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Review

A Systematic Review of Drug-Related Interactions—Utilizing Deep Learning and LLMs for Prediction and Mitigation

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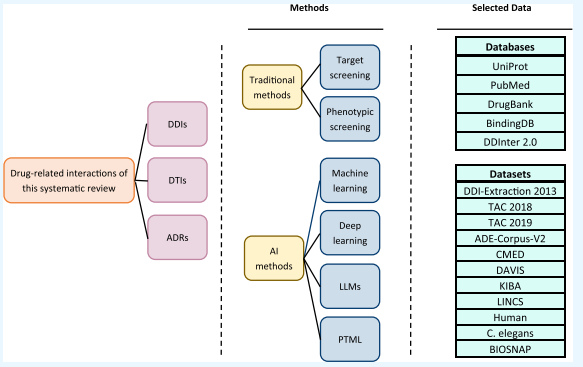
ABSTRACT: Computational drug discovery is essential for screening potential treatments and reducing the costs and time associated with proposing or combining drugs for disease management. Despite the extensive research conducted in this field, it remains an emerging area, particularly with the advent of machine learning, deep learning, and large language models (LLMs). This systematic review examines the integration of machine learning and deep learning techniques in drug discovery, concentrating on three critical areas: drug−drug interactions (DDIs), drug-target interactions (DTIs), and adverse drug reactions (ADRs). The review analyzes over 100 papers published between 2020 and 2025, categorizing the methods into deep learning, machine learning, graph learning, and hybrid models. It highlights the transformative impact of natural language processing (NLP) and LLMs in extracting meaningful insights from biomedical literature and chemical data. Furthermore, this work introduces key databases and data sets widely utilized in drug discovery. Additionally, this review identifies gaps in the existing research, such as the lack of comprehensive studies that simultaneously address DDI, DTI, and ADR extraction, and it proposes a more holistic approach to fill these gaps. The paper concludes by thoroughly evaluating various models, underscoring their performance metrics.



1. INTRODUCTION

Drug discovery (DD), as a systematic scientific process, aims to identify, design, and develop new therapeutic agents to cure or prevent diseases and improve medical conditions. The term "pipeline" is frequently used to describe the unidirectional progression from the hit or the lead to the candidate and the marketed drug, which is supported by both scientific and clinical research. In fact, the process is iterative in nature, diverse, and complicated. It has several steps, including target identification, lead optimization, clinical trials, regulatory assessment, and postmarketing surveillance. Several techniques are used to support the process, i.e., computational modeling, high-throughput screening, and biological testing.[1] Traditional methods require a large amount of clinical tests, whereas novel methods rely on modeling and bioinformatic techniques that accelerate the discovery of new drugs.[2,3] In addition, drug discovery requires a significant investment in finance and expert human resources.[4]

Traditional drug discovery involves screening methods, such as target-based or phenotypic screening. In target-based screening, compounds are selected for their ability to bind to a biological target, while phenotypic screening tests compounds against an organism without prior knowledge of the target.[5−8] These methods are complex, time-consuming, and costly.[9]

Drug research requires understanding disease biology at the cellular and molecular level, identifying drug targets, and selecting chemical molecules for testing. These molecules undergo efficacy and safety assessments in preclinical phases before clinical trials.[10] Bringing a new drug to market takes 10−15 years and costs 800M−1.5B, with recent estimates reaching 2.5B dollars.[11] However, the drug development process faces high failure rates due to toxicity and side effects.[4]

For over three decades, computer-aided DD/design (CADD) has been essential in developing small therapeutically relevant compounds.[12,13] CADD is divided into structure-based, ligand-based, and systematic-based approaches.[14,15]

Structure-based approaches, similar to high-throughput screening, require structural data of both the target and the ligand. Researchers study proteins or biomarkers related to pathophysiology and use 3D target protein structures to calculate interaction energies.[15] Key methods include DMAP, molecular docking, and molecular dynamics simulations.[16−18] Ligand-based approaches estimate activity based on ligand similarities when 3D protein structures are unavailable.[14] They focus on identifying features in chemical compounds that influence biological activity.[15]

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Systematic-based approaches, such as Proteochemometric Modeling, view biological data holistically to assess how chemical compounds affect cellular interactions, aiding in drug repurposing.[14,19]

The integration of data science, informatics, and AI has revolutionized drug discovery, improving efficiency and reducing costs.[20,21] AI, particularly machine learning and deep learning, is increasingly used to handle large, complex data sets, making drug research more efficient.[20,22−24] These technologies automate the drug discovery pipeline, especially in preclinical stages, enhancing productivity and lowering costs.[1,4,25]

AI accelerates drug discovery by improving target identification, drug screening, and lead optimization.[26] Traditional methods are labor-intensive and time-consuming, but AI efficiently analyzes genomic and protein data to identify drug targets.[20] Machine learning models process complex biological data and predict DTIs, aiding in target discovery. AI also predicts bioactivity and molecular properties, such as toxicity and ADME profiles, reducing the need for expensive screening methods.[25] Deep learning offers superior accuracy in predicting molecular properties, while AI tools like reinforcement learning and generative models optimize lead compounds, enhancing pharmacological properties and trial success rates.[25]

Traditional approaches that focus on only one target often struggle to treat complex conditions like cancer and neurodegenerative diseases. With more biological data and better algorithms, machine learning has become a useful tool to help develop drugs that work on multiple targets. Recently, the method of discovering drugs is moving away from the old idea of "one drug, one target" to a more complete system approach called multitarget DD. This change is because many diseases involve multiple genes, proteins, and pathways, so targeting just one is often insufficient. Designing drugs that hit several targets at once can improve treatment, decrease resistance, and be safer. This idea is part of systems pharmacology, which uses network biology, pharmacokinetics, and computer models to understand how drugs work in the body.[27] PTML, or Perturbation-Theory Machine Learning models, can predict multiple biological effects (such as activity, toxicity, and pharmacokinetics) simultaneously against different targets, including proteins, microbial strains, cell lines, laboratory animals, and humans, among others. It also considers information from various test conditions. Therefore, PTML modeling has been used in the discovery and design of molecules to fight microbial infections, neurological disorders, nanosystems for drug release or treatment, and various areas at the border of immunology and toxicology.[28] Therefore, PTML is a sophisticated computational modeling approach that combines perturbation theory principles with machine learning algorithms to analyze complex biological networks and molecular data.[29]

PTML models utilize perturbation operators derived from Markov linear indices to investigate local and global variations in Metabolic Reaction Networks (MRNs) across different organisms, which enables accurate prediction of network connectivity patterns and validation of metabolic models with high precision.[29] PTML integrates chemical descriptors, such as fragment-based topological indices and physicochemical properties, with experimental conditions to develop interpretable models capable of predicting biological activities and designing compounds with specific multitarget effects, including dual inhibitors for therapeutic applications.[30,31] Furthermore, PTML leverages graph-based descriptors and machine learning techniques like multilayer perceptrons (MLPs) to understand how molecular structures and experimental variations influence biological responses. This framework facilitates virtual screening and the in silico development of bioactive molecules, exemplified by its application in the design of versatile anticancer agents.[31] Overall, PTML provides a versatile platform that combines perturbation theory, structural descriptors, and machine learning to predict and optimize biological and chemical properties, advancing DD and systems biology research.[29−31]

Some work has been done on this topic: The model proposed by Kleandrova and Speck-Planche[32] integrates PTML via MLPs to predict multiprotein and multicell inhibitors targeting pancreatic cancer (PANC), using molecular descriptors from topological indices, physicochemical properties, and atom-based quadratic indices, achieving over 78% accuracy in classifying active compounds and enabling rational therapeutic design. Another work developed a PTML-MLP model predicting dual NET and SERT inhibitors from ChEMBL data, demonstrating high accuracy, robustness, and key structural features, such as reduced hydrophobicity and specific aromatic rings that guide DD for mood disorders.[31] Also, Diéguez-Santana et al.[29] introduced the CPTML model, which generalizes atom-based linear indices to Markov linear indices for analyzing complex metabolic networks across different organisms, including random and real networks. In addition, PTML was used to identify chemicals, like Linagliptin, Icariin, and Rolipram, as potential dual inhibitors of key inflammatory proteins, making it useful for developing broad anti-inflammatory treatments, including for COVID-19.[33] Another work included a multitask PTML model for predicting antibacterial activity against Gram-negative pathogens and safety profiles, which employed linear discriminant analysis and molecular fragments; an MLP-based PTML model for designing inhibitors against pathogenic parasites; a PTML model for virtual screening of antituberculosis agents targeting multiple strains; and a PTML model for designing drugs with pan-antiviral and anticytokine storm properties utilizing artificial neural networks, all integrating molecular topology with machine learning for multiend point and multitarget predictions in anti-infective DD.[34]

In summary, AI has transformed drug discovery by improving various stages through computational models such as RNNs,[35−37] VAEs,[38] GNNs,[39] transformers,[40,41] and MPNNs.[42,43] These models enable the generation of novel molecules by exploring chemical spaces based on properties like toxicity and binding affinity.[35−38,44] They also facilitate accurate predictions of molecular attributes and chemical reactions, improving drug screening and lead optimization via data analysis and pattern recognition.[40−43] AI's impact extends to drug target identification, clinical trial optimization, and personalized medicine, cementing its role in modern therapeutic development.[25]

NLP plays a key role in computational drug discovery, transforming both human language modeling and chemistry, which is central to drug development.[45,46] Just as human language uses tokens (words and subwords), chemistry is represented by sequences of amino acids, atoms, or chemical reactions,[46] enabling the application of NLP techniques like transformer models in chemical research.[47−50]

Transformers excel at capturing contextual relationships, making them effective for tasks like translation and summarization.[51] In chemistry, they are critical for protein structure prediction (e.g., AlphaFold2[52,53]) and reaction outcome prediction.[46] The integration of multimodal data, including

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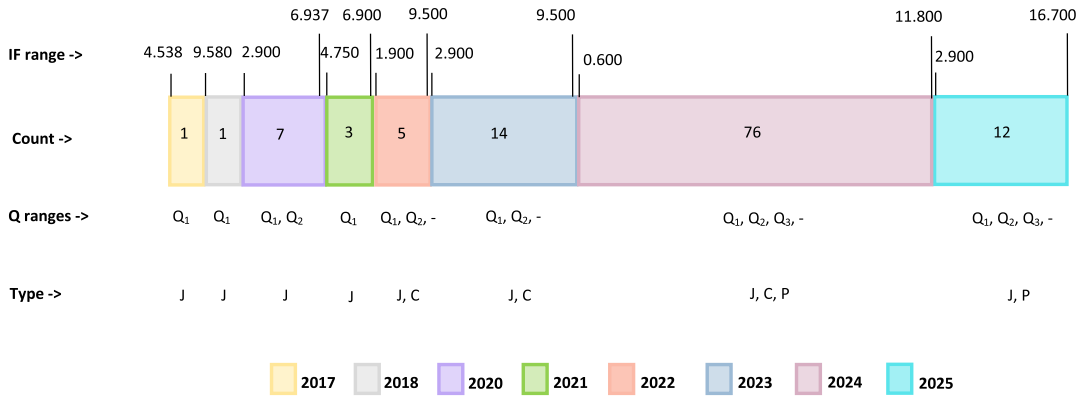

Figure 1. Overview of the studied journal (J), Conference (c), and preprints (P) articles based on impact factor (IF) range, count of articles, and Q ranges for each year.

chemical structures and human language (e.g., synthesis procedures), has further expanded NLP's potential, with LLMs like ChatGPT[54] being explored as tools for chemical reasoning and DD.[46]

SMILES, a chemical string used in drug discovery, represents molecular structures through ASCII characters, describing atoms, connectivity, bond order, and chirality.[55] This notation system is crucial for computational applications, including NLP.

