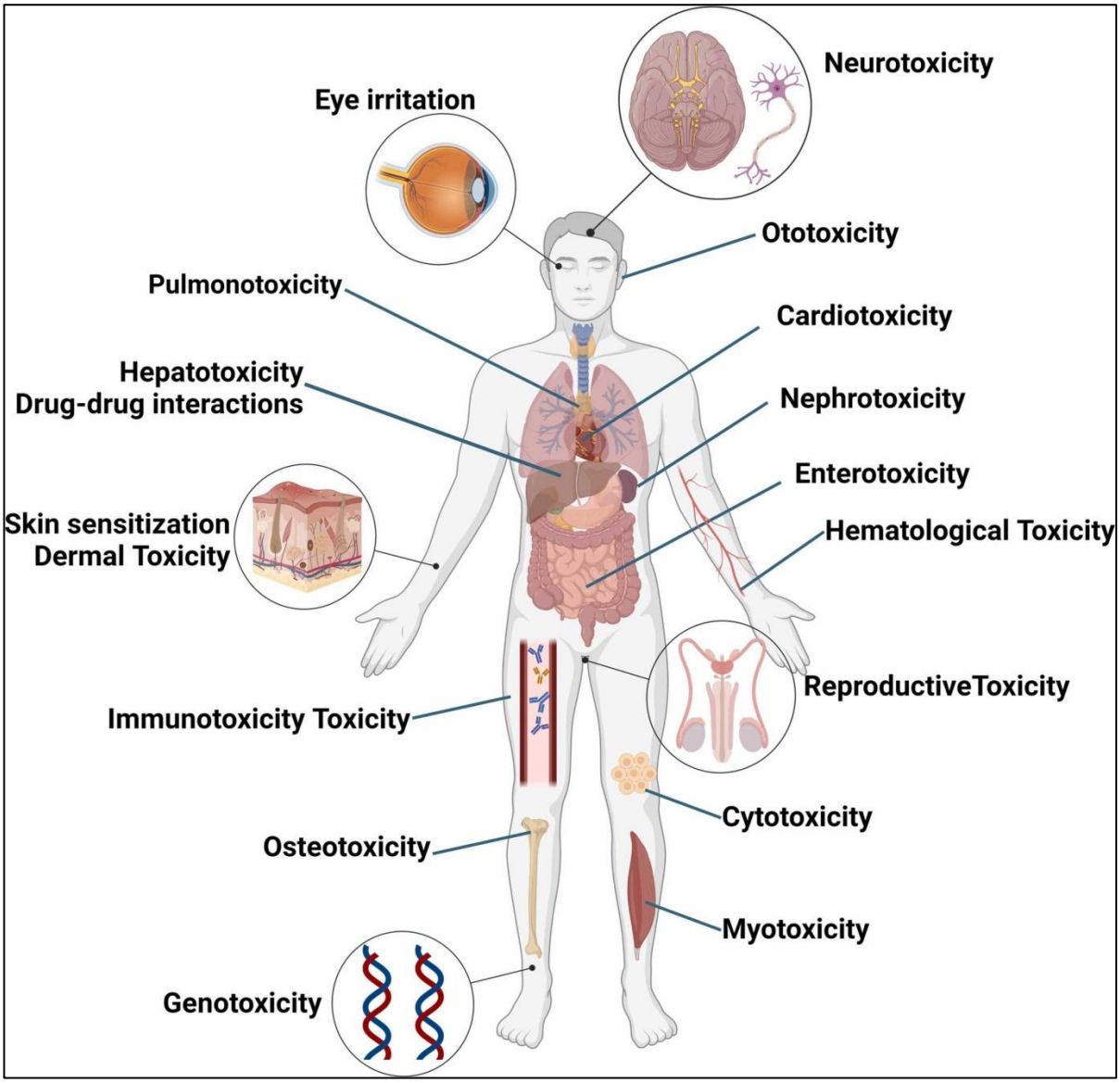

Fig.1. Major ADRs and drug-induced toxicities for the human system. (89)

Key Drug-Induced Toxicity Types

6.4.1 Hepatotoxicity

Liver injury from medications—known as **drug-induced liver injury (DILI)**—ranges from mild enzyme elevations to lethal liver failure (90). Over a thousand drugs are implicated. DILI is typically classified into **intrinsic types** (predictable, dose-dependent, e.g., acetaminophen overdose) and **idiosyncratic types** (unpredictable, often immune-mediated) Histologically, DILI may manifest as hepatocellular damage, cholestatic injury, or mixed-pattern disease. Risk factors encompass drug-specific characteristics (e.g., metabolic activation pathways), dose, duration, patient genetics, age, comorbid liver disease, and concurrent medication use. Diagnosis remains complex, often requiring exclusion of other liver pathologies and supportive tools like the RUCAM/CIOMS scale for causality estimation.

6.4.2 Nephrotoxicity

Adverse renal effects from drugs—termed **drug-induced nephrotoxicity**—include acute kidney injury (AKI), interstitial nephritis, glomerular syndrome, chronic kidney disease, and electrolyte disturbances. Common culprits include aminoglycosides, NSAIDs, contrast dyes, platinum-based chemotherapy agents (like cisplatin), and immunosuppressants. Nephrotoxicity can be **dose-dependent** (predictable) or **idiosyncratic** (unpredictable).

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Major risk enhancers include pre-existing kidney disease, advanced age, volume depletion, diabetes, heart failure, and use of multiple nephrotoxins. Early detection and mitigation strategies emphasize careful dosing, hydration protocols, medication review, and monitoring renal function — strategies summarized by the "6Rs" framework (risk assessment, recognize, respond, renal support, rehabilitation, research).

6.4.3 Cardiotoxicity

Cardiotoxicity encompasses a spectrum of drug-triggered cardiac abnormalities such as arrhythmias, cardiomyopathy, myocardial ischemia, and blood pressure disturbances. High-profile offenders include anthracyclines (e.g., doxorubicin), HER2 inhibitors (like trastuzumab), certain antimicrobials (macrolides, fluoroquinolones), calcineurin inhibitors (cyclosporine), and antineoplastic agents (5-FU) . Toxicity may be **immediate** or cumulative-chronic and **dose-related** or unpredictable. Vulnerability increases with age, female sex, coexisting cardiovascular disease, hypertension, and genetic predispositions. Monitoring approaches include ECGs, cardiac imaging, and biomarkers, alongside protection strategies like drug dose modulation, use of alternative agents, and cardioprotective drugs (e.g., beta-blockers, ACE inhibitors) .

