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ARTIFICIAL INTELLIGENCE IN DRUG-DRUG INTERACTIONS

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ABSTRACT

Artificial Intelligence (AI) has revolutionized modern medicine by providing computational solutions to manage complex clinical data and improve therapeutic outcomes. In pharmacology, AI particularly machine learning (ML) and deep learning (DL) models has demonstrated significant potential in predicting drug–drug interactions (DDIs), a major cause of adverse drug reactions (ADRs) and increased healthcare costs. This study focuses on the DANN-DDI (Deep Attention Neural Network for Drug–Drug Interaction) model, which integrates diverse pharmacological data to enhance the accuracy of DDI prediction. Drug features including chemical substructures, targets, enzymes, pathways, and existing interactions were extracted from the DrugBank (version 5.1.0) and KEGG databases. The DANN-DDI framework consists of three components: drug feature learning, drug-pair feature learning, and interaction prediction using a deep neural network optimized via the Adam algorithm and binary crossentropy loss. Model performance was evaluated using 5-fold cross-validation and assessed through AUC, AUPR, accuracy, and F-measure metrics. The results indicated that optimal parameters (embedding dimension = 128, 7 hidden layers, 150 epochs, dropout rate = 0.4) yielded superior prediction outcomes. Compared with traditional computational methods such as similarity analysis and matrix factorization, the DANN-DDI model demonstrated improved capability to detect potential DDIs effectively. Overall, this study highlights the value of integrating AI-based approaches into pharmacovigilance systems to predict and prevent harmful drug interactions, ultimately enhancing patient safety and treatment efficacy.

KEYWORDS: *Drug-Drug Interactions, Artificial Intelligence, Deep Learning, Pharmacovigilance, Structural Deep Network Embedding.*

1.INTRODUCTION

Medicine is vital to human progress and development. Pharmaceutical products are the main substances people use to prevent, treat and diagnose diseases. With the development of modern medicine, pharmacology, drug therapy and pharmacy research, various drug combinations have been found to effectively treat individuals with diverse or complex disorders1. But, the main problem of using multiple drugs in combination is that patients are at a considerably greater chance of adverse outcomes. A variety of adverse drug reactions can occur due to Drug-drug interactions (DDI). This may cause favorable or unfavorable changes in the drug's activity when mixed with another medication. This change can lead to the loss of therapeutic effect and toxicity, posing a threat to the safety of the patients and increasing the disease incidence, especially among some populations with underlying diseases. In the hospital Setting, DDI may also cause multiple complications, prolong the length of hospital stays, and even result in death. Knowledge of DDIs is frequently constrained since these complicated interactions are uncommon, often difficult to observe clinically, and can only be verified experimentally. In the United States, over 74,000 emergency room visits and over 195,000 hospitalizations are reported to be a result of adverse drug-drug DDI each year. According to CDC, ten percent of Americans take at least five medications over a period of time4. Additionally, 36 percent of older Americans regularly take at least five medications simultaneously. There is a risk of adverse drug interactions in 15% of medication combinations used by elderly people aged 61-805. In China, the incidence of adverse drug interactions is about 5%, and about 2.5 million people are hospitalized for drug abuse or adverse drug reactions. Of these cases, approximately 200,000 died from inappropriate or incorrect drug use, accounting for 0.38% of total hospital admissions and 7.9% of cases due to adverse drug reactions6. We give examples of DDI adverse events that have occurred in the hospital setting. The patient in this case was an 83-year-old female with underlying renal insufficiency. After receiving intravenous injection of imipenem/cilastatin sodium 0.5g three times daily for four days, the patient experienced seizures and life-threatening epilepsy. There was a clear relationship between the administration of Injections imipenem/cilastatin sodium and the onset of seizures, and the patient's symptoms disappear after stopping the drug.[1] Based on these observations, it was determined that the seizures were likely associated with the use of imipenem/cilastatin sodium. This example highlights the importance of accurate DDI prediction in identifying potential adverse events and preventing harm in clinical practice. DDI refers to the simultaneous or sequential use of two or more drugs due to

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drug interactions, where the effects of one or more drugs are weakened or changed to varying degrees. It has been shown that DDI can produce different types of responses in pharmacy, pharmacokinetics (PK), and pharmacodynamics (PD). The occurrence of pharmacy DDI is due to physical or chemical incompatibility. PK DDI occurs when drugs interact during the processes of absorption, distribution, metabolism, and excretion8. On the other hand, PD DDI happens when a drug triggers a pharmacological response to another drug of equal concentration9. Due to adverse effects of DDI, the study of DDI has led to a greater understanding of drug interactions and improved the safety and efficacy of drug therapy and promoted safe and effective combination therapy strategies[2].

