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Artificial Intelligence in Pharmacology, Drug Safety and Toxicity

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ABSTRACT

Artificial intelligence (AI) is transforming pharmacology, drug safety, and toxicology by accelerating the drug development process to be more efficient, precise, and economical. Conventional drug discovery, pre-clinical testing, and post-marketing surveillance methods frequently encounter high costs, long lead times, ethical constraints, and low predictive validity in human outcomes. Utilizing machine learning (ML) and deep learning (DL), AI combines heterogenous datasets chemical structures, genomics, clinical data, and imaging to bridge these gaps.In drug design and discovery, AI has hastened predictions of protein and RNA structures (e.g., AlphaFold), enhanced virtual screening, and enabled de novo drug design with generative models. It has also hastened peptide-based drug development and improved pharmacokinetic prediction of absorption, distribution, metabolism, excretion, and toxicity (ADMET) and reduced failure rates.

Key boards: Artificial intelligence, Pharmacology, Drug discovery, Compound Pharmacokinetic Prediction, Clinical Pharmacology, Toxicity, Pharmacovigilence, Machine Learning, Deep Learning, Adverse Drug Reactions.

INTRODUCTION

To achieve tremendous success in both theory and practice, advances in computing power, machine learning, and deep learning have been evolving rapidly[1]. Artificial Intelligence is describe as the use of intelligence to solve problems. Pharmacology was first studied in the mid-1900s. Even though techniques like neural networks were then suggested for use in QSAR models[2]. Numerous AI techniques have been applied in research pharmacology, including compound pharmacokinetic prediction, AI-assisted drug discovery, and design which are among the most popular fields.[3]

Medicine safety and toxicology are vital for guaranteeing pharmaceutical products' efficacity and safety. In vivo beast testing is generally used for drug safety assessments and toxicological exploration; still, it can be time-consuming, expensive, and immorally problematic. likewise, these approaches generally fail to precisely predict mortal responses, raising safety enterprises in clinical trials and post-marketing surveillance.[4]

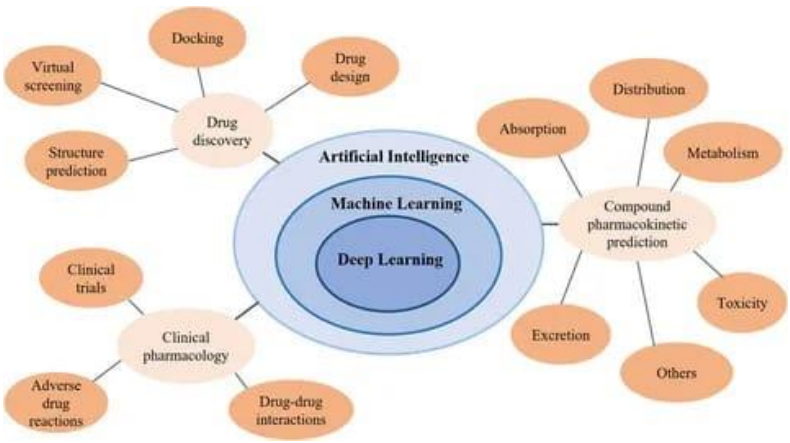

Figure 1 The realationship between artificial intrlligence, machine learning, and deep learning and the applications of artificial intelligence in pharmacology research.

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The latest diagnostic tools, modern devices, accurate data collection techniques, and technologies such as X-ray and abdominal examinations outperform older models[5]. Artificial Intelligence has also expanded its medical services to include animal studies, such as veterinary medicine, focusing on disease prevention and targeted therapies[6].

Drug safety and toxicology involve the thorough investigation of the safety profiles of pharmaceutical products and their potential harmful effects[7]. It includes assessing the risks linked to drug use, identifying adverse reactions, and understanding the mechanisms of toxicity involved. The primary aim of medication safety and toxicology is to protect patients by minimizing harm while maximizing the therapeutic benefits[8]. Traditionally, evaluating drug safety and conducting toxicological studies have heavily depended on in vivo research using animal models to assess the potential risks of medications[9]. These animal models were utilized to anticipate drug effectiveness, pharmacokinetics, and toxicology.

2.AI-assisted drug discovery and design:

Recently, the development and use of AI have faciliated research related to drug discovery and design, as evidenced in three major aspects[10]: 1.Using AI to anticipate protein and RNA strucutures; 2. AI-assisted drug discovery; and 3. AI-based drug design[11].