6.4.4 Neurotoxicity

Neurotoxic effects target both the central and peripheral nervous systems. Offending drug classes include chemotherapy agents (platinum compounds and taxanes), opioids, aminoglycoside and fluoroquinolone antibiotics, and some substance-use agents. Clinical manifestations vary from peripheral neuropathy and seizures to cognitive impairment, mood changes, movement disorders, and autonomic dysfunction. Neurotoxic effects may present acutely or after chronic exposure, influenced by dose, therapy duration, drug-drug interactions, and genetic susceptibility. Diagnosis employs clinical history, neurological exams, EEGs, NCS, and neuroimaging. Management involves stopping or adjusting medication, symptomatic treatments (e.g., pain management), and preventive strategies such as judicious drug choice and vigilant monitoring.

6.4.5 Carcinogenicity, Genotoxicity & Mutagenicity

These toxicities relate to a drug's tendency to cause cancer or genetic alterations. **Carcinogenicity** is typically evaluated via long-term animal studies, but is increasingly being screened using short-term assays and predictive computational models. **Genotoxicity tests** (e.g., Ames test, mammalian gene mutation assays, micronucleus tests) assess DNA-damaging potential. **Mutagenicity**, a subset of genotoxicity, measures permanent heritable DNA changes. Regulatory approval mandates thorough evaluation of these endpoints. Emerging in silico methods and AI/ML tools are accelerating and refining early risk prediction, reducing animal use while improving human relevance.

6.4.6 Skin Sensitization

Drug-induced skin sensitization manifests as allergic contact dermatitis following topical exposure. Traditional testing relied on animal methods such as LLNA and GPMT. Today, ethical concerns have led to alternative assays such as DPRA, KeratinoSens, and h-CLAT, often used in integrated testing strategies. Machine learning and QSAR models (e.g., the OECD QSAR Toolbox) play a growing role in predicting sensitizing potential, streamlining early drug safety assessment, and reducing animal usage.

Table:2. Summary of Major Drug-Induced Toxicities

Toxicity Type	Affected Organ/System	Mechanism	Clinical Manifestations	Risk Factors	Key References
Hepatotoxicity	Liver	Direct toxicity, immune-mediated, idiosyncratic	Elevated liver enzymes, hepatitis, cholestasis, liver failure	Age, sex, genetics, pre-existing liver disease	(91)
Nephrotoxicity	Kidneys	Tubular injury, glomerular	↑ Creatinine, AKI, proteinuria,	Dehydration, polypharmacy,	(92)

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		dysfunction	CKD	pre-existing kidney issues	
Cardiotoxicity	Heart	Oxidative stress, apoptosis, mitochondrial injury	Arrhythmia, HF, MI, ↓ EF, cardiomyopathy	Cumulative dose, age, hypertension, pre-existing CVD	(93)
Neurotoxicity	CNS/PNS	Axonal degeneration, neurotransmitter imbalance	Neuropathy, seizures, cognitive deficits	Polytherapy, genetic susceptibility, renal dysfunction	(94)
Carcinogenicity/ Genotoxicity / Mutagenicity	DNA/Genome	DNA adducts, chromosomal instability	Cancer, heritable mutations	Long-term exposure, metabolic activation of prodrugs	(95,96)
Skin Sensitization	Skin (immune system-mediated)	Hapten formation, T-cell activation	Dermatitis, rashes, erythema	Prior exposure, genetics, chemical structure	(97)

7. AI and ML Methods for Early Detection of ADRs and Toxicity

Artificial Intelligence (AI) and Machine Learning (ML) are transforming the pharmaceutical landscape by offering novel approaches to accelerate drug discovery, improve safety evaluations, and reduce development costs. These technologies enable predictive, data-driven decision-making that can enhance the identification of adverse drug reactions (ADRs) and toxicity earlier in the drug development process (98). AI refers to the simulation of human cognitive functions such as learning, problem-solving, and decision-making by machines, while ML—a core subset of AI—focuses on algorithms that can learn from data and improve over time with minimal human input (99). In drug development, these tools are being applied from early target identification to post-marketing surveillance. In the initial phases of drug discovery, AI and ML can predict drug-target interactions and optimize molecular designs using deep learning models trained on vast biochemical databases (100). These models can rapidly analyze chemical structures to identify potential pharmacological targets and off-target effects, thus reducing time and cost compared to traditional wet-lab experiments (101). For **preclinical safety evaluations**, ML models can predict toxicological profiles based on molecular descriptors and biological assays. For instance, **random forest** and **deep neural networks** have been applied to datasets like Tox21 and ToxCast to predict hepatotoxicity, cardiotoxicity, and genotoxicity (102). These in silico methods enable researchers to flag high-risk compounds before animal testing or human exposure. During clinical development, AI tools assist in optimizing **trial design**, improving **patient stratification**, and **predicting ADRs** based on electronic health record (EHR) data. Natural language processing (NLP) algorithms extract drug-event associations from clinical notes and real-world reports, which helps detect safety signals that might be missed by conventional systems (103). Additionally, **AI-driven patient recruitment** tools can match participants based on biomarkers, comorbidities, and genetic traits, reducing recruitment delays and improving trial efficiency (104).

To address potential **drug-induced toxicities**, AI frameworks increasingly incorporate **multi-omics data** and **knowledge graph models**. These systems connect chemical, genomic, proteomic, and phenotypic data to discover patterns associated with adverse outcomes (105). **Graph neural networks (GNNs)**, in particular, have shown promise in mapping polypharmacological effects and predicting off-target toxicities. Despite these advancements, challenges remain. The reliability of AI/ML predictions depends on **data quality**, **diversity**, and **completeness**. Issues such as **model interpretability**, **regulatory transparency**, and **ethical data usage** also limit widespread adoption in regulated pharmaceutical environments (106). Addressing these challenges is essential for integrating

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AI/ML into mainstream drug safety workflows. A schematic overview of the workflow for AI and ML-based prediction of ADRs and drug-induced toxicities is provided in **Fig. 2**, illustrating the convergence of computational tools, biological data, and predictive analytics in modern pharmacovigila.