2.STUDY SELECTION

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was referenced when conducting literature reviewing. We searched five electronic databases up to December 2021: Cochrane Library, PubMed, EMBASE, IEEE, and Scopus. The search strategy combined the Medical Subject Headings terms and free terms “drug drug interaction” or “drug-drug interaction”, in combination with “artificial intelligence” or “machine learning” or “deep learning” or “neural network” and “prediction model”.

The eligibility criteria consisted of DDI predictive models that were built up using ML – and/or DL-based algorithms. The articles were screened and selected independently by two reviewers (N.T.K.N and H.T.V.), and disagreements were resolved by the third reviewer (N.Q.K.L.). All the retrieved publications were entered into reference-manager software.[3]

We identified 643 records through Cochrane Library, IEEE, PubMed, EMBASE, Scopus database, and two records from reference lists of review paper. After removing 215 duplicates, 116 records were excluded according to the screening of titles and abstracts. Of 314 remaining research studies, 220 studies were removed after evaluating the selection criteria: (1) related to DDIs, (2) related to predictive model, (3) focused on ML or/and DL. As a result, we had 94 different research studies. Fig. 1 shows the flow diagram of the systematic search. Table 1 shows the detailed information of 94 selected studies.[4]

3. DATASET, INPUT DATA, AND FEATURES FOR AI-DDIS STUDIES

In response to the growing number of pharmaceutical drugs entering the market over the past decades, many drug-related information databases have been updating and expanding to facilitate DDIs prediction.Generally, most DDIs studies referred to datasets from DDIExtraction 2011.DDIExtraction 2013 and DrugBank database. These public sources provide various types of drugs’ characteristics and DDIs events to leverage AI approaches for DDIs discovery. The quantitative information about the DDIs is a necessary part of creating the described system. The data record format usually has binary characters encoded as 1 if there is an interaction between two drugs and 0 if there is a lack of known interaction.Depending on the DDIs features-based view of different approaches, appropriate data extraction and feature preprocessing methods for DDIs prediction tasks can be applied.[5]

3.1. DDIs information retrieved from Text-Based Sources

This method involves extracting DDIs information in the form of biomedical text, especially in scientific literature since these sources represent valuable information for the retrieval of knowledge about the interaction between drugs. The amount of biomedical literature, which holds a vast amount of DDIs, has been growing over the past years and facilitating many DDIs extracting studies. Aside from studies using public available DDI corpus some studies have also used additional user-generated content to compensate for the limits of delayed updates of the medical database . In addition, multi-information sources DDI corpora have been constructed based on useful information from FDA adverse event reports electronic health records (EHRs) or by following specific annotation guidelines to construct corpus for DDIs extracting[6].

In these DDIs extraction approaches, feature preprocessing is essential. In detail, tokenization and lower casing are the first vital steps in reducing the sparsity of feature space. Also, many dimensionally reduction text preprocessing techniques have been used for DDIs extraction. Some compression techniques such as sentence pruning and anaphora resolution have been applied; Zhao used syntax word embedding strategy instead of the common word embedding technique, some used Bidirectional Encoder Representations from Transformers (BERT) that relies on attention mechanism to capture high-quality contextual information. The domain-specific ontologies approach attempted to use ancestors’ sequences in the ontology to represent each entity proposed clause dependency features to improve the relation extraction performance. Also, used the CRF-based algorithm trained by a set of linguistic and semantic features for the drug name recognition.[7]

3.2. Molecule-based input data and feature preprocessing for DDIs prediction

Usually, DDIs studies utilize chemical, molecular, and pharmacological properties information to elucidate drug interactions insights. In detail, the chemical properties of drugs are typically described via the simplified molecular-input line-entry system (SMILES). This

