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Review paper

Elucidating the role of artificial intelligence in drug development from the perspective of drug-target interactions

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ABSTRACT

Drug development remains a critical issue in the field of biomedicine. With the rapid advancement of information technologies such as artificial intelligence (AI) and the advent of the big data era, AI-assisted drug development has become a new trend, particularly in predicting drug-target associations. To address the challenge of drug-target prediction, AI-driven models have emerged as powerful tools, offering innovative solutions by effectively extracting features from complex biological data, accurately modeling molecular interactions, and precisely predicting potential drug-target outcomes. Traditional machine learning (ML), network-based, and advanced deep learning architectures such as convolutional neural networks (CNNs), graph convolutional networks (GCNs), and transformers play a pivotal role. This review systematically compiles and evaluates AI algorithms for drug- and drug combination-target predictions, highlighting their theoretical frameworks, strengths, and limitations. CNNs effectively identify spatial patterns and molecular features critical for drug-target interactions. GCNs provide deep insights into molecular interactions via relational data, whereas transformers increase prediction accuracy by capturing complex dependencies within biological sequences. Network-based models offer a systematic perspective by integrating diverse data sources, and traditional ML efficiently handles large datasets to improve overall predictive accuracy. Collectively, these AI-driven methods are transforming drug-target predictions and advancing the development of personalized therapy. This review summarizes the application of AI in drug development, particularly in drug-target prediction, and offers recommendations on models and algorithms for researchers engaged in biomedical research. It also provides typical cases to better illustrate how AI can further accelerate development in the fields of biomedicine and drug discovery.

1. Introduction

The drug development process is a complex and multifaceted journey that spans several stages, including discovery, preclinical testing, clinical trials, and regulatory approval [1,2]. This endeavor, characterized by high costs and a significant time investment, is driven by the urgent need to address a myriad of diseases and health conditions [3–5]. Despite advances in technology and a greater understanding of biological systems, the success rate of bringing a new drug to market remains low, with only a small fraction of compounds progressing through the entire pipeline. In recent years, there has been a surge of innovative approaches, such as high-throughput screening, computational drug design, and the integration of artificial intelligence (AI), which have the potential to revolutionize the landscape of drug development. However, the industry still faces considerable challenges, including high attrition rates in clinical trials, regulatory hurdles, and the need for substantial financial resources. Addressing these challenges is crucial for accelerating the development of effective and safe therapeutics, ultimately improving global health outcomes.

In recent years, AI has emerged as a transformative force in biomedical research, particularly in drug development, which has historically faced significant challenges in both efficiency and effectiveness. Traditional drug discovery methods, such as high-throughput screening and the one-drug-one-target paradigm, often struggle with the complexity of biological systems and the

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multifactorial nature of diseases. These methods are time-consuming, costly, and frequently result in high attrition rates during clinical trials, highlighting a critical need for more innovative approaches. The introduction of AI offers a compelling solution to these challenges by providing powerful algorithms capable of analyzing and interpreting complex biological data with unprecedented speed and accuracy [6–8]. The capacity of AI to process vast amounts of information has opened new avenues for understanding intricate biological processes and disease mechanisms, providing insights that were previously unattainable [9–11]. By leveraging machine learning (ML) and deep learning techniques, AI can identify patterns and relationships within large datasets, predict potential drug-target interactions, and optimize drug design, thus significantly reducing the time and cost associated with traditional drug discovery [12,13]. This ability to process vast amounts of information has rapidly and accurately provided new approaches for understanding intricate biological processes and disease mechanisms [14,15]. This technological advancement is not just an improvement but represents a paradigm shift in how we approach drug development. Simultaneously, network pharmacology has gained prominence as a complementary approach to AI in drug discovery. Network pharmacology focuses on the complex interactions within biological networks and offers a holistic framework for studying the interconnectedness between genes, proteins, and metabolic pathways [16–18]. This approach emphasizes the importance of systems-level insights, which are critical for understanding complex diseases and developing multitargeted therapies. By integrating AI and network pharmacology, researchers can overcome traditional barriers, generate comprehensive models of biological systems, uncover novel biomarkers, and gain deeper insights into the molecular underpinnings of health and disease. This integration not only represents a significant shift toward a more interconnected and predictive understanding of biology but also lays the groundwork for future scientific breakthroughs, potentially transforming the landscape of drug development.