The convergence of NLP and chemistry accelerates drug discovery by enabling efficient analysis of large chemical data sets, predicting molecular behaviors, and bridging chemical and natural language modeling.[50] Thus, NLP enhances our understanding of the "language of chemistry" and shapes pharmaceutical research and development.[46]

Drug discovery involves various branches aimed at improving disease treatment. A key focus is predicting DTI, which involves interactions with proteins or viruses.[56] However, DTI is not the only area of interest; DDI are also crucial for effective treatment.[57] DDI is closely related to ADR, where DDI examines drug interactions, and ADR focuses on harmful side effects, either from a single drug or multiple drugs in combination.[58]

The significance of computational drug discovery has led to surveys exploring the role of AI in this field. This survey reviews over 100 papers published from 2020 to 2025, focusing on DDI, DTI, and ADR extraction. Figure 1 highlights the progress in drug repurposing methods, while Table 3 lists the studied papers. Although existing reviews address these topics, they often focus on only one aspect—e.g., DDI[59−62] or DTI.[63] Some reviews like[64] critique the lack of structured categorization, while others limit themselves to machine learning, especially deep learning.[62,65] Notably, there are few studies on ADR.

In contrast, our survey covers the interconnected topics of DTI, ADR, and DDI. It includes a broader range of models, such as those using NLP techniques for biomedical text data sets and non-NLP models for chemical data sets. We categorize NLP-based models as "Record-based" and non-NLP models as "Structured-based", providing a more comprehensive view. This approach bridges gaps left by previous reviews, offering a thorough analysis of current research in DDI, DTI, and ADR extraction.

This survey systematically examines the use of AI methods in drug repurposing, excluding DTIs involving viruses, as guided by ref 66.

In this survey, we provide a background in Section 2 that defines ADR, DDI, and DTI. The next section is dedicated to databases and data sets in Section 3 used in the studied models. Next, we will have a review of some models in Section 4 and summing up all of the methods used in their structure, then, evaluation of models in Section 5. Furthermore, the challenges in Section 6 in the drug discovery field are summarized, and finally, we will have an outlook section in Section 7 to discuss the drug discovery opportunities and sum up the survey.

2. BACKGROUND

This section outlines the foundational concepts of DTI, DDI, and ADR. It also introduces key methodologies such as AI, machine learning, deep Learning, graph learning, and NLP, which are widely employed in drug repurposing research. The advantages, limitations, and future directions of each approach are briefly discussed. Expert readers may choose to skip this section and proceed directly to the subsequent parts of the paper. Additionally, we introduce AI models in the Supporting Information for interested readers.

2.1. Adverse Drug Reaction (ADR). Adverse drug events (ADEs) refer to unintended and undesired reactions to medications and have become more prevalent with the rise in the variety of drugs available worldwide since the 1950s.[67−69] Despite various safety and healthcare systems in place, medical professionals often report adverse events late, underscoring the need for systems that can extract necessary data from biomedical research and articles.[70] For instance, Thalidomide, used in the 1950s and 1960s to treat morning sickness during pregnancy, caused abnormalities in newborns, affecting over 10,000 cases across 17 countries.[71−74] Another example is the diet pill Fenfluramine, which was popular in the early 1980s but had adverse effects on the heart valves and rhythm of hundreds of thousands of people in the United States.[74−76]

ADRs, a subset of ADEs, are harmful side effects that occur when medications are taken at the recommended dose, including lack of efficacy, that occur during their use for prevention, diagnosis, or treatment of illnesses, or for modifying physiological functions.[77−81] Despite advancements in medicine over the past three decades, the rate of ADRs has remained consistent.[80] As laboratory samples are small, and initial clinical drug trials have limited observation time and scope, many potential adverse reactions go undetected.[74] These reactions contribute to 5−10% of hospital admissions globally and are a leading cause of death worldwide. In Australia, ADRs account for 2−4% of hospital admissions and are a significant source of patient illness.[80] Also, 4.2−30% of hospital admissions in the USA and Canada, as well as 2.5−10.6% of hospital admissions in

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Table 1. Datasets Used in the Studied Articles

type	data set	models
ADR	FDA drug label Link	173
	ADE-corpus-v2[174] Link	142
DDI	DDI-Extraction 2013	175,176,177,178,177,179,96,151,70,95,180
	TAC 2018	95
	TAC 2019	101,95
	Deng[181]	182,181,183
	PK DDI[184]	101,180
	CHEMDNER[185]	96
	ChChMiner Link	186
	ZhangDDI Link	186
	OGB-biokg[187]	188
	KEGG-drug[189]	188
DTI	Luo et al.[190]	192,193,194,195,196,190,197
	BIOSNAP[198]	199,148,200,201,202,203,204,205,206,207,208
	DAVIS	209,210,199,211,212,200,213,214,215,216,217,218,219,220,196,221,206,163,208,222,223
	KIBA	210,224,212,213,215,216,217,218,219,211,220,221,196,163,222
	DUD-E[225,226]	227
	Human	148,201,203,214,228,204,202,205,207,227
	DTPKS[229]	230
	Data setKS	230
	Data setKSE	230
	DRKG[231]	230
	LINCS L1000[232]	230
	OncologyScreen[233]	234
	C. elegans[235]	214,205,228,208
	Wang[236]	196
	Yamanishi[237,238]	118,194
	Zheng[239]	193
	PrimeKG (DS1, DS2, DS3)[240]	241
	HIV Drug Interaction[242]	243
	Qmugs[244]	212
	CASF-2016[245]	212
	DUD-E[225,226]	212
	DrugProt[246]	247
	248	224
		210
	249	249

Europe, are caused by ADRs. In the US and Australia, the estimated costs of ADEs and ADR management are annually 30.1−130B US dollars and 4.83−9.00B Australian dollars per year, respectively.[82−84] In 2021 alone, China reported 597,000 new and severe ADEs, 11% of which were serious, posing a significant threat to patients' lives.[74]

2.2. Drug−Drug Interaction (DDI). In the US, DDIs result in approximately 74,000 emergency room visits and 195,000 hospitalizations annually.[85,86] A 2007 study analyzing 23 global clinical studies found that DDIs accounted for 0.054% of emergency room visits, 0.57% of hospital admissions, and 0.12% of rehospitalizations.[86,87] Between 1988 and 1994, 39.1% of Americans took prescription medications; this figure increased to 47.5% between 2007 and 2010.[86,88] DDIs affect 20−40% of patients and are a frequent cause of ADRs, particularly in the elderly due to polytherapy.[89−92] Polytherapy complicates treatment and increases the risk of clinically significant drug interactions, which may lead to ADRs and alter clinical efficacy.[86,93,94]

DDIs are classified into two main categories:[92,95]

- Pharmacokinetic (PK): Involves absorption, distribution, metabolism, and excretion, potentially causing treatment failure or toxicity.
- Pharmacodynamic (PD): Includes effects on receptor function, interference with biological or physiological control processes, and additive or opposing pharmacological effects.

DDI extraction identifies and classifies drug interactions within a given sentence.[95,96] Text mining plays a vital role in medical science and healthcare systems by extracting valuable information from unstructured text.[97−101] However, traditional methods like pattern-based and feature-based models are limited in capturing textual context and are time-consuming.[95]

Although DDIs have received less attention than gene−gene or protein−protein interactions,[70] events like SemEval 2013-Task 9 have increased interest in the field.[70,102,103] Machine learning approaches show promise, but deep learning techniques such as CNNs and RNNs provide greater flexibility and performance for large NLP data sets.[70,104−107] By utilizing these methods, studies aim to construct databases of known DDIs by extracting novel findings from scientific articles.[70]

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Table 2. Overview of SE Datasets

type	models	databases/web sites
ADR	250,[251,252],142,74,253,252,254	MIMIC-III[256]
		Twitter
		Health Web sites and social media
		MedDRA Link
		PubMed[257]
		ChEMBL[258]
		China Pharmaceutical Information Query Platform Link
		Commonwealth Bank Health Society (CBHS) Link
		SIDER[259]
		DrugBank[143] Link
DDI	260,179,261,262,263,264,265,186,266,267,268,269,175,270,271,180	DrugBank[143]
		TWOSIDES[272]
		PubMed[257]
		ChemProt[273]
		DDIMDL Link
		DAS-DDI Link
		KEGG[274]
		Offside[272]
		STITCH[275]
		PubChem[276]
		14 data sets from[277]
DTI	278,279,234,247,192,280,220,204,281,282,216,203,214,201,283,200,212,224,148,284,285,286,287,288,206,207,211	DrugBank
		UniProt[140]
		MalaCard[289]
		BindingDB[146]
		HPRD[290]
		CTD[291]
		SIDER[259]
		KEGG[274]
		sc-PDB[292]
		Protein Data Bank (PDB) Link
		Binding MOAD database[293]
		PDBbind database[294]
		2P2I[295]
		GDSC[296]
		COSMIC[297]
		PubChem[276]
		pdbBIND[294]
		GPCR[298]
		ChEMBL[258]
		PharmGKB[299]

2.3. Drug−Target Interaction (DTI). The term "drug repurposing" was introduced in 2004 to address the limitations of traditional drug discovery methods,[108] though its origins date back to the 1950s.[109] This approach focuses on identifying new uses for existing and approved drugs.[110] Drug repurposing offers significant potential, especially given the high costs and long timelines of developing new drugs.[110,111] Research in this field has grown substantially due to advances in biological sciences and interdisciplinary fields such as bioinformatics, with increasing interest since 2011.[112] For example, "Sildenafil citrate" initially developed in 1980 for treating chest pain due to restricted blood flow,[113] was ineffective in clinical trials, halting its market introduction. However, reports of a side effect—prolonged erections led Pfizer to re-evaluate the drug in 1998. After trials with more than 3700 male volunteers showed positive results, Sildenafil was rebranded as "Viagra" to treat sexual disorders, becoming a best-selling drug with annual sales exceeding 1.5 billion dollars.[114,115]

One of the most important steps in drug discovery is accurately predicting DTIs.[116,117] So, prediction using computational techniques is vital for drug repurposing, as it is more cost-effective and time-efficient than biochemical experimental methods.[118] Drug developers screen compounds for interactions with targets showing desirable biological activities.[117] DTI can identify new drugs for a specific target or uncover new targets and applications for known drugs.[119] However, identifying DTIs through experiments typically takes 2−3 years and incurs significant costs.[116,120−122] Several computational techniques are created for DTI prediction, and a crucial problem is how to predict it accurately and quickly.[119] Consequently, as data on drugs, targets, and interactions continues to grow, various computational methods have been

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developed to predict potential DTIs, enhancing the efficiency of drug discovery.[121]

Traditional methods for predicting DTIs are primarily categorized into structure-based and ligand-based approaches. Structure-based methods often utilize molecular docking tools to identify new ligands for proteins with known 3D structures or to discover new protein targets for existing drugs. In contrast, ligand-based methods typically employ pharmacophore searches and similarity assessments based on 3D shapes, substructures, and physicochemical properties.[119,123−126]

Public databases enhance the effectiveness of computational strategies for DTI prediction.[127] Recently, machine learning methods have gained popularity for identifying potential drug targets, assuming similar drugs share similar targets.[128,129] These methods often utilize kernel-based approaches, which map various drug−drug and target−target similarity matrices to DTI labels.[128,129] A new trend is the use of graph-based methods, which improve upon kernel-based methods by better representing the interactive relationships between drugs and targets through vertices and edges and extracting topological features from DTI networks for DTI predictions.[118,130] Also, deep learning methods have recently been applied extensively to DTI prediction and have shown notable performance gains.[64,117,121]

3. DATABASES AND DATA SETS

In the field of computational drug discovery, several common data sets are frequently used. These data sets typically include designated training and test sets. However, some researchers opt to use databases to create their custom data sets, which we will refer to as "SE" in this context.