2.1 Using AI to predict the structure of proteins and RNA

Understanding the 3D structure of proteins and related compounds is essential for medication discovery and design[12]. Physical and chemical experiments can accurately determine the 3D structure of proteins and RNA, but they are time-consuming and costly. Recent research uses computational algorithms to estimate the 3D structure of molecules[13]. Classical 3D structure prediction methods consist of de novo modeling, fragment assembly, and homology modeling, the mechanism of which are based on rule-based computing and splicing but not using AI for 3D structure prediction[14]. Thus, before AlphaFold was innovated, the application of AI in structure prediction focused more on the prediction of features related to primary and second structures rather than very complicated 3D structures.

2.2AI- assissted drug discovery

The GAN technique has been used in medicinal chemistry for molecular de novo design, biochemical research for de novo peptide and protein design, and dimensionality reduction for single-cell data in preclinical development[15]. AI models require two types of data: input X, which can be a fixed-length vector (e.g., molecular descriptors, fingerprints), a sequence (e.g., SMILES strings, biomacromolecule structures), or a molecular structure graph, and output Y, which can be real-valued numbers, binary values, integer values, fixed-size vectors, sequential data, and single or multiple data columns[16]. Several database libraries, such as DisGeNET, CTD, LinkedOmics, Open-Target, DepMap, HMDD, STRING, and the Therapeutic Target Database (TTD), have helped manage heterogeneous omics data for biomolecule target identification[26].

2.3 AI in peptide-based drug discovery

ACP_S based on ML and DL offer benefits such as excellent selectively and minimal toxicity under normal conditions. During the COVID-19 pandemic, a peptide library was developed to battle the SARS-Cov-19 virus[17]. Four peptides were identified as effective, with high binding affinity for protease enzymes using AI. Researches used AI algorithms to study the role of dietary peptides in immunomodulation[18]. They discovered that this bioactive peptide has a high affinity for inflammatory receptors and suppresses pro-inflammatory cytokines like TNF-α and nitrogen oxides[19].

Structure based virtual screening:

To identify drug-target interactions in virtual screening (VS), advanced machine learning techniques have been used to construct predictive models by confirming physicochemical features of compound structures and target receptors[20]. There are two types of virtual screening (VS): structure-based (SBVS) and ligand-based (LBVS).

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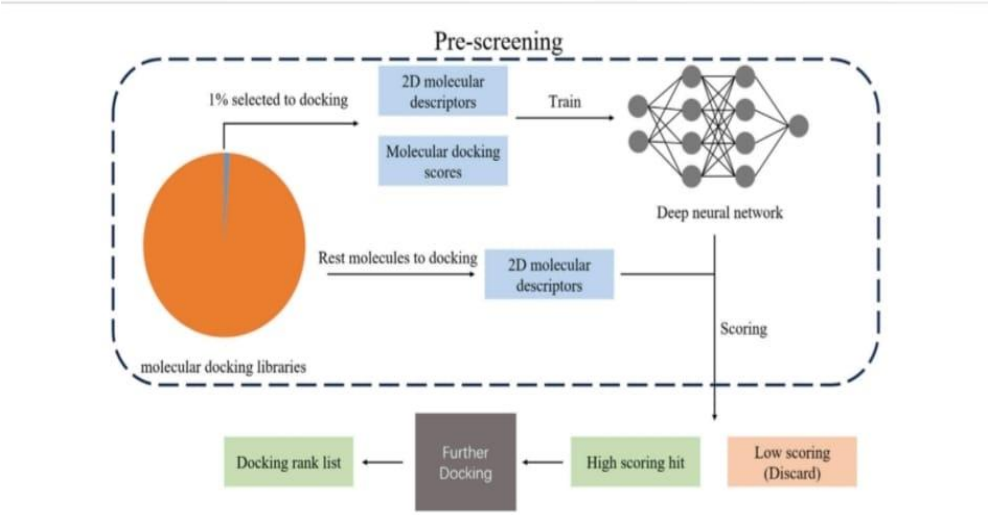
Ligand based virtual screening:

Ligand based virtual screening is the prefered method when the target compunds's 3D structure is unavailable. The idea suggests that similar structure lead to similar biological consequences[21]. The AI method has been effectively implemented in QSAR-based LBVS. QSAR-based LBVS uses AI algorithms such as ANN, RF, SVM, which are similar to the SBVS approaches listed above[22]. The most commonly used nonlinear modeling paradigm in QSAR is ANN, which mimics the human nervous system's process with many neuron layers.