The integration of AI and network pharmacology into drug development is transforming the landscape of therapeutic discovery and design [19–21]. AI-driven tools are being utilized to streamline various stages of drug development, from the identification of novel drug targets to the optimization of lead compounds [22–24]. ML and deep learning algorithms can sift through extensive biological data to predict potential drug candidates and their interactions with biological targets, significantly reducing the time and cost associated with traditional drug discovery methods [2,25,26]. On the other hand, network pharmacology [27–29] offers a systems-level perspective by mapping out the complex interactions within biological networks, enabling researchers to identify multitarget strategies and potential side effects early in the development process. This holistic approach is particularly valuable in addressing multifactorial diseases such as cancer and neurodegenerative disorders, where traditional single-target therapies often fall short. By leveraging the predictive power of AI and providing comprehensive insights into network pharmacology, researchers can develop more effective and safer drugs, ultimately accelerating the transition from bench to bedside. The synergy of these technologies holds great promise for the future of personalized medicine, offering tailored therapeutic solutions on the basis of the intricate biological profiles of individual patients.

A key application of AI and network pharmacology in drug development is the prediction of drug-target interactions [19,30,31], which is crucial for identifying potential therapeutic targets and understanding drug mechanisms. AI algorithms, particularly deep learning and ML models, can analyze large-scale biological and chemical data to predict which molecules are likely to interact with specific targets. This capability accelerates the identification of promising drug candidates and reduces the reliance on traditional high-throughput screening methods, which are often time-consuming and costly. Network pharmacology complements this approach by providing a comprehensive view of the biological networks involved in disease processes, highlighting potential multitarget interactions and off-target effects [32,33]. By integrating AI's predictive power with the systems-level insights of network pharmacology, researchers can more accurately pinpoint viable drug targets and anticipate possible side effects, addressing the long-standing challenges of inefficiency and unpredictability in drug development. This synergy not only enhances the efficiency of the drug discovery process by reducing time and cost but also presents new strategies for tackling complex diseases through multi-targeted strategies. Ultimately, this integration contributes to the development of more effective, safer, and personalized medical treatments, representing a crucial advancement in the pursuit of precision medicine.

2. Association-based drug target prediction

Association-based drug target prediction plays a pivotal role in AI-driven drug development [34]. By leveraging advanced ML algorithms and large-scale biological data, this approach identifies potential drug targets through the analysis of complex biological networks and associations between drugs, targets, and diseases (Fig. 1). This method enhances our understanding of drug mechanisms and facilitates the discovery of novel therapeutic targets. In the realm of AI drug development, association-based predictions provide a robust framework for identifying key interactions, streamlining the drug discovery process, and ultimately contributing to the development of more effective and targeted therapies.

2.1. Biological network-based association algorithms for drug target prediction

Network pharmacology aims to elucidate the mechanisms of drugs and their complex combinations by leveraging biological networks from the perspectives of systems biology and systems medicine. Network target [6–8] is a theory originating from network pharmacology and has been widely used in traditional Chinese medicine (TCM) research [20,35]. Algorithms based on network pharmacology have inherent advantages in solving zero-sample and few-sample problems by utilizing network information such as biomolecular networks (Table 1) [36–41]. In the early stage of "network target", methods composed of statistics and similarities in features made great improvements in the prediction of disease–gene associations and drug-target associations. As a pioneering algorithm in "network target", the correlating protein interaction network and phenotype network to predict disease genes (CIPHER) [36] has achieved great performance in few-shot or zero-shot gene-phenotype predictions. The core idea of this algorithm is to take already known phenotype-phenotype networks, phenotype-gene networks, and protein-protein networks as inputs, use a regression model to construct associations at both the macro- and micro-levels, and establish similarity associations between query phenotypes, reference phenotypes, and genes via known associations as bridges. This method is particularly advantageous for predicting genetically uncharacterized phenotypes. On the basis of CIPHER, CIPHER-like algorithms in different research areas have been gradually developed. For drug–gene association prediction, DrugCIPHER [37] takes already known drug-drug networks, drug–gene networks, and protein-protein networks as inputs and was proposed to construct unknown associations between compounds and genes via a regression model, thereby enabling high-precision prediction of drug targets across the entire genome.