Tables 1 and 2 present the common data sets and databases employed by researchers, respectively.

3.1. Databases. *3.1.1. UniProt.* The UniProt database[1] is a pivotal resource for protein sequence and functional information, boasting a capacity of 80 million sequences, which has doubled recently. Key features include the distinction between UniProtKB/Swiss-Prot (manually curated)[131,132] and UniProtKB/TrEMBL (unreviewed)[133,134] sections, as well as the introduction of a proteome identifier for unique organism assemblies.[135] Recent enhancements encompass a redesigned Web site focused on user experience, an annotation score to evaluate protein characterization, and automatic annotation systems like UniRule[136] and SAAS[137] to manage the entry of new sequences. With extensive cross-referencing to over 150 other databases and continuous effort toward high-quality curation based on literature, UniProt supports scientific discovery and offers valuable data for a broad spectrum of research fields.[138−140]

3.1.2. PubMed. PubMed is a free archive of biomedical and life sciences journal literature and is considered a reference for biomedical publications.[141] Some publications require licensed access but still provide a free version of the corresponding abstract. Therefore, PubMed was used as the main data source for literature monitoring to build the system.[142]

3.1.3. DrugBank. The DrugBank[2], introduced in 2006, served as a pioneering resource aimed at compiling comprehensive drug-related data, including information on FDA-approved drugs, investigational drugs, and their interactions.[143] This initial release focused on providing a centralized platform for drug data that included various pharmacological properties, biochemical pathways, and DTIs, facilitating research and education in pharmacology and related fields.[144] DrugBank 6.0, launched in 2024, significantly increased its resources such as FDA-approved drugs, investigational drugs, and DDIs, which have risen from 2646 to 4,563, from 3394 to 6,231, and from 365,984 to over 1.4M, respectively; it also features detailed pathways for drug mechanisms and improved accessibility through a refined user interface.[144] DrugBank 5.0, 2018 version, reported a 300% increase in investigational drugs and nearly 600% rise in DDIs, alongside new data sets in pharmacometabolomics and pharmacotranscriptomics, aiming to enhance the quality of drug information and support pharmacology research and education.[143]

3.1.4. BindingDB. BindingDB[3] is a comprehensive and publicly accessible database that has expanded significantly since its inception in 2001, now housing approximately 2.9 million binding measurements related to small molecules and proteins, making it essential for research in drug discovery and cheminformatics.[145−147] Its advanced search capabilities, user-friendly interface, and support for both manual curation and user contributions enhance its role as a vital resource for medicinal and computational chemistry, facilitating the development of new therapeutics through improved access to binding affinity data.[146]

3.1.5. DDInter 2.0. DDInter 2.0[4], designed to enhance clinical decision-making and patient safety, expands its predecessor's scope by covering 2310 drugs and 302,516 DDI records. It also includes 857 Drug−Food Interactions (DFIs), 8359 Drug−Disease Interactions (DDSIs), and 6033 Therapeutic Duplications, along with 8398 high-quality mechanism descriptions and management recommendations.[148]

The redesigned interface offers advanced filtering for mechanism- and risk-based screening, improving accessibility for healthcare providers. Integration with ADMET 3.0 enhances predictive capabilities, including Cytochrome P450 interactions.[149,150] DDInter 2.0 provides a comprehensive, freely accessible platform for managing drug interactions and improving patient outcomes.[148]

3.2. Data Sets. This section offers an overview of the data sets employed in the papers being reviewed. Certain studies may utilize either the entirety or a segment of the data sets listed below. We present the general details of each data set here. The Supporting Information includes specifics on how each reviewed paper managed its respective data set.

3.2.1. DDI-Extraction 2013. One of the well-known data sets used in DDI tasks is the DDI-Extraction 2013 corpus, an updated version of the Extraction 2011 data set provided by SemEval DDI 2013.[95,151] This data set is a collection of information on drug interactions and substances, derived from two different sources: DrugBank and PubMed article abstracts that are stored in MEDLINE.[70] The DrugBank subset comprises 730 documents, while the MEDLINE subset contains 175 abstracts for DDI extraction, further divided into training and testing sets of 714 and 191 documents, respectively.[95] Additionally, it includes 18,502 manually annotated drug entities and 5028 DDIs.[70]

3.2.2. TAC 2018 and 2019. TAC2018[5] and TAC2019[6] are curated data sets by the US Food and Drug Administration (FDA) and the National Library of Medicine (NLM),[152] designed to facilitate DDI research. TAC 2018 includes 325 Structured Product Labels (SPLs), divided into 22 training and 57 testing labels, categorizing DDIs into PK, PD, and Unspecified (U).[152,153] It also incorporates diverse data, such as articles and social media content.[95,154] TAC 2019 contains 400 SPLs in XML format, with 211 training and 81 testing labels, adding a "none" category for no DDI.[101,153] It includes four

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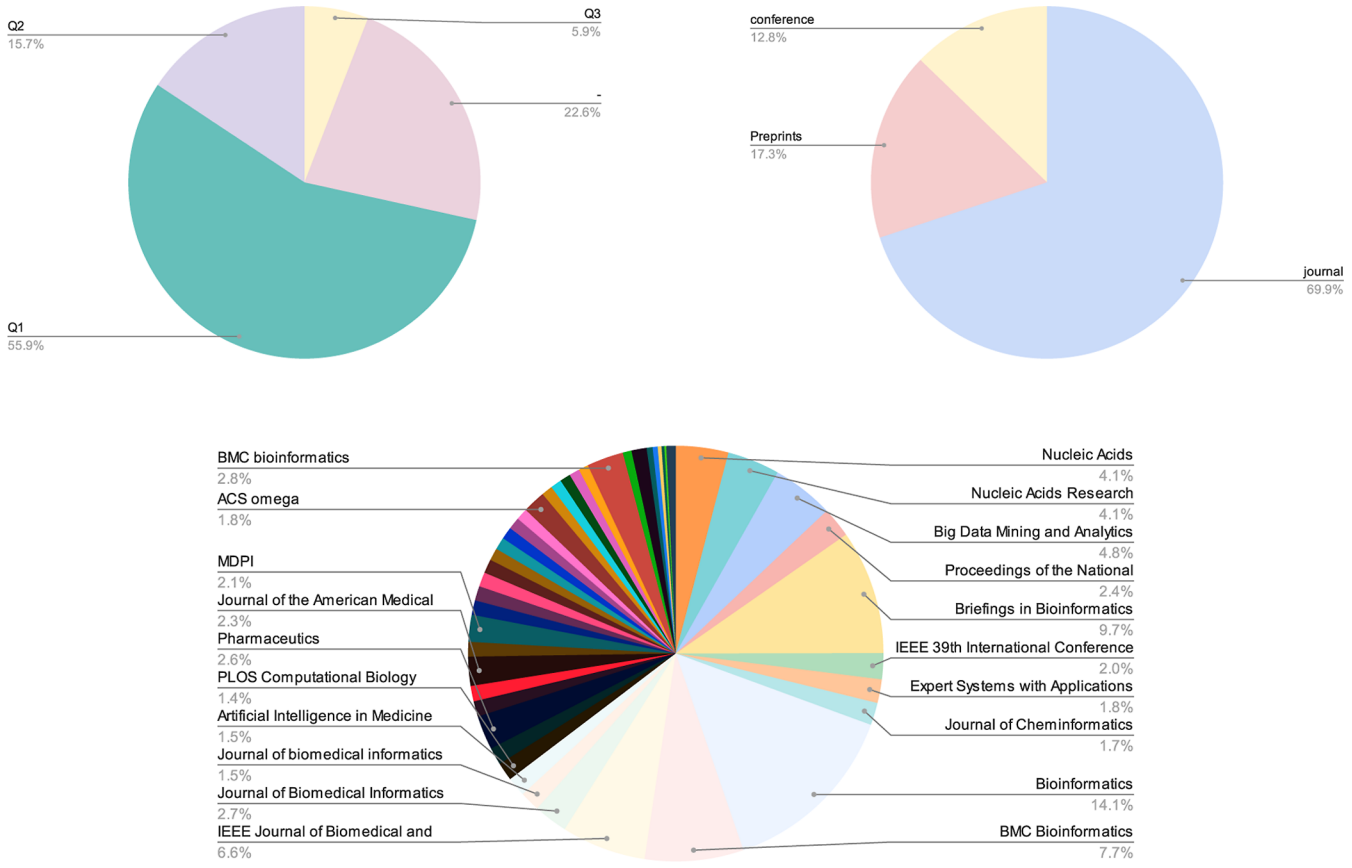

Figure 2. Percentage of articles by source name, ranks, and types.

training data sets, with 22 FDA labels fully annotated per TAC 2018 guidelines, plus reannotated labels for broader DDI classification.[95,101]

3.2.3. ADE-Corpus-V2. ADE-Corpus-V2 contains more than 20,000 sentences extracted from PubMed and prelabeled for drug-AE causality classification.[142] The ADE-Corpus-V2 is a specialized data set designed for pharmacovigilance research, focusing on ADE identification and extraction. Derived from medical case reports and summaries, the meticulously annotated corpus contains rich information on drug usage and associated ADEs. The data set comprises 4271 documents, covering 5063 drugs and 6821 ADE instances. ADE-Corpus-V2 is a valuable resource for developing and evaluating NLP models in drug safety research.[155]

3.2.4. CMED. Accurate medication history is essential for healthcare, but critical details often appear only in unstructured clinical notes, making analysis challenging.[156] Prior research classifies medication changes without full contextual labeling, a gap addressed by the Contextualized Medication Event Data set (CMED).[157]