Figure 2: Illustration for pre-screening DNN model.



A study optimized ANN architectures and analyzed six methods (partial derivative-PaD, pairwise partial derivative, weights, perturbation, profile methods, and sum of ranking differences) to determine the correlation between quantum mechanical molecular descriptions and output (Trolox-equivalent antioxidant capacity of 33 flavonoids)[23].

2.4 Using AI for drug design

De novo drug et al., 2021 design involves creating novel molecules that fit specific constraints using generative algorithms[24]. This technique allows for more precise drug design in a larger chemical space, potentially leading to better disease treatment. The objective is to create a stable and simple new molecule without a starting template. Mouchlis provide a comprehensive overview of traditional de novo drug design methods, including structure-based, ligand-based, sampling-based, and evolutionary algorithm-based approaches[25].

This review discusses many methods for ensuring synthetic feasibility, including synthesis planning, prediction, fragment-driven molecular construction, and generative models. While AI has significant potential for de novo drug creation, research is still in its early stages. More research is needed to fully understand algorithmic exploration and practical applications[26].

3 Artificial intelligence for compound pharmacokinetics prediction

In drug development scenarios such as drug design and dosage exploration, the pharmacokinetic studies of potential compounds, which examine properties like absorption, distribution, metabolism, excretion, and toxicity (ADMET), are crucial. This is because it is necessary to assess any drug candidate's ADMET characteristics to ensure the drug's effectiveness and safety[27]. Consequently, by utilizing AI technology to create predictive models for pharmacokinetics, we can significantly narrow the chemical search space, enhance the likelihood of successful drug development, and reduce overall costs . Moreover, these models can help validate ADMET properties for drug candidates in the early stages of development and eliminate undesired drugs[28]. When predicting ADMET and physicochemical properties, each step corresponds to several significant features, including, but not limited to, those listed in Table 3.

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Table 1 Important features for ADMET and Physicochemical properties.

Important features

Absorption	Human intestinal absorption (HIA), Humanoral bioavailability (HOB,F%), P-Glycoprotein inhibitor/substrate, Caco-2/MDCK
Distribution	Plasma protein binding (PPB), fraction unbound in plasma (Fu), blood-brain barrier (BBB),Volume pf distribution (Vd)
Metabolism	Cytochrome P450 isoforms inhibitor/substrate
Excretion	Clearence (cl), Half-life
Toxicity	Acute toxicity, Carcinogenecity, and Ames test
Physicochemical properties	Lipophilicity (log P), Aqueous solubility (log S), Acid dissociation constant (Pka)

4 Artificial intelligence for clinical pharmacology

4.1 AI in clinical trails:

Clinical trials are an important stage in the development of medications. Failure in clinical trials can be costly and time-consuming. AI can increase clinical trial efficiency and success rates. Recruiting appropriate participants is a tough phase in clinical trial design. To ensure patient eligibility for clinical trials, we use machine learning algorithms to screen and match patients to inclusion criteria based on various data points. AI can detect and pick patients who are likely to progress and attain their endpoints faster. Lee suggest reducing the duration of medication studies. AI can identify dropouts during trials and boost completion rates by reminding experimenters to focus on these subjects[29].

4.2 AI in optimizing drug treatment:

Individualizing treatment plans is crucial for many marketed medications. Therapeutic drug monitoring (TDM), is used to tailor doses for medicines with limited therapeutic windows. Statistical prediction models are commonly used to extrapolate TDM data and determine appropriate treatment options. AI applications in this field are less established than in drug discovery due to the necessity for substantial clinical datasets for model training, which are not easily available[30].

5 The challenge of keeping drugs safe:

Drug safety is a significant barrier to bringing novel medications to market. Toxicities are a primary cause of attrition in clinical trails, and post-marketing safety concerns lead to avoidable morbidity and mortality[31]. Adverse events (AEs) or adverse drug reactions (ADRs) are unanticipated consequences caused by a regular drug dose that can be proven to be responsible. From 2008 to 2017, the FDA authorized 321 new medications. Over the same period, the FDA Adverse Event Reporting System (FADERS) documented over 10 million AE reports, with 5.8 million being serious and 1.1 million resulting in death. Annually, Aes cause 2 million hospital stays and extend visits by 1.7 to 4.6 days, putting a strain on the healthcare system. There are two complementary systems for addressing medication safety. Clinical studies assess the safety and efficacy of a medicine before it is approved for use[33]. Pharmacovigilance (PV) involves monitoring a drug's safety information through adverse event reports (AEs) after it is marketed. Clinical trials have structural limitations that make them prone to errors[34]. It is impossible to test for all potential synergistic effects or conduct trials on large populations to detect unusual adverse events. Previously, women and the elderly were regarded as unique subgroups in clinical trials.