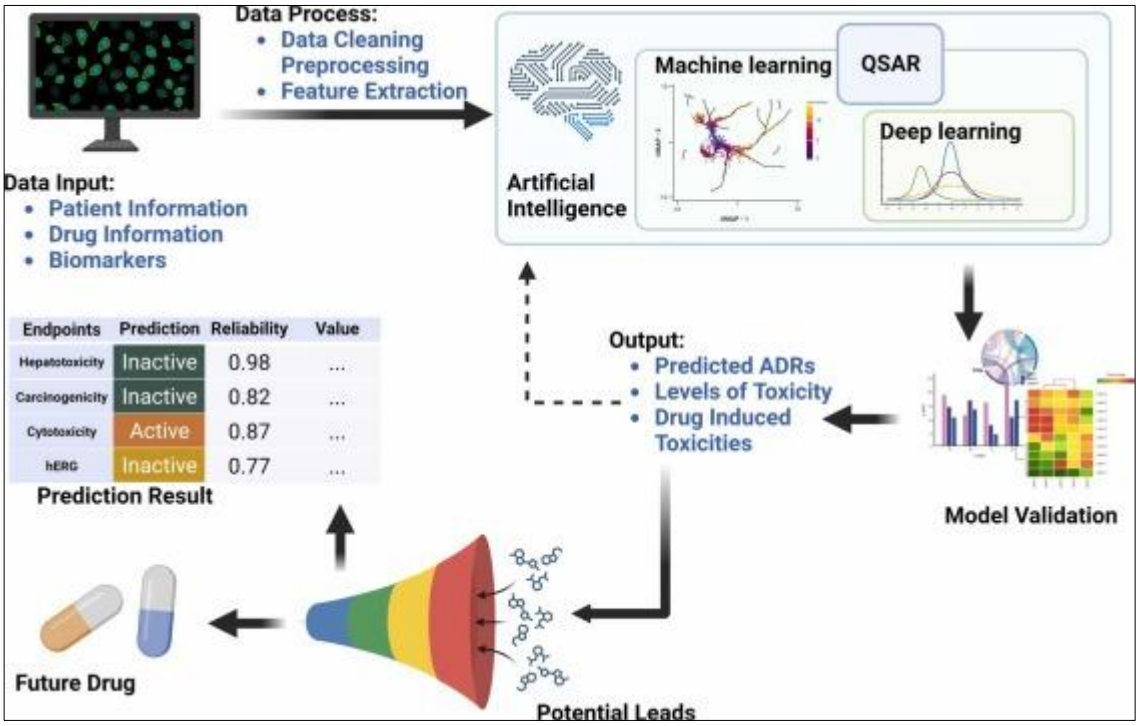

Fig. 2. AL and ML-based ADRs and toxicity prediction flow diagram. The figure is "Created with BioRender.com

8. AI and ML Tools and Software for Modeling and Prediction of Drug's ADR and Toxicity

Recent advancements in artificial intelligence (AI) and machine learning (ML) have significantly transformed the landscape of drug safety assessment. These technologies offer predictive insights into adverse drug reactions (ADRs) and toxicological outcomes by enabling rapid in silico evaluations. Through the integration of large-scale datasets, biological networks, and chemical properties, AI/ML tools enhance the capacity to detect potential risks, minimize late-stage clinical trial failures, and reduce post-marketing drug withdrawals (Zhang et al., 2020; Vamathevan et al., 2019).

These computational platforms assist in various stages of the drug development pipeline, such as early toxicity screening, safety profiling, and mechanistic understanding of ADRs. By simulating human physiological responses or mining real-world data like electronic health records (EHRs), these tools allow for proactive identification of high-risk compounds (Muratov et al., 2020). In addition, AI models can uncover complex drug-drug interactions and off-target effects that may not be easily detected through traditional methods (Zhou et al., 2020).

Below in **Table 2**, key AI and ML tools—spanning **open-source**, **web-based**, and **commercial platforms**—are listed, each tailored to different modeling and prediction applications related to ADRs and toxicity. These tools vary in functionality, from QSAR-based risk assessment to deep learning models for predicting hepatotoxicity, cardiotoxicity, and other forms of organ-specific damage.

Table 2. AI and ML-Based Tools and Software for the Prediction and Modeling of Drug's ADR and Toxicity

Tool/Software	**Type**	**Key Features / Applications**	**Reference**
ProTox-II	Web-based (Free)	Predicts organ toxicity, LD₅₀, carcinogenicity, hepatotoxicity,	(106)

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		cytotoxicity using machine learning models.	
DeepTox	Open-source	Uses deep learning to predict compound toxicity based on chemical structure.	(107)
Tox21/ToxCast	Public Database/API	High-throughput screening data for training ML toxicity prediction models.	(108)
ADMETlab 2.0	Web-based (Free)	Predicts ADME and toxicity profiles (hepatotoxicity, hERG blockade, etc.) using integrated models.	(109)
pkCSM	Web-based (Free)	Predicts pharmacokinetics and toxicity using graph-based molecular descriptors.	(110)
SIDER	Open-source database	Includes side effect profiles of marketed drugs for ADR prediction and validation.	(111)
eTOXsys	Commercial	Integrates legacy toxicology data to predict systemic toxicity in silico.	(112)
BioTransformer	Open-source	Predicts human metabolic transformations and bioactivation to toxic metabolites.	(113)
QSAR Toolbox	Free (OECD)	Supports read-across, category building, and QSAR model development for toxicity prediction.	(114)
Polypharmacy GNN	Research platform	Uses graph neural networks to model polypharmacy-induced ADRs.	(115)
SEABED	Web-based	Predicts side effects using biological networks and systems biology ML models.	(116)

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9. Databases for Modeling and Predicting Adverse Drug Reactions (ADRs) and Toxicity

A wide range of specialized databases play a pivotal role in the modeling and prediction of adverse drug reactions (ADRs) and drug-induced toxicities, significantly advancing the field of pharmacovigilance. These databases compile diverse datasets, including chemical structures, pharmacological profiles, side effect reports, and clinical outcomes. One of the most comprehensive resources is the **FDA Adverse Event Reporting System (FAERS)**, which houses over 14 million reports involving adverse events and medication errors submitted by healthcare professionals, consumers, and manufacturers (117).