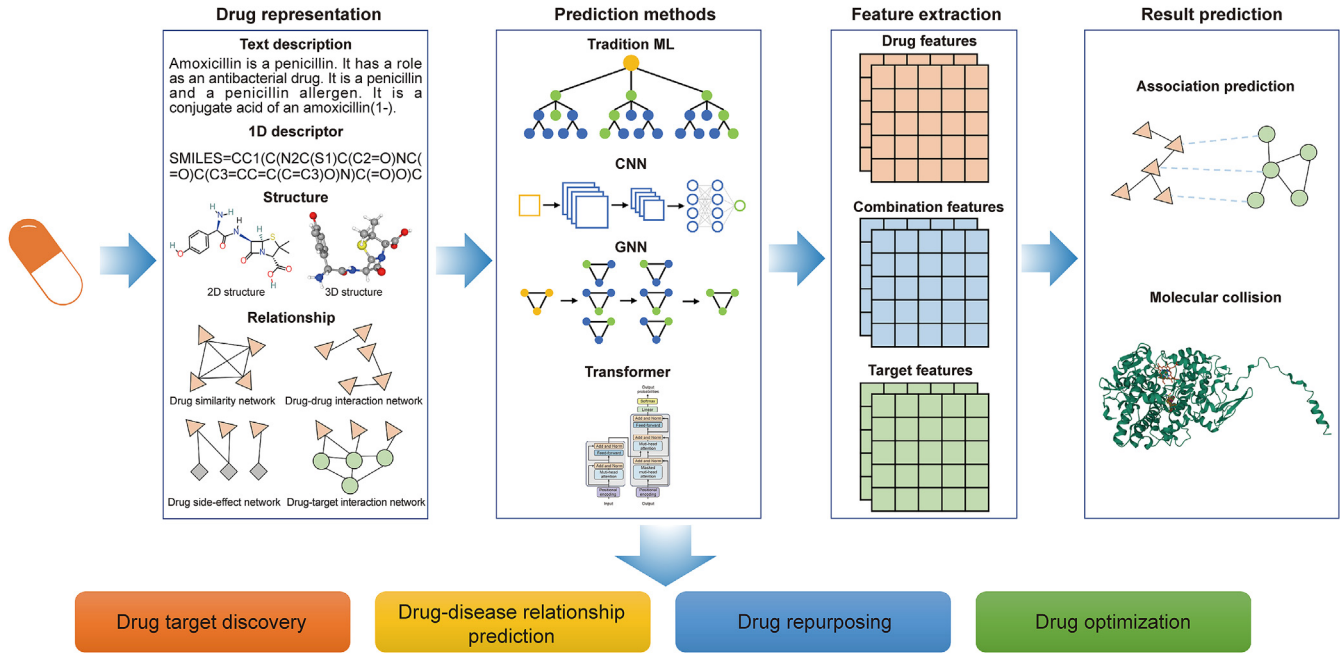

Fig. 1. End-to-end prediction and application in artificial intelligence (AI)-assisted drug development, guiding drug target discovery, drug-disease relationship prediction, drug repurposing, and drug optimization. 1D: one-dimensional; SMILES: simplified molecular input line entry system; ML: machine learning; CNN: convolutional neural network; GNN: graph neural network; Add: addition; Norm: normalization.

Table 1
Studies for drug-target prediction.

Type	Model	Name	Input	Refs.
Association-based	Network-based	CIPHER	Phenotype-phenotype, phenotype-gene, and protein-protein networks	[36]
		DrugCIPHER	Drug-drug, drug-target, and protein-protein networks	[37]
		–	Drug-target, disease-gene, and protein-protein networks	[38]
		–	Drug-target, protein-protein networks, and gene expression data	[39]
		DREAMwalk	Drug-gene-disease network	[40]
		DTINet	Drug-related network	[41]
	CNN and GCN-based	DLEPS	Gene expression profile and compound structure	[42]
		DEEPScreen	Compound structure image	[43]
		3D-KINEssence	Protein 3D-structure and compound descriptor	[44]
		GCN-DTI	Drug-target network	[45]
		GADTI	Drug-target network	[46]
		DrugAI	Compound structure, compound-target network, and protein sequence	[47]
		GLIM	Tissue-cell-molecule network	[48]
	Transformer-based	MolTrans	Drug descriptor and protein sequence	[49]
		MRBDTA	Drug descriptor and protein sequence	[50]
		MDCT-DTA	Protein sequence and compound graph structure	[51]
		TDGraphDTA	Protein sequence and compound graph structure	[52]
		BERT-GCN	Drug descriptor, protein sequence, and drug-target network	[53]
		Geneformer	Single-cell transcriptomes	[54]
Molecular collision-based	ML-based	–	Protein 3D-structure and compound descriptor	[55–57]
	CNN-based	DeepBindBC	Protein 3D-structure and compound descriptor	[58]
		–	Protein 3D-structure and compound descriptor	[59]
		K_{DEEP}	Protein 3D-structure and compound 3D-structure	[60]
		–	Protein 3D-structure and compound 3D-structure	[61]
		–	3D protein-ligand and complexes-structure	[62]
	GCN-based	–	Protein 3D-structure and compound graph structure	[63]
		PIGNet	Protein graph structure and compound graph structure	[64]
	Transformer-based	ViTScore	Protein 3D-structure and compound 3D-structure	[65]
		ETDock	Protein graph structure and compound graph structure	[66]
		–	3D point clouds of protein-ligand complexes	[67]
		MT-DTA	Protein sequence and compound descriptor	[68]