6 Pre-clinical drug safety:

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AI can significantly improve pre-market medication safety, particularly in toxicity evaluations. Medication toxicity evaluation is a crucial phase in medication design, determining the adverse effects of compounds on humans, plants, animals, and the environment. Pre-clinical examinations are necessary to avoid harmful medications from entering clinical trials. High toxicity remains a significant cause of medication failure, accounting for two-thirds of post-market withdrawals and one-fifth of clinical trial failures. Accurate toxicity estimations ensure drug safety and save research costs and time to market. Traditionally, animal studies have been the primary method for assessing toxicity. However, this research is limited by budget, time, and ethical constraints[35].

6.1 Post marketing survelliance:

Post marketing survelliance AI can significantly improve pre-market medication safety, particularly in toxicity evaluations. Medication toxicity evaluation is a crucial phase in medication design, determining the adverse effects of compounds on humans, plants, animals, and the environment. Re clinical examinations are necessary to avoid harmful medications from entering clinical trails. High toxicity remains a significant cause of medication failure, accounting for two-thirds of post-market withdrawls and one-fifth of clinical trail of failures[36]. Accurate toxicity estimations ensure drug safety and save reasearch costs and time to market. Traditionally, animal studies have been the primary method for assessing toxicity.

7 Endpoint-specific toxicity prediction:

Endpoints differ in data qualities, sources, and volumes. This includes databases. The level of interpretability needed for specific toxicity pathways varies. Models for each endpoint are tailored to their specific properties, resulting in varying features and methods . Although molecular data serve as the foundation for many of these models, the characteristics and strategies used vary depending on the endpoint and aims[37].

7.1 Hepatotoxicity:

The liver plays a crucial role in maintaining systemic homeostasis by detoxifying, synthesizing plasma proteins, regulating lipid and glucose metabolism, producing bile, and modulating immunity. The liver's metabolic activities can both reduce and increase the toxicity of substances, potentially harming the liver[38]. Liver pathologies like steatosis and fibrosis can disrupt nutritional, endocrine, and pharmacological metabolism, affecting overall physiological balance.

7.2 Cardiotoxicity prediction:

Cardiotoxicity is a significant issue in medication development, resulting in late-stage failures or market withdrawals[39]. Compounds with cardiovascular hazards have been withdrawn, and others are under regulatory scrutiny, highlighting the necessity for early risk assessment procedures. Janus kinase (JAK) inhibitors, including tofacitinib, baricitinib, and upadacitinib, are used to treat rheumatoid arthritis. In 2021, the FDA issued a boxed warning for these agents, citing increased risks of cardiovascular events, cancer, thrombosis, and mortality.

7.3 Neurotoxicity prediction:

Neurotoxicity signifies the harmful effects on both the central and peripheral nervous systems, leading to dysfunction and structural impairment[40]. The mechanisms underlying neurotoxicity can generally be classified into neuronopathy, axonopathy, myelinopathy, and toxicity related to neurotransmission. Even medications used for treatment can exhibit neurotoxic properties; for example, vincristine, an alkaloid derived from plants used in chemotherapy, is recognized for causing peripheral neuropathy, which is characterized by sensations of numbness, tingling, and weakness in movement. Due to these risks, it is crucial to assess neurotoxicity during the development of new drugs to ensure the safety of novel chemical entities.

CONCLUSION:

Artificial intelligence (AI) is transforming pharmacology, drug discovery, safety, and toxicology by overcoming the drawbacks of convential methodologies such as high expense, long lead time, and poor predictability[41]. By

means of sophisticated machine learning (ML) and deep learning (DL) methodologies, AI streamlines protein and RNA structure prediction, improves virtual screening, and facilitates de novo drug design, thus expanding the therapeutic development scope. Tools powered by AI also maximize pharmacokinetics (ADMET) prediction, enable patient-specific treatment regimens, and enhance clinical trail design through increased recruitment, monitoring, and compliance[42].

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