CMED enhances medication timeline generation and reconciliation by annotating 9013 medication mentions from 500 clinical notes.[157−159] It categorizes events by Action, Temporality, Certainty, and Actor.[157,160] Developed using clinical notes from the 2014 i2b2/UTHealth NLP shared task, CMED's 2021 release included annotation guidelines and baseline assessments.[157,161]

3.2.5. DAVIS. The DAVIS data set provides experimental results on how kinase proteins interact with their inhibitors, including measurements called dissociation constants (K_d values). This data set includes information on the strength of interactions for 442 target proteins and 68 chemical compounds, with K_d values ranging from 5.0 to 10.8.[162,163]

The Davis data set contains pairs of kinase proteins and their respective inhibitors with experimentally determined dissociation constant (K_d) values. The data set comprises 442 proteins and 68 ligands, consisting of a total of 30,056 samples. The K_d values were transformed into pK_d values using the equation: pK_d = $-\log_{10}(K_d/1 \times 10^9)$.[164]

3.2.6. KIBA. The KIBA data set assesses how well drugs bind to their targets using a scoring system called the KIBA score, which is based on the analysis of related activity metrics. The KIBA data set features 467 target proteins and a large collection of 52,498 small drug molecules. After filtering, it includes 2111 distinct drug molecules and 229 distinct target proteins.[163,165] The KIBA data set comprises scores from different sources (K_i, K_d, and IC50) combined using the KIBA approach. Initially, the data set contained 467 proteins and 52,498 ligands, but was filtered to keep only drugs and targets with at least 10 samples. The final data set has 229 unique proteins and 2111 unique ligands, with a total of 118,254 samples.[165]

3.2.7. LINCS. NCBI GEO provided LINCS data for a landmark gene set of 978 genes (accessions GSE92742 and GSE70138), which included expression data from 83 cell types treated with 21,280 chemicals at varying doses and periods, 19,692 of which were matched to SMILES codes.[166,167] The expression data were analyzed using linear regression versus compound doses, resulting in pooled Z scores for all cell types and treatment periods that were subsequently discretized. For predictive modeling, each compound's transcriptional profile was coupled with a less comparable decoy profile, ensuring that

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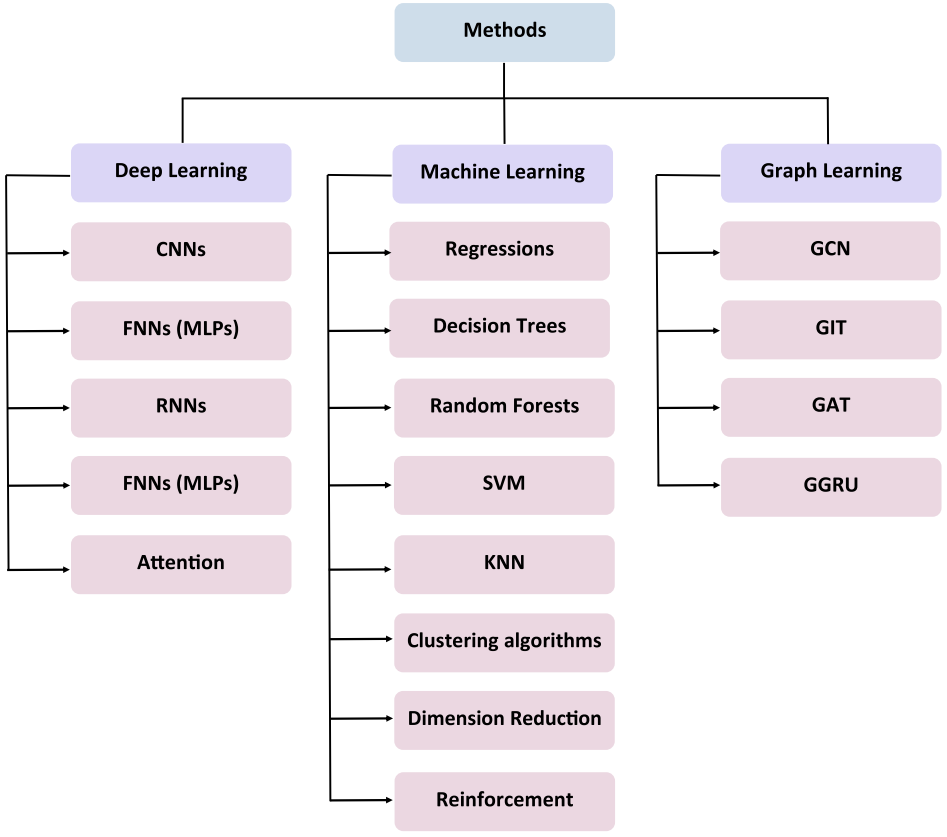

Figure 3. Overview of the general models for each method selected from papers.

the training and testing data sets did not contain any overlapping compounds.[168]

3.2.8. Human. The 2001 draft human genome sequence provided a foundational human data set, covering about 94% of the genome.[169] It is estimated that 30,000−40,000 protein-coding genes, with alternative splicing greatly increasing protein diversity.[170] The data set revealed that nearly half of the genome consists of transposable elements, showed segmental duplications near centromeres and telomeres, and suggested bacterial horizontal gene transfer in evolution. It also highlighted higher mutation rates in males and distinct recombination patterns, and identified over 1.4 million SNPs.[171] Using a hierarchical shotgun sequencing approach, the project ensured open data access, accelerating genomic research and future advancements.[172]

Some self-extracted (SE) data sets refer to collected data sets from different databases or Web sites and Table 2 summarizes them.

4. METHODS

This systematic literature review was conducted, adhering to the established guidelines outlined in ref 66. To gather relevant conference and journal papers, our strategy involved screening the Google Scholar search engine for English-language publications, primarily focusing on papers published from 2020 to 2025, with a strong emphasis on those in 2024. These articles are extracted from different journals, conferences, and preprint versions of arXiv[7] and BioRxive[8] (statistics about the articles are shown in Figure 1 and Figure 2), etc. The keywords utilized in the search included: "Drug−Drug Interactions", "Drug−Target Interactions", "DDI extraction", "DTI prediction", "Deep neural DDIs", "Machine learning DDIs", "Machine learning DTIs", "Adverse drug reactions", "Adverse drug events", and "ADRs extraction".

As previously discussed, the methods were categorized based on the employed models (Figure 3). Four categories were considered: Deep Learning models (i.e., CNN-based and RNN-based), Machine Learning models (regression and RF (Random Forest)), graph learning models (GCN) and hybrid models, which integrated deep, machine and graph approaches.

To illustrate the functionality of various approaches, a concise overview of several existing DDIs, DTIs, and ADRs prediction models will be provided. These examples serve to elucidate the diverse methodologies employed within the field. For a comprehensive analysis, including detailed information on over 100 relevant publications, refer to the Table 3. This table offers a comprehensive compilation of the literature, enabling a thorough understanding of the current state-of-the-art in computational drug discovery.

4.1. A Few Examples for ADR Extraction Model. First, it is important to clarify that this review specifically focuses on ADE-related publications that address ADRs. Consequently, to respect the authors' original terminology and perspective, we may use "ADE" interchangeably with "ADR" in certain instances. This will ensure consistency with the source material while maintaining clarity regarding the context of ADR prediction and analysis.

ADE extraction from social media involves three components: a RoBERTa-based classifier, a span extractor identifying ADE mentions in tweets, and a normalizer mapping them to MedDRA concepts.[251] FDA drug label ADE detection employs CRF, biLSTM + CRF, and BERT models, with ensembles improving accuracy. These models predict OSE ADE, non-OSE ADE, and Not ADE Candidate categories.[173] Predicate-ADR

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Table 3. All Methods

model	output	approach	year	NLP	E2E	encoder	decoder	loss func	ratio pos2neg
250	ADR(c)	deep L	2020	√	√	for embedding one of the Glove, w2v, FastText, and BERT, BiLSTM	attention, GRU, MLP	cross-entropy	1:2
173	ADR(c)	deep L	2020	√	×	biLSTM, BioBERT	NB	-	-
251	ADR(c)	deep L	2021	√	√	BERT, GRU, MLP	RoBERTa	cross-entropy	-
142	ADR(c)	deep L	2022	√	×	Aho-corasick, BERTs	BERTs, fuzzy matching	-	-
74	ADR (c)	deep L	2023	√	×	ALBERT, BiLSTM	CRF	-	-
253	ADR(c)	hybrid	2024	×	√	w2v, n2v	ML classifiers (logistic regression, RF, KNN, SVM, XGBoost)	-	-
254	ADR(b)	hybrid	2024	×	×	DistMult,[302] HolE,[303] CNN	FC (one of: LR, RF, KNN, DT, NB, CNN, GBDT)	cross-entropy	12435/119,131 = 0.14
304	ADR(b)	-	2024	×	√	-	-	-	1:7.8
255	ADR(b)	deep L	2025	×	×	WAEs	FNN	Huber	-
260	DDI(c)	deep L	2018	√	×	PCA, DNN	SSP	cross-entropy	-
95	DDI(c)	deep L	2020	√	×	BioBERT	BioBERT, BiLSTM	-	1:5.9,1:4.9
183	DDI(n)	deep L	2020	×	×	Jaccard similarity, CNN	MLP	cross-entropy	-
181	DDI (b)	deep L	2020	√	×	Jaccard similarity, VGG16	MLP	cross-entropy	-
70	DDI(c)	deep L	2022	√	×	w2v, attention, GRU	RNN	cross-entropy	-
151	DDI (c)	deep L	2022	√	×	BiGRU, CNN, Max pooling, attention pooling	MLP	cross-entropy	-
101	DDI(n)	deep L	2023	√	×	BERT	BERT	-	-
96	DDI(b)	deep L	2023	√	√	BioBERT, w2v, d2v, TF-IDF, N-gram	various Machine Learning classifiers: Logistic Regression, SVM.	cross-entropy	-
182	DDI(n)	deep L	2023	×	×	Jaccard similarity, CNN	MLP	focal	-
261	DDI(b)	deep L	2023	×	√	GNN, ESPF and k-mer, attention	CASTER	cross-entropy	1:1
179	DDI(c)	deep L	2024	√	×	BERT	SVM, KNN, RF	-	-
262	DDI(c)	deep L	2024	×	×	attention or GAT (for d) and autoencoder (for binding), PCA, GCN	MLP	cross-entropy	-
177	DDI(c)	hybrid	2024	√	×	GloVe, BiLSTM, Attention, GGNN,UGC, CNN	linear layer	focal	-
263	DDI(n)	hybrid	2024	√	×	GCN,GAT, Jaccard similarity	average pooling layer, sigmoid	cross-entropy	-
264	DDI(n)	deep L	2024	√	√	attention, Pykeen deep learning framework, TransE algorithm, convolutional module	MLP	cross-entropy	
265	DDI(n)	hybrid	2024	×	×	knowledge graph, GNN	MLP	cross-entropy	-
186	DDI(b)	hybrid	2024	×		Tanimoto coefficient, RDkit, attention, RDkit, GAT, GCN	attention	cross-entropy	-
266	DDI(n)	hybrid	2024	×	×	DICnet module, se GNN, attention	MLP	multitask loss function	-
188	DDI(b)	hybrid	2024	×	√	KG2ECapsule, CapsGNN, CNN	MLP	cross-entropy	1:1
178	DDI(c)	deep L	2024	√	√	BioBERT, attention, LM, BIOES tagging, DNER module	MLP	cross-entropy	-
267	DDI(b)	deep L	2024	×	×	GAT, attention, GNN	sigmoid function	cross-entropy	-
175	DDI(c)	deep L	2024	√	×	Bert, BiLSTM, Scifive	MLP	cross-entropy	-
176	DDI(c)	deep L	2024	√	×	SubAGCN, attention, BiLSTM, CNN	Softmax layer	multifocal	-
177	DDI(c)	hybrid	2024	×	×	GLoVe, BiLSTM, attention, CDM, GCN	linear layer	Focal, margin	-
268	DDI(b)	hybrid	2024	×	×	GraphSAGE, Node2Vec, GNN, attention	MLP	cross-entropy	1:1
269	DDI(b)	hybrid	2025	×	×	attention, Mean shift algorithm, Conditional Domain Adversarial Network (CDAN), GAT	MLP	cross-entropy	1:1