–: model without name. CIPHER: correlating protein interaction network and phenotype network to predict disease genes; DTINet: drug target interaction (DTI)Net; CNN: convolutional neural network; GCN: graph convolutional network; DLEPS: deep learning-based efficacy prediction system; 3D: three-dimensional; GADTI: graph autoencoder approach for DTI prediction; GLIM: graph local infoMax; MRBDTA: molecule representation block-based drug-target binding affinity (DTA) prediction; MDCT: multi-scale diffusion and interactive learning with CNN-transformers; BERT-GCN: bidirectional encoder representations from transformers-GCN; ML: machine learning; MT-DTA: mutual transformer-DTA.

There are also several network pharmacology algorithms that focus on the attributes of nodes in biological networks. On one hand, many methods for estimating distances in biological networks have been promoted. By quantifying the network proximity of disease genes and drug targets within the human protein-protein interactome, Cheng et al. [38] identify hundreds of new drug-disease associations for over 900 U.S. Food and Drug Administration (U.S. FDA)-approved drugs. The researchers selected four network-predicted associations to test their causal relationships using extensive healthcare databases containing data from over 220 million patients, applying state-of-the-art pharmacoepidemiologic analyses and propensity score matching. Kong et al. [39] introduced a ML framework designed to identify robust predictive biomarkers for anticancer drug responses, leveraging network-based analyses of pharmacogenomic data derived from three-dimensional (3D) organoid culture models. The framework first filters out pathways most closely related to drug response by calculating the distances between pathways and drug targets. Next, the gene expression data of these pathways are used as features input into the ML model to predict the drug half-maximal drug inhibitory concentration (IC_{50}). Pathways with a high predictive performance are potential drug response biomarkers. The framework aims to overcome the limitations of current ML methods, which often fail to identify translational biomarkers from preclinical models.

On the other hand, random walk-based methods have also been developed to predict drug-target associations. Bang et al. [40] proposed DREAMwalk, an innovative algorithm designed for computational drug repurposing by leveraging high-throughput biomedical knowledge graphs. Traditional approaches face challenges due to the dominance of genes and the relatively small number of drug and disease entities, leading to less effective representations. DREAMwalk addresses these issues by employing a "semantic multilayer guilt-by-association" approach, which is based on the principle that "similar genes share similar functions" at the drug—gene—disease level. The algorithm uses a teleport-guided random walk method, where drugs and diseases are mapped into a unified embedding space via a heterogeneous skip-gram model. The final output, which represents drug–disease association probabilities, is predicted via an XGBoost classifier and leads to more accurate predictions of drug–disease associations. Luo et al. [41] proposed drug target interaction (DTI)Net, a computational pipeline designed to predict novel drug-target interactions. It constructs a heterogeneous network that integrates diverse types of drug-related information. The core of DTINet involves learning a low-dimensional vector representation of features, which accurately captures the topological properties of individual nodes within the heterogeneous network. Predictions are then made on the basis of these representations via a vector space projection scheme.

2.2. Convolutional neural network (CNN)- and graph convolutional network (GCN)-based association algorithms for drug target prediction

With the development of AI and multiomics technologies, high-dimensional data suitable for constructing deep learning models have accumulated. Deep learning algorithms, such as CNNs and GCNs, were subsequently promoted to solve many problems in this field, such as mechanism revealing and drug development (Table 1) [42—48].