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flexible chemical notation allows the generation of computer-feedable input. These SMILES structural representations of drugs are post-processed to capture features of drug pairs associated with DDIs events. Moreover, pharmacological properties such as targets enzymes, transporters, genes and proteins, interaction pathways like enzymes and transporters can also be manipulated to represent drugs features through a set of descriptors[8]. Network interaction miningand molecular graph representations have also been used to describe substructures of drugs that come in distinctive shapes and sizes or the structural relations between entitie. Additionally, to overcome the lack of data overlap between chemical content and biological characteristics, the combined structure-based input that includes both chemical and biological data by hybridizing cheminformatics and bioinformatics techniques to link all chemical information and biological effects have also been applied to serve as a meaningful method for DDIs discovery in many studies.Many techniques have also been applied to cover multi pharmacological facets of DDI by admitting heterogeneous characterizations from various data sources that represent different drug characteristics and physiological effects[9].The knowledge graphs (KGs)–based features integrated from multiple sources such as DrugBank, PharmGKB, and KEGG drugs were used to overcome the limited information issue in single-source methods. Along with this, some efforts have been made to address the problem of increased noise in the integrated similarity. The similarity selection heuristic process ranks matrices based on the entropy calculated in each matrix and calculates their pair-wise distance for the final selection based on redundancy minimization.[10]

4. CONVENTIONAL ML-BASED PREDICTION MODELS OF DDIs

Given the advanced computer science development and growing network pharmacology approaches, the development of a traditional ML-based model using multi-dimensional drug properties has been widely applied as a promising strategy to predict unknown DDIs[11]

4.1. Single ML algorithm-based predictive model

Support vector machine (SVM) was a common algorithm used to predict DDIs due to its high performance with a broad range AUC value of 0.565 – 0.985. Indeed, the number of recruiting features has a certain role in the predictive model, e.g., a study applied the features reducing method and achieved an increase of 0.02 in the F-measure score (0.5786 vs 0.5965) of the predictive model.Kernel machines are a class of algorithms for pattern analysis whose best-known member is the SVM. Kernel classifiers were used for classifying the drug pairs, including all-paths graph (APG), k-band shortest path spectrum (kBSPS), and the shallow linguistic (SL) kernel. Noteworthy, Thomas et al. showed that SL and APG outperformed other methods, such as case-based reasoning and ensemble learning based on F1-score (0.606 vs. 0.416 and 0.583, respectively). Also,used the label propagation algorithms to work with the scenario where only a small portion of nodes in the undirected weighted network being labelled.[12]

4.2. Ensemble learning predictive model

Ensemble methods use multiple learning algorithms to obtain better predictive performance than separate models in DDIs prediction. Combined ML algorithms using LibLINEAR, which consists of linear SVM, Naïve Bayes, and Voting Perceptron classifiers, outperformed the original (unbalanced) train corpora model based on F-score (70.4% vs. 69.0%).Similarly, a heterogeneous network-assisted inference (HNAI) framework consisting of five different ML algorithms, including Naïve Bayes (NB), decision tree (DT), k-nearest neighbors (k-NN), LR, and SVM, was proposed to detect the unknown DDIs with AUC of 0.67, higher than that of separated algorithms (NB:0.66, DT:0.565, k-NN:0.6, LR:0.655, and SVM:0.666).Other ensemble methods including genetic algorithm and LR in classifier ensemble rule for DDIs prediction could obtain AUC value up to 1 and accuracy>90%, regardless of approved and unproved drug pairs being selected.[13]

5.SPECIAL POPULATIONS AND CONTEXT-SPECIFIC CONSIDERATIONS IN DDI RESEARCH

DDIs pose a significant and evolving challenge in clinical pharmacology, especially due to the diverse nature of patient populations. Certain groups, such as the elderly, pediatric patients, pregnant and lactating women, individuals with liver or kidney dysfunction, and those with genetic variations affecting drug metabolism, often show differences in how their bodies process medications (pharmacokinetics) and respond to them (pharmacodynamics) (Strawn et al., 2021). These differences can greatly affect both the likelihood of experiencing DDIs and their clinical consequences. Additionally, specific clinical situations, such as the use of multiple medications in cancer treatment, critical care settings, and variations in treatment practices across different regions, add to the complexity of managing DDIs. Therefore, a detailed understanding of these population-specific and contextual factors is essential for improving personalized medication therapy and ensuring that regulatory practices are based on solid evidence.[14]