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Table 3. continued

model	output	approach	year	NLP	E2E	encoder	decoder	loss func	ratio pos2neg
270	DDI(b)	hybrid	2025	×	√	BRICS alg., GAT, HDN Blocks, attention	attention	cross-entropy	1:1
271	DDI(b)	hybrid	2025	×	×	attention, PCA, NNPS,[305] BERT	MLP	cross-entropy	-
180	DDI(b)	deep L	2025	√	×	LLMs	-	-	1:1
190	DTI(n)	machine L	2017	×	×	DCA	inductive Matrix completion	-	-
206	DTI(n)	deep L	2020	×	√	ChemBERTa (for chemical compounds), ProtBERT (for amino acid sequences)	MLP	SmoothL1	-
288	DTI(n)	deep L	2021	√ (inspired)	√	Ngram, CNN	MLP	-	-
118	DTI(b)	hybrid	2021	×	×	BiNE,[306] heuristic algorithm,path-based heterogeneous information	RF	cross-entropy	-
163	DTI(n)	deep L	2022	×	√	GRU (for p sequence), GNN (for d melcule)	MLP	MSE	-
164	DTI(n)	deep L	2022	×	×	one-hot encoding, CNN	MLP	MSE	-
227	DTI(b)	Graph	2022	√ (inspired)	√	GCNN with an attention pooling mechanism, attention	MLP	cross-entropy	3974731218 = 10.88
222	DTI(n)	hybrid	2023	×	×	GNNs(GAT, GCN, GIN, GINE, GMF)	MLP	MSE	-
278	DTI(n)	hybrid	2023	×	×	Cosine similarity, smith waterman algorithm, VGAE, GAE	RF	KL divergence, reconstruction error	-
279	DTI(n)	hybrid	2023	×	×	node2Vec, CNN	MLP	cross-entropy, triplet	-
207	DTI(n)	deep L	2023	×	×	GCN, LLM, attention	MLP	cross-entropy	BindingDB: 1.41(d),7.87(p); BioSNAP: 3.07(d), 6.34(p); Human: 1.23(d), 1.68 (p)
230	DTI(b)	hybrid	2023	×	√	attention, ConvE, GAT, GRU	MLP	cross-rnttopy	1:2
234	DTI(n)	hybrid	2023	×	×	n2v, attention, Dot product layer	MLP	cross-entropy, Lsynergy, LToxic	-
208	DTI(b)	deep L	2023	×	×	CNN, attention, k-gram	MLP	cross-entropy	0.84:1; 0.93:1; 0.98:1
223	DTA(n)	deep L	2023	×	×	RDKit, BiLSTM, attention, GIN	MLP	MSE	-
197	DTI(b)	deep L	2023	×	√	L-DLE, Jaccard similarity, attention	MLP	contrastive loss	1:1
196	DTI(c)	deep L	2024	×	×	CNN and n2v, attention	MLP	triplet	-
195	DTI(b)	graph L	2024	×	√	LM (ESM-2 and CHemBERT), GAT	MLP	cross-entropy	1:10
247	DTI(b)	deep L	2024	√	×	Pubtator, BERT	BERT	focal	-
205	DTI (n)	deep L	2024	×	√	BCM, CFM, CNN, attention	maximum pooling, MLP	cross-entropy	1:1
194	DTI (n)	machine L	2024	×	×	d similarity matrix, Similarity Selection	similarity matrix, random walk	-	1:1
193	DTI (n)	hybrid	2024	×	×	BIONIC,[307] attention, Jaccard similarity, GCN	MLP	cross-entropy	1:1, 1:5, 1:10 on all data sets
192	DTI (n)	hybrid	2024	×	×	Jaccard (for d), Tanimoto coefficient (for structures), Deepwalk, GraphSAGE	RF	cross-entropy	-
241	DTI (n)	deep L	2024	×	×	Attribute Masking, Average Pooling, attention, ComplEx embedding, GraphSAGE	MLP	focal, cross-entropy	-
243	DTI(n)	hybrid	2024	×	×	MLP, BPE, ChemBERT	MLP	cross-entropy	-
280	DTI(n)	deep L	2024	×	×	graph attention, latent information	MLP	cross-entropy, Kullback–Leibler divergence	-
220	DTI(n)	hybrid	2024	×	×	one-hot encoding, GIN, CNN, attention	MLP, max pooling	MSE, RWing[308]	-
204	DTI(n)	hybrid	2024	×	×	GCN, CNN, attention	MLP	cross-entropy	1:1
281	DTI(n)	machine L	2024	×	×	SVM	SVM	-	-
228	DTI(n)	hybrid	2024	×	√	PCA, Cosine similarity, GAT, attention	MLP	MSE	1:1
221	DTI(n)	deep L	2024	×	×	CNN, BiLSTM	MLP	MSE	

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Table 3. continued

model	output	approach	year	NLP	E2E	encoder	decoder	loss func	ratio pos2neg
282	DTI(n)	machine L	2024	√	×	UMAP, CHEMBERT, BiGRU	regression	MAE, MSE, RMSE, RMSLE	
219	DT(n)	hybrid	2024	×	×	GVP, GIN, attention	MLP	MSE	-
309	DTI(n)	hybrid	2024	×	×	InfoGraph, CPCProt, Tanimoto coefficient, GCN, attention	sigmoid	MSE	-
310	DTI(n)	hybrid	2024	×	×	w2v, attention, GCN, random walk	MLP	cross-entropy	
218	DTI(n)	hybrid	2024	×	√	GCN, Fusion module, CNN, attention	MLP	MSE	-
217	DTI(n)	hybrid	2024	×	√	Morgan fingerprint, CNN, GVP, GNN, attention	MLP	MSE	-
216	DTI(n)	deep L	2024	×	×	MACCS, CNN, attention	MLP	MSE	-
212	DTI(n)	deep L	2024	×	×	ESM-fold, CNN, attention	MLP	cross-entropy, MSE	-
215	DTI(n)	deep L	2024	×	×	GCN, cross-scale	MLP	contrastive loss, MSE	-
203	DTI(n)	hybrid	2024	×	×	CNN, GNN, attention	MLP	cross-entropy	0.725 (binding), 1.014 (BioSNAP), 1 (Human)
214	DTI(b)	hybrid	2024	×	×	VGNAE, GCN, Hierarchical Graph Pooling with Structure Learning (HGP-SP), Fusion module	MLP	cross-entropy	1:2.5
213	DTI(n)	deep L	2024	×	×	VAE, GatedCNN, attention	MLP	MSE	-
201	DTI(n)	deep L	2024	×	√	GCN, ACmix, attention, BiIN	MLP	cross-entropy	1:2
283	DTI(n)	hybrid	2024	×	×	TAPEtokenizer, BERT, HAKE, GAT, cosine similarity	NIMC	contrastive loss, cross-entropy, triplet	1:all
200	DTI(b)	deep L	2024	×	×	ChemBERTa, ProtBERT	MLP, GeLU	cross-entropy	-
247	DTI(b)	deep L	2024	×	×	BERTs	MLP	cross-entropy	
224	DTI(n)	hybrid	2024	×	×	GCN, Attention, PLM, ChemBERTa	cross-attention	-	-
191	DTI(b)	hybrid	2024	×	×	3-g embedding, GNN, attention	MLP	cross-entropy	
148	DTI(b)	hybrid	2024	×	×	SELFormer, Saprot, SVM, RF, attention	MLP	cross-entropy	1:1
199	DTI(n)	hybrid	2025	×	√	GCN, attention, ChemBERTa	MLP	cross-entropy	-
210	DTI(n)	deep L	2025	×	√	BiGRU, fusion module, CNN, attention	MLP	MSE	-
284	DTI(b)	hybrid	2025	×	×	MLPS algorithm, attention, GCN	MLP	cross-entropy	15,250/17,341 = 0.879
249	DTI(n)	deep L	2025	×	×	attention, GNN	MLP	cross-entropy	1:1
285	DTI(b)	hybrid	2025	×	×	Self-supervised Learning, HGCN, GCN, attention	attention fusion, GCN	BPR	-
286	DTI(b)	hybrid	2025	×	×	Random Walk, CNN, BiAN (BiLSTM with attention)	MLP	cross-entropy	1:5
287	DTI(b)	hybrid	2025	×	×	USE, GCN, CNN, RNN, RNN	MLP, Logistic regression	-	-
209	DTI(b)	hybrid	2025	×	×	CNN, attention, BFIM, SFM	MLP	-	-
211	DTI(b)	hybrid	2025	×	×	CharVec, CNN	MLP	MSE	1:1
202	DTI(b)	hybrid	2025	√	×	LLMs (MoLFormer (4 d), ProtT5 (4 p)), GNN	MLP	cross-entropy	16,463/19,998 = 0.968