Compared with network-based approaches, drug-target prediction algorithms based on drug and protein structures operate on the basis of the intrinsic properties of these molecules. These methods typically follow a process of feature extraction followed by prediction. Common techniques in this category include methods based on CNNs. Zhu et al. [42] proposed deep learning-based efficacy prediction system (DLEPS), which uses 1D-CNNs and gene expression profiles for predicting drug efficacy. The method first encodes chemical structures via the simplified molecular input line entry system (SMILES) and divides them into grammar trees, which are then encoded into a high-dimensional latent space through a 1D-CNN. The latent vector then passes through a five-layer dense network for the prediction of chemically induced transcriptional profiles of 978 landmark genes, facilitating drug repurposing and discovery across a wide range of diseases, particularly those lacking well-defined targets. Rifaioglu et al. [43] proposed a system called DEEPScreen, which uses a 2D-CNN for predicting drug targets. Unlike traditional methods that rely on descriptors, DEEPScreen employs 2D structural images of compounds as input data. This image-based representation captures complex features of the compounds, naturally reflects their molecular states, and significantly enhances the prediction accuracy. Another method, 3D-KINEssence [44], uses a 3D-CNN to predict the potency and target profile of kinase inhibitors. The approach involves training the 3D-CNN on the biomolecular structures of kinases, allowing the model to learn essential structural features that distinguish individual kinases. The learned 3D fingerprints encapsulate these unique features and are combined with molecular Morgan fingerprints of kinase inhibitors to predict the potency and target profile of kinase inhibitors.

GCNs can perform exceptionally well in network-based prediction tasks. By continuously aggregating neighboring nodes, GCNs can capture information at different scales around each node. In the drug-target network, this allows GCNs to not only focus on the direct interactions between drugs and targets but also consider other indirect associations. Zhao et al. [45] proposed GCN-DTI, a combination approach including a GCN and deep neural networks (DNNs). The method first involves constructing a drug-protein pair (DPP) network in which nodes represent drug-protein pairs and edges represent their interactions. The GCN is then used to extract features from each DPP on the basis of the network topology, capturing both the structural information of the network and the intrinsic properties of the drugs and proteins involved. These features, comprising the combined characteristics of drugs and proteins, are input into a DNN, which classifies each DPP as a true or false interaction. Another GCN model, graph autoencoder approach for DTI prediction (GADTI) [46], predicts drug-target interactions by constructing a heterogeneous network that integrates multiple drug- and target-related datasets. The model then uses a graph autoencoder with an encoder consisting of a GCN and a random walk with a restart model to generate node embeddings. The decoder, DistMult, is a matrix factorization model that reconstructs the original network from the embeddings. By reconstructing the connections in a heterogeneous graph, potential drug-target interactions can be predicted.

As a representative deep learning algorithm for drug-gene association predictions, DrugAI [47] is a multiview deep learning model designed to understand the mechanisms of candidate drugs, particularly with a focus on activating and inhibiting interactions between drugs and their targets. It integrates multimodal information, including compound structure information extracted by a GCN, compound similarity networks, and multidimensional representations of targets extracted by a CNN, to achieve directed prediction of drug-target associations. Another algorithm that integrates multimodal information, graph local infoMax (GLIM) [48], is designed to systematically uncover associations among multilevel biological elements, including disease phenotypes, tissues, cell types, and molecules; this addresses the challenges posed by their heterogeneity and incompleteness. GLIM operates within a human multilevel network (HMLN), which incorporates multiple

tissues and cell types in addition to molecular networks. By embedding the features of the HMLN through the GCN and contrastive learning, the GLIM algorithm can systematically mine potential relationships between these elements.