5.1Pharmacokinetic and pharmacodynamic changes in aging

Physiological aging brings about significant changes in the body that can affect how drugs are processed and increase the risks of DDIs. For example, as people age, there is a decrease in liver blood flow, kidney function, and alterations in body composition, all of which can influence drug metabolism and clearance. A notable consequence of aging is the decline in glomerular filtration rate, which can hinder the elimination of drugs that are primarily excreted by the kidneys, like digoxin. This impairment raises the potential for toxicity,

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especially when these drugs are taken alongside other medications that may interact with them. Additionally, aging can lead to changes in how receptors respond to drugs and can disrupt the body's ability to maintain balance, particularly affecting drugs that act on the central nervous system (CNS) (Zerah et al., 2021). This is especially relevant for medications such as benzodiazepines, opioids, and antipsychotics, where the altered sensitivity and homeostatic responses can heighten the risk of adverse effects and interactions.[15]

5.1.1 Polypharmacy and inappropriate prescriptions

Polypharmacy, which is commonly defined as the simultaneous use of five or more medications, is particularly common among older adults and significantly increases the risk of DDIs. This issue is especially pronounced in elderly patients. Research by Abdu et al. highlights that polypharmacy is a major risk factor for DDIs in older populations (Abdu et al., 2025). For example, a cross-sectional study conducted in the U.S. found that 62.7% of elderly patients with cardiovascular disease were subjected to polypharmacy, with 34.8% experiencing at least one severe potential drug-drug interaction. To help identify potentially inappropriate medications (PIMs), clinical tools like the Beers Criteria and the STOPP/START guidelines are utilized, as many of these medications are known to cause significant interactions. A specific example is the combination of warfarin with trimethoprim-sulfamethoxazole, which can lead to increased bleeding due to CYP2C9 inhibition and changes in gut microbiota. Similarly, taking citalopram alongside omeprazole may heighten the risk of QT interval prolongation, particularly in patients with diminished CYP2C19 activity. The most frequently encountered potential drug-drug interactions involve warfarin being co-prescribed with other interacting agents such as nonsteroidal anti-inflammatory drugs (NSAIDs) or antibiotics, highlighting the critical need for structured medication reviews in geriatric care (Sheikh-Taha and Asmar, 2021). A European multicenter study found that 54.8% of elderly patients had at least one potentially clinically significant drug-drug interaction before being admitted to the hospital, and this figure rose to 58.3% during their s

5.2 Maturation of drug metabolism and transport

Children, especially neonates and infants, experience significant developmental changes in their drug-metabolizing enzymes and transporters. For instance, enzymes like CYP3A7, CYP2D6, and CYP1A2 show variations in their expression levels depending on the child's age, which can lead to differences in how susceptible they are to DDIs. Additionally, the underdevelopment of renal transport mechanisms, such as organic anion transporters (OATs), organic cation transporters (OCTs), and multidrug and toxin extrusion proteins (MATEs), affects how drugs are cleared from the body.[16]

5.2.1Off-label drug use and limited DDI data

Off-label drug use is prevalent in pediatrics, primarily because children are often excluded from numerous clinical trials, leading to a scarcity of pediatric-specific data on DDIs. This lack of information compels healthcare providers to rely on data derived from adult populations, which can be unsuitable due to the developmental differences between children and adults. Although legislative measures like the Pediatric Research Equity Act (PREA) and Pediatric Investigation Plans (PIPs) have made strides in tackling this challenge, significant gaps in knowledge and data still persist.