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Table 4a. Evaluation of Studied Models (Accuracy, *P*, *R*, *F*1, ROC-AUC, PR-AUC)

output	model	accuracy	*P*	*R*	*F*1	ROC-AUC	PR-AUC
ADR	250	-	micro: 0.9455	micro: 0.9429	micro: 0.9442	-	-
			macro: 0.9377	macro: 0.9407	macro: 0.9379		
	173	-	0.8046 (CRF)	0.7879 (CRF)	0.7961 (CRF)	-	-
			0.8263 (BiLSTM-CRF)	0.8327 (BiLSTM-CRF)	0.8295 (BiLSTM-CRF)		
			0.7689 (BioBERT)	0.8345 (BioBERT)	0.8004 (BioBERT)		
	251	-	0.432 (GloVe)	0.171 (GloVe)	0.245 (GloVe)	-	-
			0.571 (w2v)	0.182 (w2v)	0.276 (w2v)		
			0.741 (FastText)	0.192 (FastText)	0.304 (FastText)		
			0.785 (BERT)	0.200 (BERT)	0.319 (BERT)		
	142	-	max: 0.95 (PubmedBert)	max: 0.93 (UMLSBERT and BioBERT)	Max: 0.93 (BioBERT SciBERT and Bio-Clinical Bert)	-	-
	74	-	0.8988	92.55	91.19	-	-
	253	0.8332 (RF)	0.8100 (RF)	0.8709 (RF)	0.8391 (RF)	0.9079 (RF)	-
		0.8148 (KNN)	0.7591 (KNN)	0.9243 (KNN)	0.8332 (KNN)	0.8925 (KNN)	
		0.8380 (LR)	0.8202 (LR)	0.8663 (LR)	0.8423 (LR)	0.9049 (LR)	
		0.8428 (SVM)	0.8094 (SVM)	0.8976 (SVM)	0.8509 (SVM)	0.9115 (SVM)	
		0.8443 (XGB)	0.8390 (XGB)	0.8532 (XGB)	0.8454 (XGB)	0.9157 (XGB)	
	254	0.886	0.867	0.914	0.891	0.959	-
	255	0.9604	0.9604	0.852	0.8875	0.927	
	304	-	-	-	-	-	-
	260	mean: 0.87 (from graph)	macro: 0.85	macro: 0.84	macro: 0.83	-	-
			micro: 0.87 (from graph)	micro: 0.86 (from graph)	micro: 0.84 (from graph)		
	95	-	-	-	weighted: 0.9179, macro: 0.8332 (DDI2013)	-	-
					weighted: 0.6053, macro: 0.8023 (TAC 2018)		
	183	0.8871	0.8556	0.722	0.7496	0.998	0.9251
	181	0.8852, (task 1)	0.8471 (task 1)	0.7182 (task 1)	0.7585 (task 1)	0.9976 (task 1)	0.9208 (task 1)
		0.6415 (task 2)	0.5607 (task 2)	0.4319 (task 2)	0.4460 (task 2)	0.9799 (task 2)	0.6558 (task 2)
		0.4075 (task 3)	0.2408 (task 3)	0.1452 (task 3)	0.1590 (task 3)	0.9512 (task 3)	0.3635 (task 3)
	70	-	0.8381	0.8159	0.8268	-	-
	151	-	0.7619	0.7334	0.7474	-	-
	101	-	0.827	0.806	0.816	-	-
	96	-	0.856849 (LR)	0.794636 (LR)	0.813400 (LR)	-	-
			0.851789 (SVM)	0.772669 (SVM)	0.795577 (SVM)		
			0.808146 (DT)	0.676117 (DT)	0.713850 (DT)		
			0.845322 (RF)	0.709323 (RF)	0.743582 (RF)		
			0.830406 (NB)	0.672542 (NB)	0.711865 (NB)		
			0.797973 (KNN)	0.619668 (KNN)	0.665580 (KNN)		
	182	-	0.9237	0.9237	0.9237	0.9986	0.9627
	247	-	-	-	0.806	-	-
	179	0.788 (ChemProt) 0.815 (DDI 2013)	-	-	-	-	-
	262	0.9589	-	-	0.9173	0.9992	0.9847
	261	-	-	-	0.8921 (TWOSIDES)	0.9625 (TWOSIDES)	0.9653 (TWOSIDES)
					0.9461 (DrugBank)	0.9869 (DrugBank)	0.9868 (DrugBank)
	177	0.726	0.697	0.758	-	-	-
	263	0.9120 (DS1)	0.8402 (DS1)	0.8578 (DS1)	0.8394 (DS1)	0.9523 (DS1)	0.9231 (DS1)
		0.8839 (DS2)	0.7353 (DS2)	0.7085 (DS2)	0.7329 (DS2)	0.9259 (DS2)	0.8470 (DS2)
	264	0.5129 (DS1)	-	-	0.4698 (DS1)	0.9649 (DS1)	0.4648 (DS1)
		0.6696 (DS2)			0.6537 (DS2)	0.9886 (DS2)	0.7197 (DS2)
	265	0.9409 (T1),0.6805 (T2) ———-	0.9132 (T1)	0.8876 (T1)	0.8958 (T1)	0.9989 (T1)	0.9786 (T1)
		note:T 4 Task	0.6063 (T2)	0.5106 (T2)	0.5394 (T2)	0.9673 (T2)	0.7049 (T2)
	186	0.9847	-	-	0.9845	0.9974	-

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Table 4a. continued

output	model	accuracy	*P*	*R*	*F*1	ROC-AUC	PR-AUC
		(DrugBank) ————- 0.9509 (ChChMin) ————- 0.9548 (ZhangDDI)			(DrugBank) ———— 0.9704 (ChChMiner) ————- 0.9085 (ZhangDDI)	(DrugBank) ———— 0.9983 (ChChMiner) ————- 0.9898 (ZhangDDI)	
	266	-	-	-	-	-	-
	188	0.9519 (DS1-OGB-biokg) 0.9027 (DS2-KEGG-drug)	0.9371 (OGB-biokg) 0.8863 (KEGG-drug)	0.9715 (OGB-biokg) 0.9237 (KEGG-drug)	0.9528 (OGB-biokg) 0.9046 (KEGG-drug)	0.9928 (OGB-biokg) 0.9573 (KEGG-drug)	0.9921 (OGB-biokg) 0.9428 (KEGG-drug)
	178	-	0.9816 (DNER) 0.8985 (RC)	0.9865 (DNER) 0.8483 (RC)	0.9840 (DNER) 0.8726 (RC)	-	-
	175	-	0.875 (DDI 2013) 0.823 (ChemProt)	0.841 (DDI 2013) 0.774 (ChemProt)	0.849 (DDI 2013) 0.798 (ChemProt) 0.721 (DDIs data set)	0.603 (DDIs data set)	-
	176		macro: 0.8502 micro: 0.8922	macro: 0.8282 micro: 0.8072	macro: 0.8391 micro: 0.8475	macro: 0.9913 micro: 0.9796	macro: 0.9096 micro: 0.7300
	177	-	0.7789	0.8247	0.8012	-	-
	268	0.99	0.99	0.99	0.99	-	-
	269	0.9725 (DrugBank) 0.9443 (TWOSIDES)	0.9611 (DrugBank) 0.8631 (TWOSIDES)	0.9788 (DrugBank) 0.9668 (TWOSIDES)	0.9717 (DrugBank) 0.9245 (TWOSIDES)	0.9927 (DrugBank) 0.9563 (TWOSIDES)	-
	270	0.7984 (DrugBank) 0.8943 (TWOSIDES	-	-	0.8948 (DrugBank) 0.9592 (TWOSIDES)	-	-
	271	-	0.909	0.97	0.938	-	-
DDI	180	max: 0.7358 (0 shot Claude) 0.9260 (fine-tune GPT-4o)	max: 0.9212 (0 shot Qwen2.5) 0.9230 (Fine-tune Gemma2)	max: 0.9982 (0 shot LLaMa-3.2) 0.9690 (Fine-tune Qwen2.5)	max: 0.6957 (0 shot LLaMa-3.3) 0.9260 (Fine-tune GPT-4o)	-	-
	190	-	-	-	-	0.923 (extracted from chart)	0.935
	206	-	-	0.863 (BioSNP) 0.889 (DAVIS) 0.928 (BindingDB)	-	0.914 (BioSNP) 0.942 (DAVIS) 0.926 (BindingDB)	0.901(BioSNP) 0.517 (DAVIS) 0.639 (BindingDB)
	288	0.873	0.876	0.882	0.868	0.961	0.985
	118	-	-	-	-	Mean 0.9915 (Yamanishi) 0.429 (Olayan RS)	Mean 0.9545 (Yamanishi) 0.881 (Olayan RS)
	163	-	-	-	-	-	-
	164	-	-	-	-	-	0.450 (DAVIS) 0.601 (KIBA)
	227	-	0.951 (HUMAN)	0.975 (HUMAN)	0.963 (HUMAN)	-	0.971 (DUD-E Data set) 0.991 (HUMAN)
	222	-	-	-	-	-	-
	278	-	-	-	-	0.9840 (DS1) 0.9485 (DS 2)	0.8247 (DS1) 0.7302 (DS2)
	279	0.942	0.931	0.95	0.94	0.994	0.993
	207	0.911 (Binding) 0.876 (BioSNAP)	-	0.920 (Binding) 0.876 (BioSNAP)	-	0.97 (Human; from chart) 0.965(Binding) 0.941 (BioSNAP)	0.97 (Human; from chart)— 0.955(Binding) 0.942(BioSNAP)
	230	-	-	-	0.951	0.9706	-
	234	-	-	-	-	-	-

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Table 4a. continued

output	model	accuracy	*P*	*R*	*F*1	ROC-AUC	PR-AUC
	208	-	0.961 (Human), 0.959 (C. elegans) 0.895 (DAVIS)	-	0.987 (Human) 0.992 (C. elegans) 0.922 (DAVIS)	0.989 (Human) 0.994 (C. elegans) 0.492 (DAVIS)	-
	223	-	-	-	-	-	-
	197	-	-	-	0.9871	0.9895	-
	196	0.971	0.935	0.991	0.962	0.991	0.985
	195	-	-	-	-	0.951 (DrugBank) 0.939 (BindingDB) 0.974 (Yamanishi) 0.944 (Luo)	0.953 (DrugBank) 0.934 (BindingDB) 0.966 (Yamanishi) 0.948 (Luo)
	247	-	-	-	0.806	-	-
	220	0.787 (BioSNAP) 0.950 (Human) 0.975 (C.elegans)	0.828 (BioSNAP) 0.968 (Human) 0.992 (Celegans)	0.727 (BioSNAP) 0.926 (Human) 0.976 (C.elegans)	-	0.857 (BioSNAP) 0.992 (Human) 0.996 (C.elegans)	0.872 (BioSNAP) 0.991 (Human) 0.996 (C.elegans)
	241	-	-	-	-	S1 (0.953) S2 (0.968) S3 (0.968) S4 (0.821) note S 4 setting	S1 (0.630) S2 (0.719) S3 (0.719) S4 (0.249)
	193	0.9340 0.9413 0.9539 (DS1-Luo) 0.8984 0.8986 0.8886 (DS2- Zhang) Mean 0.9275 0.9358 0.9465 (DS2- Yamanishi) note all ratios in cells are 1:1, 1:5, 1:10	-	-	-	0.9787 0.9813 0.9749 (DS1-Luo) 0.9546 0.9339 0.9134 (DS2- Zhang) Mean 0.9333 0.9308 0.9006 (DS3- Yamanishi)	0.9701 0.9075 0.8431 (DS1-Luo) 0.9497 0.9265 0.9160 (DS2- Zhang) Mean 0.9291 0.9290 0.9022 (DS3- Yamanishi)
	192	-	-	-	-	0.9818 (Luo) 0.9666 (new DS)	0.9839 (Luo) 0.9685 (new DS)
	241	0.9867	0.9788	0.9949	0.9868	0.9986	0.9985
	243	0.729 (-Sim) 0.776 (-ChemBERTa)	0.703 (-Sim) 0.752 (-ChemBERTa)	0.621 (-Sim) 0.675 (-ChemBERTa)	0.642 (-Sim), 0.695 (-ChemBERTa)	-	-
	280	0.9821	-	-	0.9779	0.9949	-
	220	-	-	-	-	-	-
	204	0.896 (BindingDB) 0.836 (BioSNAP) 0.942(Human)	-	0.884(BindingDB) 0.816 (BioSNAP) 0.929 (Human)	0.900 (BindingDB) 0.840 (BioSNAP) 0.944 (Human)	0.960 (BindingDB) 0.909 (BioSNAP) 0.983 (Human)	0.947 (BindingDB) 0.907 (BioSNAP) 0.976 (Human)
	281	0.92	0.92	0.92	0.92	-	-
	228	-	0.9962 (C.elegans) 0.9762 (Human)	0.9699 (C.elegans) 0.9395 (Human)	0.9742 (C.elegans) 0.9443 (Human)	0.9964 (C.elegans) 0.9874 (Human)	0.9956 (C.elegans) 0.9876 (Human)
	221	-	-	-	-	-	-
	282	-	-	-	-	-	-
	219	-	-	-	-	-	-
	309	-	-	-	-	0.962	0.9605
	310	0.8836 (DTKG) 0.9325 (DAVIS) 0.9080 (KIBA)	0.8291 (DTKG) 0.8348 (DAVIS) 0.7820 (KIBA)	0.8211 (DTKG) 0.8805 (DAVIS) 0.7210 (KIBA)	0.8251 (DTKG) 0.8570 (DAVIS) 0.7503 (KIBA)	0.9429 (DTKG) 0.9660 (DAVIS) 0.9320 (KIBA)	0.8844 (DTKG) 0.8930 (DAVIS) 0.8370 (KIBA)