2.3. Transformer-based association algorithms for drug target prediction

The transformer model is a state-of-the-art deep learning architecture primarily used for natural language processing tasks (Table 1) [49–54]. It leverages a self-attention mechanism to weigh the influence of different parts of the input data, allowing it to capture complex relationships and dependencies more effectively than traditional sequence models such as recurrent neural networks (RNNs) or long short-term memory networks (LSTMs). By adopting the transformer model, the significance between molecular structures can be better incorporated in the drug-target interaction prediction task. For example, Huang et al. [49] proposed MolTrans, a transformer-based method for drug-target interaction prediction. This method decomposes molecular sequences into substructures, which identify and merge frequent subsequences to generate high-quality, interpretable substructures. These substructures are then embedded through an augmented transformer module that captures the complex chemical relationships among them via self-attention mechanisms. Finally, the interaction prediction module pairs drug and protein substructures, applying a CNN to model higher-order interactions and predict the likelihood of drug-target interactions. Similarly, the molecule representation block-based drug-target binding affinity (DTA) prediction (MRBDTA) model [50] predicts DTA by first encoding the original protein fast-alignment search tool for amino acid sequences (FASTA) and drug SMILES sequences into embedding spaces and adding positional information. The molecule representation block, which improves the transformer encoder and introduces skip connections, extracts features from these encoded sequences. Finally, the interaction learning module integrates the features extracted from proteins and drugs and predicts their binding affinities via fully connected layers and a linear layer. Zhu et al. [51] proposed the multi-scale diffusion and interactive learning with CNN-transformer (MDCT)-DTA model, which improves DTA prediction by integrating multiscale graph diffusion convolution and CNN-transformer networks. The model processes protein sequences with CNNs to extract local features, followed by a transformer to capture global relationships. Simultaneously, drug molecules, represented as SMILES strings, are converted into molecular graphs and processed to extract structural features. After these features are obtained, a local interlayer interaction mechanism refines them to facilitate the exchange of information between drug and protein features. Finally, the combined data are fed into a fully connected layer for affinity prediction, allowing the model to accurately capture the intricate interactions between drugs and their targets. Another TDGraphDTA model proposed by Zhu et al. [52] predicts drug-target affinity by integrating multiscale information interactions and graph optimizations to achieve superior accuracy and interpretability. The model begins by preprocessing protein sequences into graph representations and drug molecules into SMILES-encoded molecular graphs. It then employs multilevel cascaded CNNs to extract both global and local features from protein sequences, while a diffusion-based graph optimization block enhances the drug molecular graphs by capturing intricate relationships between nodes. A cross-attention mechanism within the multi-scale interaction block further integrates features from both drug and protein inputs, effectively capturing contextual information between molecular substructures. These optimized features are then combined and processed through fully connected layers to predict DTA.

In recent years, with advancements in computational power and data availability, large language models (LLMs) have demonstrated exceptional performance in various areas, including content comprehension and reasoning. They have also been applied in the discovery of drug and disease targets. Lennox et al. [53] presented a novel approach for predicting DTA by combining pretrained bidirectional encoder representations from transformers (BERT) models and GCNs. Specifically, they used a pretrained BERT model to encode protein sequences and a pretrained RoBERTa model to encode drug SMILES strings, generating robust representations for each drug and protein. These representations are then fed into a GCN, which models the interactions between the drugs and proteins. Theodoris et al. [54] proposed Geneformer, a context-aware, attention-based deep learning model pretrained on ~30 million single-cell transcriptomes. This model uses a self-supervised masked learning objective to learn gene network dynamics and is fine-tuned for various tasks, including drug-target interaction prediction. Geneformer excels in predicting dosage-sensitive genes and identifying candidate therapeutic targets, significantly enhancing drug discovery by modeling gene deletions and activations in specific cellular contexts. Its ability to perform accurate predictions with limited data demonstrates its potential in uncovering novel drug targets and optimizing therapeutic strategies.

3. Molecular collision-based drug target prediction

On the basis of principles of molecular interactions, drug target prediction models focus primarily on identifying ligands that can activate or inhibit specific proteins. By predicting the interactions between drugs and their targets, these models help elucidate the mechanisms of action at the molecular level. Leveraging computational techniques, they efficiently identify promising drug candidates and provide insights into their molecular effects.