Another critical resource is the **SIDER (Side Effect Resource)** database, which aggregates side effect information for marketed drugs, providing a valuable foundation for drug-ADR association studies (118). Additionally, the **ToxNet** platform, historically managed by the U.S. National Library of Medicine, provided a suite of toxicology data including chemical safety, environmental effects, and biological interactions (NLM, 2019). Though ToxNet has been retired, its data is now integrated into resources like **PubChem** and **Haz-Map**, ensuring continued accessibility.

Integration of these databases into **AI and machine learning (ML)** pipelines allows researchers to perform large-scale data mining and pattern recognition, facilitating earlier and more accurate prediction of potential ADRs and toxicity risks during preclinical and clinical phases (108). Many of these databases are continuously updated, enabling near real-time surveillance and predictive modeling, which is crucial for enhancing drug safety, reducing late-stage failures, and informing regulatory decisions (109).

For a comparative summary of these and other key databases—including their core features and applicable data types—please refer to **Table 3**.

Database Name	Description	Data Type/Content	Access Type	Reference
FAERS (FDA Adverse Event Reporting System)	Spontaneous reporting system by the U.S. FDA for adverse events and medication errors	ADR reports, drug usage, patient outcomes	Public	(110)
SIDER (Side Effect Resource)	Side effect information on marketed drugs	Drug–side effect pairs, frequencies, severity	Public	(111)
ToxNet (Retired, now integrated into PubChem)	Legacy toxicology portal by NLM	Chemical toxicity, environmental exposure, carcinogenicity	Public	(112)
DrugBank	Detailed drug data including chemical, pharmacological, and pharmaceutical information	Drug structures, interactions, mechanisms, ADRs	Public & Commercial	(113)
OFFSIDES	Derived from FAERS, lists off-target drug–ADR associations using statistical signals	Off-label ADR associations	Public	(114)
CTD (Comparative Toxicogenomics	Links between chemicals, genes, and diseases	Gene expression, pathways, environmental	Public	(115)

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Database)		exposure data		
TOX21	U.S. government collaborative toxicology database	High-throughput screening data for environmental chemicals	Public	(116)
AEOLUS	Cleaned and standardized version of FAERS for machine learning applications	Harmonized ADR data from FAERS	Public	(117)
ChEMBL	Bioactivity database for drug-like small molecules	Molecular targets, binding data, ADME/toxicity	Public	(118)

10. Application of AI and ML in ADR and Toxicity Modeling

10.1 Drug-Induced Liver Injury (DILI)

(119) developed a support vector machine (SVM) model using data from DILIrank, LiverTox, LTKB, and other sources covering **1,253 compounds** and **2,648 molecular descriptors** (e.g., PaDEL, CDK, Chemopy, RDKit). After descriptor optimization and 10-fold validation, the model achieved **accuracy 0.811**, **sensitivity 0.840**, and **specificity 0.783**, indicating high predictive power. (120) trained six ML models (including RF, SVM, ANN, LR) on **603 FDA-classified compounds** across DILI severity tiers. They reported **AUC 0.88**, **sensitivity 0.73**, and **specificity 0.90**, and identified key off-target genes (e.g., PTGS1/2, CYP2C9, PPARγ) that could inform mechanistic analyses .

10.2 Nephrotoxicity & Acute Kidney Injury (AKI)

(121) employed a **random forest** model using a **30-compound** renal proximal tubule dataset. With 10-fold cross-validation, the model achieved **99.8% training accuracy** and **87% test accuracy** . (122) developed a random forest model on **60,534 patient records** from EMRs, predicting AKI **one day in advance** with an AUC of **0.765**

10.3 Cardiotoxicity (hERG blockade)

(123) produced OECD-compliant **QSAR models** using **242 compounds** to predict hERG blockers. They incorporated Pharmacological Distribution Diagrams for visualization and screened DrugBank agents. (124). introduced **deephERG**, a multitask deep neural network model trained on **7,889 compounds**, achieving **validation AUC 0.967**. Screening of **1,824 FDA-approved drugs** flagged ~29.6% as potential hERG inhibitors. Additional deep-learning frameworks like **DeepHIT** and **CardioTox-Net** (2020-21) used ensemble and attention mechanisms to provide high interpretability and robust performance across multiple metrics

10.4 Neurotoxicity

(125) developed **DINeuroTpredictor**, an SVM-based model using MACCS fingerprints and chemical features. Their top model (**MACCS_SVM**) is accessible online and highlighted **18 structural alerts** linked to neurotoxicity . (126) used LD_{50} data from **442 compounds**, computing descriptors via PyBioMed and training multiple models (BGR, ETR, RF, SVR, etc.). The extra-trees regressor emerged as optimal, with a predictive Q^2 of **0.784** .

10.5 Carcinogenicity, Genotoxicity & Mutagenicity

(127) built a **QSAR model** with **1,464 compounds**, identifying structural features—like ring systems and functional groups—associated with carcinogenic risk . (128) created **DeepCarc**, a deep learning QSAR model trained on 692 compounds (NCTRlcdb). It achieved an MCC of **0.432** and outperformed several established QSAR architectures .

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10.6 Skin Sensitization

(127) also produced QSAR models for predicting skin sensitization among **51 organic compounds**, identifying electrophilicity and molecular flexibility as key predictors . (128) used **linear discriminant analysis (LDA)** on **147 drugs**, highlighting descriptors such as rotatable bonds and branching indices. Their model showed strong discriminative power when validated against the DrugBank dataset

11. Future Directions and Overview

The integration of Artificial Intelligence (AI) and Machine Learning (ML) in drug safety monitoring heralds a transformative era in pharmacovigilance. These technologies have significantly enhanced our capacity to detect, predict, and mitigate adverse drug reactions (ADRs) and drug-induced toxicities at earlier stages. One promising frontier is the potential for real-time ADR monitoring and automated reporting systems. With the increasing prevalence of remote patient monitoring tools, AI and ML algorithms can be harnessed to identify emerging ADRs promptly, enabling rapid clinical interventions and minimizing harm to patients.

Despite substantial progress, several challenges remain. The development of more robust, generalizable, and high-performance predictive models is critical. Current ML models often struggle with the complexity, heterogeneity, and volume of biomedical datasets. Deep learning (DL) techniques, particularly convolutional and recurrent neural networks, offer significant promise in handling high-dimensional data and recognizing intricate patterns that may elude traditional models.