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Table 4a. continued

output	model	accuracy	*P*	*R*	*F*1	ROC-AUC	PR-AUC
		00.8551 (DrugBank)	0.8137 (DrugBank)	0.8551 (DrugBank)	0.8339 (DrugBank)	0.9093 (DrugBank)	0.9136 (DrugBank)
	218	-	-	-	-	-	-
	217	-	-	-	-	-	-
	216	-	-	-	-	-	-
	212	-	-	-	-	-	-
	215	-	-	-	-	-	-
	203	0.907 (Binding)	-	0.908 (Binding)	-	0.965 (Binding)	0.957 (Binding)
		0.839 (BioSNAP)		0.819 (BioSNAP)		0.909 (BioSNAP)	0.909 (BioSNAP)
		0.945		0.944 (Human)		0.988 (Human)	0.984 (Human)
	214	-	0.981 (DrugBank)	0.954 (DrugBank)	-	0.989 (DrugBank)	0.992 (DrugBank)
				(DrugBank)		0.997(Human)	0.997(Human)
						0.996(C.elegans)	0.996(C.elegans)
			0.987 (Human)	0.976 (Human)		0.991(BindingDB)	0.993(BindingDB)
						−0.976 (GPCR)	0.983 (GPCR)
			0.984 (C. elegans)	0.981 (C. elegans)			
			0.976 (BindingDB)	0.943 (BindingDB)			
			0.964 (GPCR)	0.905 (GPCR)			
	213	-	-	-	-	-	0.6629 (DAVIS)
							0.7015 (KIBA)
	201	0.9130 (BindingDB)	-	-	0.9141 (BindingDB)	0.9655 (BindingDB)	0.9519 (BindingDB)
		0.8341 (BioSNAP)			0.8373 (BioSNAP)	0.9046 (BioSNAP)	0.9061(BioSNAP)
		0.8223 (DrugBank)			0.8249 (DrugBank)	0.8881 (DrugBank)	0.8884 (DrugBank)
		0.9407 (Human)			0.9398 (Human)	0.9794 (Human)	0.9753 (Human)
	283	0.936	0.1789	0.9168	0.2988	0.9751	0.631
	200	-	-	0.848 (BIOSNAP)	-	>0.914 (BIOSNAP)	0.914 (BIOSNAP)
				0.833 (DAVIS)		0.895 (DAVIS)	0.373 (DAVIS)
				0.888 (BindingDB)		0.912(BindingDB)	0.643 (BindingDB)
	247	-	-	-	0.806	-	-
DTI	224	0.942 (BindingDB E1)	High precision	Lower recall	High F1-score	-	-
		0.947 (BindingDB E2)	4 BindingDB E2 (no value)	4 GraphDTA:0.800 (BindingDB E2)	4 BindingDB E2(no value)		
		0.744 (DrugBank E3)					
	191	-	-	-	-	0.9805	0.976
	148	0.961 (BindingDB)	-	-	-	0.989 (BindingDB)	0.990 (BindingDB)
		0.889 (BioSNAP)				0.991 (Human)	0.989 (Human)
						0.951 (BioSNAP)	0.951 (BioSNAP)
	199	-	-	0.863 (BIOSNAP)	-	0.931 (BIOSNAP)	0.930 (BIOSNAP)
				0.837 (DAVIS)		0.934 (DAVIS)	0.462 (DAVIS)
	210	-	-	-	-		
	284	-	-	>0.799(GPCR)	-	0.860 (GPCR)	0.862 (GPCR)
				0.689 (DrugBank)		0.808 (DrugBank)	0.557 (DrugBank)
	249	-	-	-	-	0.9972	0.9976
	285	0.829	-	-	0.8	0.923	0.937
	286	-	-	-		0.9811	0.9868
	287	0.8258	0.9989	0.8258	0.9041	0.9143	-
	209	-	-	-		0.9746	0.9542
	202	-	-	0.866 (BioSNAP)	-	0.939 (BioSNAP)	0.941 (BioSNAP)
						0.898 (Human)	0.837 (Human)
DTI	211	-	-	-	-	-	0.7410 (Davis)
							0.8150 (KIBA)

models extract linguistic features from social media posts using feature pooling.[183] CNN-based models (CNN, HAN, FastText with Word2Vec) classify ADR comments, with preprocessing including case conversion, stop-word removal, and lemmatization.[300]

4.2. A Few Examples for DDI Extraction Models. DDI extraction has advanced with deep learning models like CNNs and RNNs, improving performance over traditional methods.[70] The SEV-DDI model, an LSTM-based approach, enhances accuracy using a dictionary-based method to predict DDI severity, aiding clinical decisions.[70]

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Table 4b. Evaluation of Studied Models (Specificity, CI, R^2, MSE, MCC)

output	model	specificity	CI	R^2	MSE	MCC
ADR	250	-	-	-	-	-
	173	-	-	-	-	-
	251	-	-	-	-	between 1 and 2
	142	-	-	-	-	-
	74	-	-	-	-	-
	253	-	-	-	-	-
	254	-	-	-	-	-
	255	0.913	-	-	-	-
	304	-	-	-	-	-
	260	-	-	-	-	-
	95	-	-	-	-	-
	183	-	-	-	-	-
	181	-	-	-	-	-
	70	-	-	-	-	
	151	-	-	-	-	-
	101	-	-	-	-	-
	96	-	-	-	-	-
	182	-	-	-	-	-
	247	-	-	-	-	-
	179	-	-	-	-	-
	262	-	-	-	-	-
	261	-	-	-	-	-
	177	-	-	-	-	-
	263	-	-	-	-	-
	264	-	-	-	-	-
	265	-	-	-	-	-
	186	-	-	-	-	-
	266	-	-	-	-	-
	188	-	-	-	-	-
	178	-	-	-	-	-
	175	-	-	-	-	-
	176	-	-		-	-
	177	-	-	-		-
	268	-	-	-	-	-
	269	-	-	-	-	-
	270		-	-	-	-
	271	-	-	-	-	-
DDI	180	-	-	-	-	-
	190	-	-	-	-	-
	206	0.862 (BioSNP) 0.903 (DAVIS) 0.814 (BindingDB)	0.913 (BioSNP) 0.940 DAVIS) 0.927 (BindingDB)	0.467 (BioSNP) 0.201(DAVIS) 0.365 (BindingDB)	-	-
	288	-	-	-	-	-
	118		-	-	-	-
	163	-	0.75 (GCN) 0.70 (GAT) 0.83 (GIN)	-	0.75 (GCN) 0.77 (GAT) 0.57(GIN)	-
	164	-	0.876 (DAVIS) 0.836 (KIBA)	>0.637 (DAVIS) 0.614(KIBA)	0.276 (DAVIS) 0.226 (KIBA)	-
	227	-	-	-	-	-
	222	-	0.917 (DAVIS) 0.893 (KIBA)	0.722 (DAVIS) 0.784 (KIBA)	0.184 (DAVIS) 0.138 (KIBA)	-
	278	-	-	-	-	-
	279	-	-	-	-	-
	207	0.900 (Binding) 0.877 (BioSNAP)	-	-	-	-
	230	-	-	-	-	-
	234	-	-	-	-	-
	208	-	-	-	-	-
	223	0.907 (KIBA)	0.807 (KIBA)	0.124 (KIBA)	-	-

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Table 4b. continued

output	model	specificity	CI	R^2	MSE	MCC
		0.914 (DAVIS)	0.744 (DAVIS)	0.196 (DAVIS)		
	197	-	-	-	-	-
	196	-	-	-	-	-
	195	-	-	-	-	-
	247	-	-	-	-	-
	220	-	-	-		-
	241	-	-	-	-	-
	193	-	-	-	-	-
	192	-	-	-	-	-
	241	-	-	-	-	-
	243	0.836 (DeepARV-Sim) 0.878 (DeepARV-ChemBERTa)	-	-	-	-
	280	-	-	-	-	-
	220	-	0.905 (DAVIS) 0.900 (KIBA)	-	0.220 (DAVIS) 0.134 (KIBA)	-
	204	0.913 (BindingDB) 0.857 (BioSNAP) 0.957 (Human)	-	-	-	-
	281	-	-	-	-	-
	228	-	-	-	-	-
	221	-	0.901 (DAVIS) 0.886 (KIBA)	-	0.215 (DAVIS) 0.147(KIBA)	-
	282	-	-	0.83 (ALL)	1.29 (ALL)	-
	219	-	0.895 (DAVIS) 0.886 (KIBA)		0.209 (DAVIS) 0.159 (KIBA)	-
	309	-	-	-	-	-
	310	-	-	-	-	-
	218	-	0.63 (DAVIS) 0.66 (KIBA) from image		0.66 (DAVIS) 0.56 (KIBA) from image	-
	217	-	0.903 (DAVIS) 0.892 (KIBA)	0.731 (DAVIS) 0.771 (KIBA)	0.177 (DAVIS) 0.14 (KIBA)	-
	216	-	0.890 (DAVIS) 0.860 (KIBA)	0.756 (DAVIS) 0.731 (KIBA)	0.199 (DAVIS) 0.184 (KIBA)	-
	212	-	0.646	-	0.547	-
	215	-	-	0.776(DAVIS) 0.808(KIBA)	0.166(DAVIS) 0.127(KIBA)	-
	203	0.906 (Binding) 0.858 (BioSNAP) 0.957 (Human)	-	-	-	-
	214	-	-	-	-	-
	213	-	0.8696 (DAVIS) 0.8221 (KIBA)	0.5713 (DAVIS) 0.6329 (KIBA)	0.3329 (DAVIS) 0.2536 (KIBA)	-
	201	-	-	-	-	0.8242 0.6694 0.6451 0.8800
	283	-	-	-	-	-
	200	0.844 (BIOSNAP) 0.802 (DAVIS) 0.793 (BindingDB)	-	-		-
	247	-	-	-	-	-
DTI	224	-	-	-	-	-
	191	-	-	-	-	-
	148	-	-	-	-	-
	199	0.857 (BIOSNAP) 0.884 (DAVIS)	-	-	-	-
	210	-	-	-	-	-
	284	-	-	-	-	-