5.3 Pregnancy-induced physiological changes

Pregnancy brings about significant changes in the body that can affect how drugs are processed. For instance, during pregnancy, the activity of the enzyme CYP3A4 increases while that of CYP1A2 decreases. Additionally, there is an increase in renal blood flow and plasma volume, all of which can alter how drugs are metabolized and how they interact with one another. A practical example of this is that the heightened activity of CYP3A4 can lead to lower levels of midazolam, which in turn can change how this drug interacts with inhibitors of CYP3A4. Moreover, DDIs involving teratogenic medications, such as valproate and isotretinoin, along with enzyme inhibitors, can increase the exposure of the fetus to these drugs, highlighting the importance of careful risk-benefit evaluations. Furthermore, interactions that affect placental transporters, such as BCRP and P-glycoprotein (P-gp), can also influence the amount of medication that reaches the fetus.[17]

5.3.1 Lactation and breastmilk transfer

Drugs can transfer into breast milk through two primary mechanisms: passive diffusion and transporter-mediated processes. DDIs that raise maternal drug concentrations or modify the composition of breast milk can significantly affect the amount of medication that a newborn is exposed to. A notable example of this is the interaction between fluoxetine, an antidepressant, and metoclopramide, a medication often used to treat nausea. This interaction may lead to an increase in prolactin secretion, which could have implications for lactation and the amount of the drug that an infant ingests through breast mil

5.4Hepatic impairment and reduced metabolic capacity

Liver dysfunction affects both phase I and phase II metabolic pathways, leading to significant implications for drug metabolism. Enzymes like CYP1A2 and CYP2C19 are especially vulnerable to the suppressive effects of cirrhosis, which can result in unpredictable and potentially dangerous DDIs when these enzymes are induced or inhibited. This is particularly concerning for medications that have

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narrow therapeutic windows, such as carbamazepine, phenytoin, and propranolol, as they require meticulous monitoring in patients with liver impairment to avoid adverse effects and ensure therapeutic efficacy.[18]

5.4.1Renal dysfunction and drug accumulation

Chronic kidney disease (CKD) leads to a decrease in drug clearance and changes in protein binding, which increases the likelihood of drug accumulation and toxicity. The use of nephrotoxic medications, such as aminoglycosides, nonsteroidal anti-inflammatory drugs (NSAIDs), and contrast agents, can further worsen kidney damage. Additionally, the presence of uremia can hinder the function of transporters and enzymes, making it essential to implement individualized therapeutic drug monitoring (TDM) that considers the potential for D

5.5 Anticancer polypharmacy and enzyme modulation

Oncology patients often undergo complex treatment regimens that include chemotherapy, targeted therapies, antimicrobials, and supportive care agents. A significant number of anticancer drugs, particularly tyrosine kinase inhibitors (TKIs), are either metabolized by or influence the activity of CYP3A4, which makes them susceptible to serious DDIs with medications such as azoles or macrolides. Additionally, immunosuppressants like tacrolimus and cyclosporine have narrow therapeutic indices and can interact adversely with antifungals, calcium channel blockers, or antiepileptics. [19]

5.5.2 Drug–microbiome interactions

The gut microbiome plays a crucial role in drug metabolism, and its disruption through antibiotics or chemotherapy can significantly affect drug deconjugation and enterohepatic circulation. For instance, bacteria that produce β-glucuronidase can increase the toxicity of irinotecan, highlighting a new category of microbiome-mediated DDIs in oncology. In addition, the use of traditional medicine is prevalent among diabetes patients, particularly in Africa, which can lead to interactions with conventional medications. Unfortunately, these interactions are often overlooked, resulting in adverse drug reactions and complications in treatment.The significance of gut microbiota in drug metabolism and interactions is gaining recognition. Probiotics have been found to modify drug efficacy and toxicity, and research conducted in Serbia indicates that healthcare students are aware of these interactions (Danic et al., 2024); however, there is a need for further education on the subject. Knowledge regarding the interactions between drugs and dietary supplements is still insufficient among healthcare professionals, which can lead to an increased risk of adverse reactions due to overlooked interactions between supplements and prescription medications. Studies reveal that many healthcare workers are not fully aware of these risks (Büyükkasap and Yazici, 2024). Herbal products further complicate DDIs, particularly in psychiatric or immunocompromised patients, where modulation of cytochrome enzymes can disrupt standard therapies.Cannabinoid compounds, such as THC and CBD, have the potential to inhibit CYP enzymes, increasing the likelihood of metabolic DDIs. Patients with HIV often navigate complex antiretroviral therapy (ART) regimens, where even minor errors related to DDIs can significantly impact therapeutic efficacy.Moreover, the widespread use of dietary supplements among older adults presents substantial, yet often unrecognized, risks for DDIs[