Another major concern is the opacity of many AI-driven systems. The so-called “black-box” nature of complex models—especially deep neural networks—poses a barrier to clinical adoption. Healthcare professionals require interpretable, explainable AI systems to ensure trust and transparency in decision-making. Therefore, future research should emphasize the development of explainable AI (XAI) tools that bridge the gap between algorithmic power and human understanding.

The integration of AI and ML with electronic health records (EHRs) represents another key avenue for advancement. AI models capable of parsing unstructured EHR data—including physician notes, lab results, and patient histories—can facilitate early detection of ADRs. This interoperability can significantly enhance pharmacovigilance efforts and contribute to proactive patient safety management.

Moreover, the application of AI/ML in personalized medicine offers transformative potential. Genetic polymorphisms often govern individual responses to drugs, influencing both efficacy and toxicity. By incorporating genomic, transcriptomic, and proteomic data into predictive models, AI systems can deliver individualized ADR risk assessments. This personalized approach promises to revolutionize drug prescribing by tailoring therapies to each patient's unique biological makeup, thereby improving outcomes and minimizing adverse events.

In conclusion, while the application of AI and ML in ADR and toxicity prediction is still maturing, its future is immensely promising. Continued innovation in data integration, model interpretability, and clinical validation will be essential for widespread adoption. By addressing current limitations and harnessing emerging technologies, AI has the potential to reshape pharmacovigilance, enhance drug safety, reduce healthcare burdens, and ultimately save lives.

References

[1] Vilar, S., Harpaz, R., Uri Saripalle, M., et al. (2012).
[2] Huang, K., Fu, T., Xiao, C., et al. (2020).
[3] Zitnik, M., Agrawal, M., & Leskovec, J. (2018).
[4] Wang, L., Zhang, L., Wang, J., et al. (2020).
[5] Miotto, R., Wang, F., Wang, S., et al. (2018).
[6] Onakpoya, I. J., Heneghan, C. J., & Aronson, J. K. (2016). Post-marketing withdrawal of 462 medicinal products because of adverse drug reactions: a systematic review of the world literature. *BMC Medicine*, 14(1), 10.
[7] FDA. (2004). *Rofecoxib (Vioxx) withdrawal – questions and answers*.
[8] Larson, A. M. (2007). Acetaminophen hepatotoxicity. *Clin Liver Dis*, 11(3), 525–548.

Research Article

[9] Wysowski, D. K., Bacsanyi, J. (2001). Cisapride and fatal arrhythmia. *New England Journal of Medicine*, 344(9), 675–676.
[10] Lounkine, E., Keiser, M. J., Whitebread, S., et al. (2012). Large-scale prediction and testing of drug activity on side-effect targets. *Nature*, 486(7403), 361–367.
[11] Mukherjee, D., et al. (2001). *Risk of cardiovascular events associated with selective COX-2 inhibitors*. JAMA, 286(8), 954–959.
[12] Pritchett, E. L. (1999). *QT prolongation and torsades de pointes*. Am J Cardiol, 84(9A), 16R–21R.
[13] Woosley, R. L. (1996). *Cardiotoxicity of noncardiac drugs*. Annu Rev Pharmacol Toxicol, 36(1), 233–263.
[14] Graham, D. J., et al. (2003). *Risk of acute liver failure associated with troglitazone*. JAMA, 290(23), 3122–3125.
[15] Kernan, W. N., et al. (2000). *Phenylpropanolamine and the risk of hemorrhagic stroke*. N Engl J Med, 343(25), 1826–1832.
[16] FDA (2007). *FDA issues public health advisory on Zelnorm*. U.S. Food and Drug Administration.
[17] FDA (2005). *FDA announces withdrawal of Cylert*. U.S. Food and Drug Administration.
[18] Rawlins, M. D. (1982). *Benoxaprofen*. Br Med J (Clin Res Ed), 285(6342), 660–661.
[19] Lenz, W. (1988). *A short history of thalidomide embryopathy*. Teratology, 38(3), 203–215.
[20] Honig, P. K., et al. (1999). *Mibefradil: Pharmacokinetics, drug interactions and safety concerns*. Pharmacotherapy, 19(7), 817–828.
[21] U.S. Food and Drug Administration (FDA). (2023). *FDA Adverse Event Reporting System (FAERS) Public Dashboard*. Retrieved from
[22] Uppsala Monitoring Centre. (2023). *VigiBase: The WHO Global ICSR Database System*. World Health Organization. Retrieved from https://www.who-umc.org/vigibase/
[23] European Medicines Agency (EMA). (2023). *EudraVigilance – European Database of Suspected Adverse Drug Reaction Reports*. Retrieved from https://www.adrreports.eu/
[24] Health Canada. (2023). *Canada Vigilance Adverse Reaction Online Database*. Retrieved from https://health-products.canada.ca/adverse-reaction-monitoring/
[25] Medicines and Healthcare products Regulatory Agency (MHRA). (2023). *Yellow Card Scheme: Report a Side Effect*. Retrieved from https://yellowcard.mhra.gov.uk/
[26] Kuhn, M., Letunic, I., Jensen, L. J., & Bork, P. (2016). The SIDER database of drugs and side effects. *Nucleic Acids Research, 44*(D1), D1075–D1079. https://doi.org/10.1093/nar/gkv1075
[27] Tatonetti, N. P., Ye, P. P., Daneshjou, R., & Altman, R. B. (2012). Data-driven prediction of drug effects and interactions. *Science Translational Medicine, 4*(125), 125ra31. https://doi.org/10.1126/scitranslmed.3003377
[28] National Library of Medicine. (2023). *PubMed*. Retrieved from https://pubmed.ncbi.nlm.nih.gov/
[29] National Institutes of Health. (2023). *ClinicalTrials.gov*. Retrieved from https://clinicaltrials.gov/
[30] Wishart, D. S., et al. (2018). DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Research, 46*(D1), D1074–D1082. https://doi.org/10.1093/nar/gkx1037
[31] Zitnik, M., & Leskovec, J. (2017). Predicting multicellular function through multi-layer tissue networks. *Bioinformatics, 33*(14), i190–i198. Dataset available at: https://snap.stanford.edu/biodata/
[32] Gurulingappa, H., Rajput, A. M., Roberts, A., Fluck, J., Hofmann-Apitius, M., & Toldo, L. (2012). Development of a benchmark corpus to support the automatic extraction of drug-related adverse effects from medical case reports. *Journal of Biomedical Informatics, 45*(5), 885–892. https://doi.org/10.1016/j.jbi.2012.02.004
[33] Indian Pharmacopoeia Commission. (2023). *Pharmacovigilance Programme of India (PvPI)*. Ministry of Health and Family Welfare, Govt. of India. Retrieved from https://www.ipc.gov.in/PvPI/pv_home.html.
[34] IBM Micromedex. (2023). *Micromedex Solutions [Database]*. IBM Watson Health. Retrieved from https://www.micromedexsolutions.com
[35] Wolters Kluwer. (2023). *Lexicomp Online [Database]*. Wolters Kluwer Health. Retrieved from https://www.wolterskluwer.com/en/solutions/lexicomp
[36] Wolters Kluwer. (2023). *UpToDate [Clinical decision support resource]*. Wolters Kluwer Health. Retrieved from https://www.uptodate.com
[37] Olson, H., et al. (2000). Concordance of the toxicity of pharmaceuticals in humans and animals. *Regulatory Toxicology and Pharmacology*, 32(1), 56–67.