3.1. ML-based molecular collision algorithms for drug target prediction

In traditional ML approaches for predicting drug targets, there are two main methodologies (Table 1) [55–57]. The first approach involves the use of molecular docking results as inputs for ML models to predict the efficacy of potential ligands. For example, Marchetti et al. [55] integrated molecular dynamics simulations, molecular docking, and ML to predict the functional effects of allosteric ligands on the heat shock protein 90 (HSP90) protein. First, representative protein conformations are generated from simulations. Next, a library of ligands is docked to these structures. Finally, ML algorithms, specifically support vector machines, classify the ligands as activators or inhibitors based on features extracted from the docking results, achieving highly balanced accuracy in distinguishing the functional categories. The second approach involves prescreening ligands based on their molecular features via ML models and then employing molecular docking methods to refine and predict their interactions with the target protein. Salimi et al. [56] proposed a method to identify potential vascular endothelial growth factor receptor 2 (VEGFR2) kinase inhibitors. The method begins by gathering data from chemical databases and computing molecular descriptors. A random forest classifier is used to screen compounds with high prediction probabilities, followed by similarity screening to known inhibitors. The selected compounds are then subjected to molecular docking and molecular dynamics simulations to evaluate their binding affinity and to assess the stability of the ligand-protein complexes, respectively. Finally, adsorption, distribution, metabolism, excretion, and toxicity (ADMET) properties are predicted to confirm favorable pharmacokinetic profiles and low toxicity. Similarly, Yasir

et al. [57] employed a multistep approach to identify potential Janus kinase 2 (JAK2) inhibitors. Initially, a reference dataset of known JAK2 inhibitors is gathered, and molecular descriptors are generated via RDKit tools. Next, a random forest regression model is constructed using Scikit-learn to predict the pIC50 values of a large chemical library. The compounds with high prediction scores are then subjected to molecular docking to evaluate their binding affinities. Subsequently, molecular dynamics simulations are used to assess the stability of the ligand-protein complexes. Finally, ADMET properties are predicted, and selected compounds are experimentally validated for their JAK2 inhibitory activity.

3.2. CNN- and GCN-based molecular collision algorithms for drug target prediction

Models based on CNNs and GCNs have advantages in expanding the receptive field, preserving structural information, and extracting more meaningful data (Table 1) [58–64]. DeepBindBC [58] is a deep learning method for identifying native-like protein-ligand complexes through a virtual screening. The approach begins by collecting binding structures, removing complexes with rare atom types, and generating potential negative data by cross-docking nonnative ligands. Using these data, a ResNet (2D-CNN)-based model is constructed. Input data are generated by encoding the atomic types with one-hot encoding and calculating the Euclidean distances between atomic pairs. The ResNet model is trained on these structured data to distinguish binding interactions from nonbinding interactions. By using DeepBindBC, Zhang et al. [59] proposed a multistep approach that combines deep learning and molecular dynamics simulations to identify novel inhibitors of the cancer drug target tumor necrosis factor alpha (TNF-α)-induced protein-8 like2 (TIPE2). Initially, the TIPE2 protein structure is modeled, and a large chemical library is prepared. A deep learning-based dense fully connected neural network (DFCNN) was developed to predict protein-ligand binding probabilities. Preliminary screening is conducted with this DFCNN. Structural-based screening by DeepBindBC is followed, which incorporates physicochemical and spatial information. High-potential candidates are then subjected to molecular docking and stability assessments through molecular dynamics simulations. Finally, the binding affinities of the selected candidates are experimentally validated. For the 3D-CNN model, Jiménez et al. [60] proposed K_{DEEP} to predict protein-ligand binding affinity. The approach represents protein and ligand atoms in a 3D grid, capturing their physicochemical properties as voxel features. A simplified SqueezeNet architecture is employed for the 3D-CNN, which processes these voxelized representations to learn complex interaction patterns. Other methods, such as those proposed by Ragoza et al. [61] and Stepniewska-Dziubinska et al. [62], also use a similar 3D-CNN approach for drug-target prediction.

GCN models can better preserve spatial structural information in molecular collision models. By combining CNN and GCN models, Jones et al. [63] predicted protein-ligand binding affinity by integrating deep learning models with structural analysis. After essential atomic features such as element type, hybridization state, and structural properties are extracted, two main models are built: a 3D-CNN and a spatial graph CNN (SG-CNN). The 3D-CNN captures 3D atomic features and interactions via voxel grid representations, thereby learning spatial information without predefined pairwise interactions. The SG-CNN, on the other hand, models both covalent and noncovalent interactions explicitly via graph-based representations, leveraging adjacency matrices to define atomic neighborhoods. After independent training, these models are combined in the prediction module via mid-level and late fusion techniques, which harness their complementary strengths, leading to increased prediction accuracy and computational efficiency. Another GCN model is PIGNet [64], a physics-informed deep learning model. PIGNet leverages a neural network graph to represent protein-ligand complexes as molecular graphs, incorporating node features and adjacency matrices to capture covalent and intermolecular interactions. The model uses physics-based equations parameterized by neural networks to calculate interaction energies, thereby embedding the underlying physics of protein-ligand binding into the learning process. Data augmentation strategies, including generating random binding poses, are employed to increase the diversity of the training set, improving the model's generalizability. Compared with traditional methods and previous deep learning models, the performance of PIGNet shows superior docking and screening powers.