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Table 4b. continued

output	model	specificity	CI	R^2	MSE	MCC
	249	-	-	-	-	-
	285	-	-	-	-	0.687
	286	-	-	-	-	-
	287	-	-	-	-	-
	209	-	-	-	-	-
	202	0.857 (BioSNAP)	-	-	-	-
DTI	211	-	0.897 (Davis)	0.6240 (Davis)	0.242 (Davis)	
			0.890 (KIBA)	0.7070 (KIBA)	0.166 (KIBA)	

The RBioBERT-LSTM model combines RBioBERT with LSTM, surpassing RBioBERT alone in DDI classification.[95] BioBERT-directionalDDI, a BERT-based model, identifies PK DDIs and the interacting drug responsible for alterations.[301] The ALBERT-BiLSTM-CRF model improves medical entity recognition,[74] while LiSA screens biomedical literature for drug-adverse event relationships.[142] The Knowledge-based Att-BiLSTM model leverages UMLS and UIMA for entity detection, using Att-BiLSTM for relationship assignment.[250]

4.3. A Few Examples for DTI Prediction Models. A fine-tuned BERT model predicts DTIs using ChemBERTa and ProtBERT for encoding compounds and proteins, with an FCN decoder combining their outputs.[206] An end-to-end model employs GRU and GNN to extract drug-target features from SMILES sequences and molecule maps, merging them into a unified vector.[163] MPS2IT-DTI converts molecular and protein sequences into image-like matrices, applying CNNs to process them, differing from embedding-based models like DeepDTA.[164]

3DProtDTI integrates AlphaFold structure predictions with graph-based protein and ligand representations, using GNNs and FC layers for feature extraction.[222] A twin CNN model predicts DTIs from multimodal drug data, using a Siamese structure for learning chemical and biological features.[182] DTINet integrates drug−protein-disease data in a heterogeneous network, using random walk and dimensionality reduction.[190] FMCA-DTI applies a fragment-oriented multi-head cross-attention mechanism.[205]

Table 3 provides an overview of the studies reviewed, categorized by the models they employ. Note that all fully connected layers in the decoder are classified as MLP (Multilayer Perceptron). The table includes citations to each study, the type of output (ADR, DDI, or DTI), and the output format—categorized (c), numerical (n), or binary (b). The general approaches are classified as machine learning, deep learning, graph learning, or hybrid methods. The use of NLP tools is indicated in the "NLP" column, while the "E2E" column specifies whether the model operates end-to-end. The "Encoder" column describes the representation or embedding learning methods, and the "Decoder" column outlines the downstream prediction techniques. The subsequent column details the loss functions used. Due to the common imbalance in data sets, where negative samples often far outnumber positive ones, some studies select a smaller subset of negative samples. The final column, "Ratio p2n," reports the positive-to-negative sampling ratio applied in each study.

5. EVALUATIONS

Precision and recall assess systems' capability to identify relevant items, with precision focusing on correct retrievals and recall on relevant items found; their balance leads to the F-score. Metrics like accuracy, specificity, and MSE quantify overall performance, while the CI evaluates survival analysis. ROC-AUC visualizes performance, especially with imbalanced data sets, and the MCC measures binary classifiers' effectiveness, accommodating varying distributions. R^2 indicates how well a regression model explains variance in data. The Supporting Information contains the full description of evaluation metrics for interested readers.

By using these metrics, the models' evaluations are summarized in Table 4a and 4b. It should be noted that there were also other metrics used in these papers, such as Pearson[311] and Spearman.[312] However, only a few of them used these metrics; therefore, we removed them to save space in the table. Pearson was used in E-ADGCN[177] (0.232 on DAVIS and 0.215 on KIBA), and PocketDTA[217] (0.887 on DAVIS and 0.896 on KIBA), and Spearman was used in CSCo-DTA[215] with 0.231.

6. CHALLENGES

Deep learning models face several significant challenges in the pharmaceutical domain, particularly because of the need for large volumes of high-quality annotated data that are time-consuming and labor-intensive to obtain. Such challenges are compounded by model performance instability, influenced by noise and data imbalance, which complicates the understanding of complex sentences and diminishes the models' ability to capture critical meanings. Additionally, the interpretability of these models remains a concern, as the unpredictability of their outputs makes it difficult for pharmacists to identify potentially hazardous drug combinations, crucial for ensuring patient safety.[61] Specific issues such as sense ambiguity, matching errors, and relation classifier inaccuracies further hinder the accuracy of model predictions, affecting the reliability of data used in clinical settings.[250] Ambiguous concepts like "Anticoagulation", which can refer to either a drug or a condition, can result in classification errors; and matching errors may arise when systems incorrectly categorize terms due to overlapping descriptions, such as identifying "Cyanocobalamin 1000" as a medication while overlooking "1000 mcg/mL" as its strength.[250]

Beyond the technical hurdles, establishing sound business models for drug repurposing is essential, as challenges related to intellectual property rights and economic factors complicate drug approval and application for new uses.[313] Variations in patent laws across regions, such as those in the European Union and the United States, can impede the potential return on investment for new drugs.[314] Additionally, limited access to crucial data like clinical trial information, along with the complexities of data integration, presents further obstacles.[315] Moreover, the development of NER techniques is vital for identifying and classifying medical terms to enhance the detection of ADEs.[74] As the need for accurate DTI predictions grows, exploring mutual interactions between drugs and targets becomes increasingly important,[117] while advancements in NLP

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highlight the necessity for effective detection of DDIs from the expanding body of biomedical literature.[101] Additionally, the heterogeneity and high dimensionality of biological and chemical data demand sophisticated computational methods, such as graph embedding, but these methods face difficulties in effectively integrating diverse data types. Furthermore, co-occurrence-based text mining can introduce false positives-identifying associations that are not biologically meaningful-necessitating careful filtering and validation.[316]

One related area in drug discovery is the study of drug−food interactions (DFIs). To improve public understanding of DFIs, it is important to create easy-to-understand educational resources, promote awareness of reliable scientific information, and ensure access to trustworthy sources. Drug discovery in DFIs includes developing accurate, user-friendly tools and apps that can provide personalized information on drug−herb interactions. Additionally, healthcare providers face challenges in effectively educating patients about potential food and medication interactions, which requires clear communication and guidance. Pharmacists play a crucial role in counseling patients, but ensuring consistent, accessible education and fostering positive attitudes toward understanding DFIs remain significant hurdles for advancing drug discovery and personalized medicine.[317] Another issue is the limited literature and manual curation of information, leading to data scarcity and inconsistency that can cause biases and incomplete data sets, which have been discussed before. Moreover, the complexity of units such as food composition makes it difficult to generate accurate, comprehensive feature representations for food constituents, preventing precise modeling. The limited availability of validated, gold-standard data sets for model training and evaluation also poses significant challenges for developing large, generalizable predictive models for DFIs.[316] Furthermore, healthcare professionals often have limited knowledge about drug−food interactions, which can lead to medication problems and health risks. Improving their education and awareness is essential to prevent such issues and ensure safer patient care.[318]

7. OUTLOOK

This survey presents the latest research studies on computational drug discovery, focusing particularly on DTI, DDI, and ADR. We provide an overview of the deep learning and LLMs utilized in this area of research. Additionally, we highlight relevant data sets and databases that are significant to these fields. Furthermore, we report on the specifications of recent methods proposed in this area and provide an evaluation and comparison of these methods for interested readers.

The high costs and extensive labor associated with annotating large data sets present challenges but also open opportunities for enhancing data utilization through various techniques. Implementing a separate concept reasoning module alongside machine learning models trained on gold-standard concepts can improve performance significantly.[250] Methods such as semisupervised and distant supervision modeling help address limited annotated data by using knowledge bases and bootstrap learning, although issues like incorrect labeling and data sparsity remain in biomedical applications. Advanced techniques like Generative Adversarial Networks (GANs)[319] and correlated information[320] can further mitigate these challenges and enhance performance in relation extraction tasks.[61]

Strategies like joint learning, ensemble learning, and dual learning can be employed to improve the stability and accuracy of relation extraction. Joint learning enables the simultaneous extraction of entities and relations, reducing error propagation, while ensemble learning combines predictions from multiple classifiers for greater accuracy. Additionally, dual learning can capitalize on task interrelations to boost performance. Feature enrichment using deep learning allows for the integration of rich data sources, including molecular information and social media content, leading to more robust and interpretable DDI extraction models.[61]

Table 5. Abbreviation Used in This Survey

Area under the precision−recall curve: AUPR	Recall: R
Area under the receiver operating characteristic: AUROC	Receiver operating characteristic: ROC
Bayesian Personalized Ranking: BPR	Simplified Molecular Input Line Entry System: SMILES
Biased Feature Interaction Module: BFIM	Sparse Feature Module: SFM
Context-Dependent Dense Module: CDM	Synergy Loss: Lsynergy
Decision Tree: DT	Toxic Loss: LToxic
Doc2Vec: d2v	Universal Sentence Encoder: USE
Gated Graph Neural Networks: GGNN	Wasserstein Autoencoders: WAEs
Gaussian Error Linear Unit	Feed-Forward Neural Networks
GeLU	FNNs
Geometric Vector Perceptron: GVP	Word2Vec: w2v
Gradient Boosting Decision Tree: GBDT	XGBoost: XGB
Graph attention network: GAT	bidirectional Intention network: BiIN
Graph neural network: GNN	binary: b
Hypergraph Convolutional Networks: HGCN	character: c
K-Nearest Neighbor: KNN	data set: DS
Logistic Regression: LR	end-to-end: E2E
Masked Language Modeling: MLM	low-dimensional latent embeddings: L-DLE
Naïve Bayes: NB	m Structured Product Labeling: SPL
Neural Inductive Matrix Completion	neural network-based predictor
NIMC	NNPS
Nod2Vec: n2v	numeric: n
P-glycoprotein: P-gp	pretrained large model: PLM
Precision: P	structural similarity profile: SSP
Precision−recall: PR	variational graph autoencoder: VGAE

8. ABBREVIATIONS

Abbreviations used in this survey are in the Table 5.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.5c04997.

The supplementary file includes an overview of some of the most-used machine learning, deep learning, and graph learning models. It also includes information on evaluation metrics used in the studied articles, as well as a table that outlines the train-validation-test divisions used in various proposed models (PDF)

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Notes

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■ ADDITIONAL NOTES

[1]https://www.uniprot.org/.
[2]https://go.drugbank.com/.
[3]https://bindingdb.org/.
[4]https://ddinter2.scbdd.com/.
[5]https://tac.nist.gov/2018/.
[6]https://bionlp.nlm.nih.gov/tac2019druginteractions/.
[7]https://arxiv.org/.
[8]https://www.biorxiv.org/.

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