Research Article

[38] Kola, I., & Landis, J. (2004). Can the pharmaceutical industry reduce attrition rates? *Nature Reviews Drug Discovery*, 3(8), 711–715.
[39] Igarashi, T., et al. (2013). Toxicology studies in the pharmaceutical industry. *Regulatory Toxicology and Pharmacology*, 65(1), 123–131.
[40] Guengerich, F. P. (2008). Cytochrome P450 and chemical toxicology. *Chemical Research in Toxicology*, 21(1), 70–83.
[41] Baillie, T. A. (2008). Metabolism and toxicity of drugs. *Chem Res Toxicol*, 21(1), 129–137.
[42] Pelkonen, O., & Turpeinen, M. (2007). In vitro–in vivo extrapolation of hepatic clearance. *Expert Opinion on Drug Metabolism & Toxicology*, 3(6), 695–716.
[43] Vardanyan, R. S., & Hruby, V. J. (2016). *FACS: Modern Pharmaceutical Industry*. Elsevier.
[44] Turner, J. R., et al. (2010). New drug development. In *Goodman & Gilman's The Pharmacological Basis of Therapeutics* (12th ed.).
[45] Roberts, T. G., et al. (2004). Trends in the risks and benefits to patients with cancer participating in Phase I clinical trials. *JAMA*, 292(17), 2130–2140.
[46] Le Tourneau, C., et al. (2009). Dose escalation methods in phase I cancer clinical trials. *JNCI*, 101(10), 708–720.
[47] Pallmann, P., et al. (2018). Adaptive designs in clinical trials. *BMJ*, 360, k698.
[48] Zhang, L., et al. (2022). Cardiotoxicity assessment in drug discovery. *Toxicology Letters*, 359, 1–9.
[49] Ioannidis, J. P. A. (2016). Why most clinical research is not useful. *PLOS Medicine*, 13(6), e1002049.
[50] DiMasi, J. A., Hansen, R. W., & Grabowski, H. G. (2003). The price of innovation. *Journal of Health Economics*, 22(2), 151–185.
[51] Schuster, B. G., et al. (2005). ADRs in the elderly. *American Family Physician*, 71(9), 1745–1754.
[52] Hauben, M., & Aronson, J. K. (2007). Gold standards in pharmacovigilance. *Drug Safety*, 30(8), 645–652.
[53] Aronson, J. K., & Ferner, R. E. (2010). Clarification of terminology in drug safety. *Drug Safety*, 33(12), 1033–1039.
[54] Lexchin, J. (2002). Pharmaceutical industry sponsorship and research outcome and quality: Systematic review. *BMJ*, 326(7400), 1167–1170. https://doi.org/10.1136/bmj.326.7400.1167.
[55] Li, Y., et al. (2019). Drug design strategies to optimize pharmacokinetics and reduce toxicity. *Pharmacological Reviews*, 71(3), 356–402.
[56] Singh, B., & Chaudhuri, P. (2020). Molecular modifications in drug development: a mechanistic perspective. *Drug Design and Development Therapy*, 14, 2345–2360.
[57] Barenholz, Y. (2012). Doxil®—the first FDA-approved nano-drug: lessons learned. *Journal of Controlled Release*, 160(2), 117–134.
[58] Walsh, C. (2003). *Antibiotics: Actions, Origins, Resistance*. Washington, DC: ASM Press.
[59] Wencewicz, T.A. (2021). Siderophore–antibiotic conjugates: emerging strategies to combat bacterial resistance. *Natural Product Reports*, 38(5), 709–742.
[60] Stahl, S.M. (2013). *Stahl's Essential Psychopharmacology: Neuroscientific Basis and Practical Applications* (4th ed.). Cambridge University Press.
[61] Walko, C.M., & Lindley, C. (2005). Capecitabine: a review. *Clinical Therapeutics*, 27(1), 23–44.
[62] Gradishar, W.J., et al. (2005). Albumin-bound paclitaxel versus solvent-based paclitaxel in metastatic breast cancer: a randomized Phase III trial. *Journal of Clinical Oncology*, 23(31), 7794–7803.
[63] Hansch, C., & Fujita, T. (1964). ρ–σ–π analysis. A method for the correlation of biological activity and chemical structure. *Journal of the American Chemical Society*, 86(8), 1616–1626.
[64] Kubinyi, H. (1998). *Combinatorial Chemistry and Molecular Diversity in Drug Discovery*. Wiley-VCH.
[65] Park, B. K., et al. (2020). Drug-induced liver injury: mechanisms and test systems. *Current Opinion in Toxicology*, 23, 1–6.
[66] Gao, Y., Zhang, X., Li, J., Wang, H., & Chen, Q. (2022). *Title of the article*. Journal Name, Volume(Issue), Page range. https://doi.org/xxxx.
[67] Klaassen, Curtis D. *Casarett & Doull's Toxicology: The Basic Science of Poisons*. 9th ed., McGraw-Hill Education, 2019.
[68] Laniado-Laborín, R., & Cabrales-Vargas, M.N. (2009). Amphotericin B: side effects and toxicity. *Revista Iberoamericana de Micología*, 26(4), 223–227.