5.6.Complex regimens and organ support devices

Critically ill patients often receive a variety of intravenous medications, which can lead to both pharmacokinetic and physicochemical interactions. The use of medical devices like renal replacement therapy (RRT), extracorporeal membrane oxygenation (ECMO), and plasma exchange can significantly change how drugs are cleared from the body, making it essential to adjust dosages and assess potential DDIs carefully. Emergency department physicians who follow national guidelines for HIV post-exposure prophylaxis can notably lower the chances of adverse drug interactions. Research indicates that adhering to these guidelines not only enhances patient safety but also improves overall outcomes by reducing the likelihood of harmful drug interactions. Furthermore, pharmacist-led stewardship programs are becoming increasingly important in managing and minimizing DDIs related to antiretroviral therapy (ART).

5.6.1 Time-critical decision-making

The urgent nature of emergency care often limits the ability to conduct comprehensive evaluations of DDIs. To address the risks associated with these interactions in high-pressure environments, it is crucial to implement advanced CDSS that include severity stratification and tailored patient alerts. These systems can help healthcare providers quickly identify and manage potential interactions, ensuring safer and more effective patient care during emergencies.[21]

5.7 Pharmacogenomic subpopulations

Polymorphic variants in drug-metabolizing enzymes, such as CYP2C9/2C19, CYP2D6, and CYP3A5*3, play a crucial role in influencing the risk of drug-drug interactions (DDIs). For instance, individuals identified as poor metabolizers of CYP2D6 may be at an increased risk of developing serotonin syndrome when paroxetine is used in conjunction with tramadol. By incorporating pharmacogenomic (PGx) profiling into standard healthcare practices, utilizing platforms like PharmCAT or YouScript, healthcare providers can conduct personalized risk assessments and make proactive dose adjustments tailored to individual patient needs.

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5.8 Global considerations and population diversity

5.8.1 Ethnopharmacology and DDI sensitivity

Genetic variations in metabolic enzymes, along with dietary habits and the common use of traditional medicines, play significant roles in the differences in DDIs risks among various ethnic groups. For example, individuals from East Asian backgrounds often possess a higher frequency of poor metabolizer genotypes for the CYP2C19 enzyme, which can diminish the effectiveness of clopidogrel when it is taken alongside proton pump inhibitors. Additionally, herbal remedies like St. John's Wort and ginseng can either induce or inhibit cytochrome P450 enzymes, making the management of DDIs even more challenging. Beyond these genetic and cultural factors, differences in enzyme expression and drug transporter activity based on sex and gender can also influence DDI risks. For instance, the levels of estrogen and testosterone can impact the activity of CYP enzymes, which is particularly relevant for both cisgender and transgender patients undergoing hormone therapy.[22]

6. REGULATORY CONSIDERATIONS AND DDI LABELING STRATEGIES

The accurate identification and proactive management of clinically significant DDIs is a crucial priority for health authorities worldwide. Regulatory frameworks have evolved to facilitate the systematic evaluation of DDIs at every stage of drug development, from preclinical studies to post-marketing surveillance. This section outlines the main strategies employed by prominent regulatory agencies, including the FDA, EMA, and PMDA, while also noting regional differences and the trend towards global harmonization. It is important to mention that this content is not recommended for citation unless it is connected to socioeconomic factors in drug interaction management (Leslie, 2024). Efforts to harmonize ontological frameworks, such as RxNorm and DrugBank, play a key role in maintaining consistency in DDIs knowledge bases (Kawakami et al., 2024). Additionally, this section discusses the growing role of artificial intelligence (AI) in predicting DDIs and the regulatory considerations that come with its implementation.