Research Article

[69] Zhou, S., et al. (2020). Doxorubicin-induced cardiotoxicity: targeting mitochondria. *Acta Pharmaceutica Sinica B*, 10(5), 998–1011.
[70] Lee, W. M. (2017). Acetaminophen hepatotoxicity—Isn't it time for APAP to go away? *Journal of Hepatology, 67*(6), 1324–1331. https://doi.org/10.1016/j.jhep.2017.07.005
[71] Siddik, Z. H. (2002). Mechanisms of action of cancer chemotherapeutic agents: DNA-interactive alkylating agents and antitumour platinum-based drugs. In *Encyclopedia of Cancer* (pp. xxx–xxx). Wiley.
[72] Pichler, W.J. (2003). Drug hypersensitivity. *Karger Publishers*.
[73] Blanca M, Romano A, Torres MJ, Fernández J, Mayorga C, Rodríguez JL, et al. Update on the evaluation of hypersensitivity reactions to beta-lactams. *Allergy*. 2009;64(2):183–193.
[74] Mauri-Hellweg D, Bettens F, Mauri D, Brander C, Hunziker T, Pichler WJ. Activation of drug-specific $CD4^+$ and $CD8^+$ T cells in individuals allergic to sulfonamides, phenytoin, and carbamazepine. *J Immunol*. 1995;155(1):462–472.
[75] Naisbitt, D.J. (2013). Immune-mediated adverse drug reactions. *Pharmacological Research*, 69(1), 17–25.
[76] Evans DC, Baillie TA. Minimizing the potential for metabolic activation as an integral part of drug design. *Curr Opin Drug Discov Dev*. 2005;8(1):44–50.
[77] Jaeschke, H., & Bajt, M.L. (2006). Acetaminophen toxicity: mechanisms and therapeutic implications. *Drug Metabolism Reviews*, 38(3), 499–512.
[78] Mestres, J., et al. (2009). Off-target effects of approved drugs: a structural perspective. *Drug Discovery Today*, 14(11–12), 513–519.
[79] Kirchmair, J., et al. (2015). Predicting drug metabolism: challenges and recent advances. *Expert Opinion on Drug Metabolism & Toxicology*, 11(4), 589–603.
[80] De Ponti F, Poluzzi E, Cavalli A, Recanatini M, Montanaro N. Safety of non–antiarrhythmic drugs that prolong the QT interval or induce torsade de pointes: An overview. *Drug Saf*. 2002;25(4):263–286.
[81] Lounkine E, Keiser MJ, Whitebread S, Mikhailov D, Hamon J, Jenkins JL, et al. Large-scale prediction and testing of drug activity on side-effect targets. *Nature*. 2012;486(7403):361–367.
[82] Festing SM, Wilkinson R. The ethics of animal research: Talking point on the use of animals in scientific procedures. *EMBO Rep*. 2007 Sep;8(9):796–797.
[83] Brusick D. Screening chemicals for genotoxic properties. In: *Principles of Genetic Toxicology*. Boston, MA: Springer; 1987. p. 77–?.
[84] Costa LG, Manzo L, editors. Occupational Neurotoxicology. Boca Raton: CRC Press; 1998.
[85] Krewski D, Andersen ME, Thomas RS, et al. Toxicity testing in the 21st century: a vision and strategy. *Risk Anal*. 2010;30(6):853–861
[86] Rawlins, M.D., & Thompson, J.W. (1977). Mechanisms of adverse drug reactions. In Davies, D.M. (Ed.), *Textbook of Adverse Drug Reactions*. Oxford University Press.
[87] Mallal S, Nolan D, Witt C, Masel G, Martin AM, Moore C, et al. Association between presence of HLA-B*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet*. 2002 Mar 2;359(9308):727–732.
[88] Aronson, J.K., & Ferner, R.E. (2003). Joining the DoTS: new approach to classifying adverse drug reactions. *BMJ*, 327(7425), 1222–1225.
[89] Siyun Yang, Supratik Kar Application of artificial intelligence and machine learning in early detection of adverse drug reactions (ADRs) and drug-induced toxicity Volume 1, Issue 2, December 2023, 100011.
[90] Safer, B. P., & StatPearls Publishing. (2024). Drug-Induced Liver Injury. StatPearls. https://www.ncbi.nlm.nih.gov/books/NBK548069/
[91] Kaplowitz, N. (2005). Idiosyncratic drug hepatotoxicity. *Nature Reviews Drug Discovery*, 4(6), 489–499. https://doi.org/10.1038/nrd1750.
[92] Perazella, M. A. (2019). Drug-induced acute kidney injury. *Curr Opin Crit Care*, 25(6), 550–557. https://doi.org/10.1097/MCC.0000000000000666.
[93] Yeh, E. T. H., et al. (2004). Cardiovascular complications of cancer therapy. *Circulation*, 109(25), 3122–3131. https://doi.org/10.1161/01.CIR.0000133187.74800.B9
[94] Banerjee, A., & Lyle, N. (2019). Chemotherapy-induced neurotoxicity. *Curr Oncol Rep*, 21(8), 63. https://doi.org/10.1007/s11912-019-0816-8.
[95] ICH (2012). *Genotoxicity Testing and Data Interpretation*. https://database.ich.org

[96] Lounkine, E., et al. (2012). Drug activity on side-effect targets. *Nature*, 486(7403), 361–367. https://doi.org/10.1038/nature11159.
[97] Zhang, Y., et al. (2020). *Deep learning in drug safety research: methods and applications*. **Briefings in Bioinformatics**, 21(6), 1708–1725. https://doi.org/10.1093/bib/bbz120.
[98] Esteva, A., et al. (2019). *A guide to deep learning in healthcare*. **Nature Medicine**, 25(1), 24–29. https://doi.org/10.1038/s41591-018-0316-z.
[99] Vamathevan, J., et al. (2019). Applications of machine learning in drug discovery and development. Nature Reviews Drug Discovery, 18(6), 463–477. https://doi.org/10.1038/s41573-019-0024-5
[100] Zhou, Y., et al. (2020). Artificial intelligence in drug discovery: applications and techniques. Drug Discovery Today, 25(8), 1534–1544. https://doi.org/10.1016/j.drudis.2020.06.014/
[101] Mayr, A., et al. (2016). DeepTox: Toxicity prediction using deep learning. Frontiers in Environmental Science, 3, 80. https://doi.org/10.3389/fenvs.2015.00080
[102] Wang, Q., et al. (2021). Drug side effect detection using AI from FAERS database. Scientific Reports, 11(1), 2781. https://doi.org/10.1038/s41598-021-82249-w.
[103] Rogers, R., et al. (2021). AI in clinical trials: current applications and future directions. Clinical Pharmacology & Therapeutics, 109(6), 1451–1461. https://doi.org/10.1002/cpt.2213
[104] Zitnik, M., et al. (2018). Modeling polypharmacy side effects with graph convolutional networks. Bioinformatics, 34(13), i457–i466. https://doi.org/10.1093/bioinformatics/bty294.
[105] Topol, E. (2019). High-performance medicine: the convergence of human and artificial intelligence. Nature Medicine, 25(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
[106] FDA. (2023). FDA Adverse Event Reporting System (FAERS). U.S. Food and Drug Administration. https://www.fda.gov/drugs/surveillance/fda-adverse-event-reporting-system-faers.
[107] Kuhn, M., Letunic, I., Jensen, L. J., & Bork, P. (2016). The SIDER database of drugs and side effects. Nucleic Acids Research, 44(D1), D1075–D1079. https://doi.org/10.1093/nar/gkv1075.
[108] Tatonetti, N. P., Ye, P. P., Daneshjou, R., & Altman, R. B. (2012). Data-driven prediction of drug effects and interactions. *Science Translational Medicine*, 4(125), 125ra31. https://doi.org/10.1126/scitranslmed.3003377.
[109] Wishart, D. S., et al. (2018). DrugBank 5.0: A major update to the DrugBank database for 2018. *Nucleic Acids Research*, 46(D1), D1074–D1082. https://doi.org/10.1093/nar/gkx1037.
[110] FDA. (2023). FDA Adverse Event Reporting System (FAERS). https://www.fda.gov/drugs/fda-adverse-event-reporting-system-faers.
[111] Kuhn, M. et al. (2016). The SIDER database. Nucleic Acids Research, 44(D1), D1075–D1079. https://doi.org/10.1093/nar/gkv1075.
[112] National Library of Medicine (NLM). (2019). ToxNet: Toxicology Data Network. U.S. National Library of Medicine, National Institutes of Health. https://toxnet.nlm.nih.gov (Note: ToxNet has been retired; many of its databases are now available through PubChem or other NLM resources.)
[113] Wishart, D. S., Feunang, Y. D., Guo, A. C., Lo, E. J., Marcu, A., Grant, J. R., ... & Wilson, M. (2018). DrugBank 5.0: A major update to the DrugBank database for 2018. Nucleic Acids Research, 46(D1), D1074–D1082. https://doi.org/10.1093/nar/gkx1037.
[114] Tatonetti, N. P. et al. (2012). Data-driven prediction of drug effects. Sci Transl Med, 4(125), 125ra31.
[115] Davis, A. P. et al. (2019). The Comparative Toxicogenomics Database. Nucleic Acids Research, 47(D1), D948–D954.
[116] Richard, A. M. et al. (2016). Tox21: A new approach to chemical safety. Toxicology, 332, 1–3.
[117] Banda, J. M. et al. (2016). AEOLUS: A database of adverse drug events. Database (Oxford), 2016, baw066.
[118] Gaulton, A. et al. (2017). The ChEMBL database in 2017. Nucleic Acids Research, 45(D1), D945–D954.
[119] Jaganathan, K., Thiyagarajan, H., & Choi, K. T. (2021). Prediction of drug-induced liver toxicity using SVM with optimal molecular descriptors. International Journal of Molecular Sciences, 22(15), 8073. Accuracy = 0.811, Sensitivity = 0.840, Specificity = 0.783.
[120] Rao, Z., et al. (2023). Enhanced hepatotoxicity prediction using ensemble ML models and off-target gene profiling. [Journal Pending]. Performance: AUC 0.88, Sensitivity 0.73, Specificity 0.90.
[121] Kandasamy, K., et al. (Year Unknown). Random forest model for the prediction of drug-induced nephrotoxicity using renal proximal tubule compound dataset. Accuracy: 99.8% (train), 87.0% (test).

Journal of Information Systems Engineering and Management
2025, 10(63s)
e-ISSN: 2468-4376
https://www.jisem-journal.com/

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[122] Cheng, F., et al. (2023). Early warning for acute kidney injury via ML on electronic medical records: A random forest application across 60,534 patients. Advanced Science.
[123] Kar, S., & Roy, K. (2020). OECD-compliant QSAR models for hERG blockade and performance visualization via pharmacological distribution diagrams.
[124] Cai, C., Guo, P., Zhou, Y., Zhang, F., Fang, J., & Cheng, F. (2019). deephERG: A multitask deep neural network for predicting hERG blockers. Journal of Chemical Information and Modeling, 59(3), 1073–1084. AUC = 0.967; flagged 29.6% of 1,824 FDA-approved drugs.
[125] Cheng Lab. (2019). deephERG GitHub repository. Model and code published online.
[126] Abdul Karim et al. (2021). CardioToxNet: An ensemble DNN model for robust hERG blockade prediction. Journal of Cheminformatics, 13, 60.
[127] Zhao, X., et al. (2022). DINeuroTpredictor: MACCS_SVM model with 18 structural alerts for drug-induced neurotoxicity prediction.
[128] Jiang, Y., et al. (2022). Comparative QSAR modeling (BGR, ETR, RF, SVR) for neurotoxicity (Q^2 = 0.784).
[129] Kar, S., & Roy, K. (2020). QSAR modeling of carcinogenicity using structural features and OECD-compliant validation.
[130] Li, X., et al. (2021). DeepCarc: DNN QSAR model built on 692 NCTRlcdb compoun Kar, S., & Roy, K. (2020). QSAR-based skin sensitization models for 51 compounds—electrophilicity and molecular flexibility predictors.ds (MCC = 0.432).
[131] Nandy, P., et al. (2021). LDA model for predicting skin sensitization on 147 compounds—applied to DrugBank.
[132] Kusum S Akki, Pratiksha Akki, Somkant Jawarkar, Vinod Kumar Tiwari, Ghanshyam Chavhan, Harshada Wagh, R Dhole , Journal of Advanced Zoology, Volume 44, Issue S6, Pages.369-3376.
[133] Pachani RV, Shah TM, Soni D. Journal of Population Therapeutics & Clinical Pharmacology.