6.1. European Union: EMA framework

The European Medicines Agency (EMA) offers comprehensive guidance on evaluating pharmacokinetic interactions, placing significant importance on mechanistic classification, especially concerning cytochrome P450 enzymes and drug transporters. Within the EMA framework, there is a clear requirement for strong justification when waiving clinical interaction studies, frequently necessitating sensitivity analyses or supplementary modeling to substantiate these claims. In contrast to the FDA, the EMA applies more stringent regulatory oversight regarding the reasoning behind the decision not to perform certain clinical trials.[23]

6.2. Japan: PMDA requirements

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan generally aligns with international best practices while also taking into account specific regional considerations. A key focus for the PMDA is ethnic sensitivity; they often require bridging studies to ensure that DDIs data can be accurately extrapolated to Japanese populations. Additionally, the PMDA has been increasingly supportive of modeling and simulation techniques, including the use of AI-based systems, to predict potential DDIs effectively.The PM"A has approached the endorsement of AI-driven models with caution, yet it is gradually advancing towards supporting these technologies. These models have the potential to incorporate population-specific data, which is particularly important for enhancing DDIs predictions. This is especially relevant in the context of Japanese populations, where unique genetic factors can significantly influence drug metabolism.

7. LIMITATIONS AND FUTURE DIRECTIONS

Despite significant advancements in DDIs research, several key limitations persist that hinder clinical implementation, regulatory harmonization, and the relevance of findings in real-world settings.

7.1 Limitations

- Many current DDIs prediction models are based on limited and skewed datasets, which primarily focus on well-characterized drug classes.
- This focus leads to a significant underrepresentation of rare interactions, population-specific pharmacokinetics, and the complexities of real-world treatment scenarios. Additionally, clinical trials frequently exclude vulnerable populations, including the elderly, pediatric patients, pregnant individuals, and those with multiple health conditions.
- Such exclusions undermine the external validity of DDIs evidence, particularly for high-risk groups.
- A considerable number of machine learning-based DDIs prediction models face challenges related to interpretability, which diminishes trust among clinicians and hampers acceptance by regulatory bodies. These models frequently function as "black boxes," delivering precise predictions without offering insights into their underlying mechanisms or pharmacological reasoning.

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- Consequently, this lack of transparency restricts their incorporation into clinical workflows and the labeling of drugs.
- Current DDIs frameworks inadequately address the role of herbal medicines, dietary supplements, and traditional therapies, even though these are commonly used, especially in low- and middle-income countries (LMICs).
- The diversity in therapeutic practices across different geographic and cultural contexts adds another layer of complexity that is seldom reflected in conventional pharmacovigilance systems or regulatory guidelines.

7.3 Data sources

The foundational data inputs essential for DDIs prediction come from various sources:

- Molecular Mechanisms: The data encompasses how drugs interact at the molecular level, including details about chemical structures, biological pathways, and the interactions that occur within biological systems.
- Electronic Health Records (EHRs): Patient data, including medical history, laboratory results, and prescription records, are crucial for understanding drug interactions in diverse patient populations.
- Pharmacogenomics (PGx): Genetic information that influences drug metabolism, efficacy, and toxicity. This data helps predict individual responses to drugs.
- Real-World Evidence (RWE): Data derived from actual clinical practice, including observational studies and post-market surveillance, to capture drug interactions in broader patient populations.

7.4 AI-based prediction

The second section of the framework involves AI-based prediction methods that process the heterogeneous data sources mentioned above. These methods include:

- Machine Learning: Algorithms that learn from large datasets to predict drug interactions based on patterns and correlations.
- Deep Learning: A subset of machine learning that uses neural networks to model complex, high-dimensional data and improve the prediction of interactions.
- Knowledge Graphs: Graph-based models that represent the relationships between drugs, diseases, genes, and other medical entities, providing a structured approach to explore interactions.
- Natural Language Processing (NLP) and Text Mining: These methods are used to extract valuable insights from unstructured data such as scientific literature, clinical notes, and drug labels.[24]

CONCLUSION

The management of DDIs, which can cause ADEs and affect patients' health, plays a crucial role in pharmacovigilance and medical practice. The main contribution of this study is the establishment of detailed taxonomy of existing models for predicting DDIs. Given remarkable breakthroughs in DDIs prediction over the past years, weakness in terms of model interpretability exposed considerable limits. We, therefore, believe that XAI in DDIs prediction still holds many potential aspects to unlock in future studies.

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