3.3. Transformer-based molecular collision algorithms for drug target prediction

By utilizing transformer models (Table 1) [65–68], Guo et al. [65] proposed ViTScore, a novel method for predicting protein-ligand docking poses via a vision transformer (ViT). ViTScore voxelizes the protein-ligand interaction pocket into a 3D grid, where each voxel encodes the occupancy of atoms on the basis of their physicochemical properties. This voxelized representation is then processed by a ViT model, which processes the 3D grid through a series of transformer blocks. These blocks leverage self-attention mechanisms to capture intricate spatial and energetic patterns between atoms, enabling the ViTScore to distinguish between near-native and nonnative docking poses effectively. Another transformer method, ETDock [66], uses an equivariant transformer for predicting protein-ligand docking poses by integrating atomic-level and graph-level features through a feature processing module and a TAMformer module. The ligand is represented as a molecular graph, with node embeddings learned via a graph isomorphism network (GIN), whereas protein embeddings are obtained via geometric vector perception (GVP). These features are fused via a learnable outer product to capture protein-ligand interactions. The TAMformer module, consisting of triangle, attention, and message layers, processes these features to predict a protein-ligand distance matrix and iteratively refines the ligand pose, significantly enhancing docking accuracy by enforcing geometric constraints and improving information exchange. From the perspective of 3D point clouds, Wang et al. [67] proposed a method that involves generating 3D point clouds, with each point representing an atom's coordinates, van der Waals radius, atomic weight, and source. These data are then processed by PointTransformer, a model that incorporates hierarchical spatial structures and self-attention mechanisms to predict binding affinity. This approach allows the model to accurately predict binding affinity by preserving the original geometric information of the protein-ligand complex. Zhu et al. [68] proposed the mutual transformer (MT)-DTA model, which innovatively combines a CNN and transformer-based molecular sequence encoded with a self-attention mechanism; this combination leads to accurate and consistent drug-target affinity predictions. The model first uses CNN and transformer blocks to effectively encode drug and protein sequences, capturing both local and global molecular features. In addition, it introduces a self-attention mechanism to simulate detailed interactions between these sequences, addressing the need to capture complex intermolecular relationships. Finally, these interaction features are fed into a fully connected network to accurately predict drug-target affinity.

4. Drug combination target prediction

Drug combination target prediction is also a crucial component of AI-driven drug development [69,70]. This approach uses

advanced computational models to identify synergistic interactions between multiple drugs and their targets. By analyzing large datasets and leveraging ML algorithms, drug combination target prediction helps uncover complex biological interactions that single-drug treatments may miss (Fig. 2). This method not only aids in understanding the combined effects of drugs but also enhances the efficacy and safety profiles of therapeutic regimens. In the context of AI drug development, predicting drug combination targets has accelerated the discovery of novel, more effective treatment strategies, paving the way for personalized and precision medicine.

4.1. Biological network-based algorithms for drug combination target prediction

Modern medicine has gradually transformed from "one drug, one target" to "multiple drugs, multiple targets". Therefore, developing algorithms for predicting the efficacy and mechanism of drug combinations is crucial for drug development (Table 2) [71–78]. Network pharmacology is suitable for predictions related to drug combinations owing to its hypothesis on biological networks. Li et al. [71] introduced a virtual screening paradigm based on "network target", which is different from the traditional "single target" concept. The proposed algorithm, termed network target-based identification of multicomponent synergy (NIMS), is designed to prioritize synergistic agent combinations in a high-throughput manner. Candidate agents labeled as "n" are used as inputs for NIMS and can be translated into network interactions among molecular entities such as targets or responsive gene products within the network pharmacology theory. The model then computes the synergy scores between a specified agent and every candidate agent and ranks the effective agent pairs. In biological networks, nodes representing biomolecules might play different roles with different functions. Identifying communities or modules in a biological network could help determine the synergistic relationships among drug combinations and thus increase the

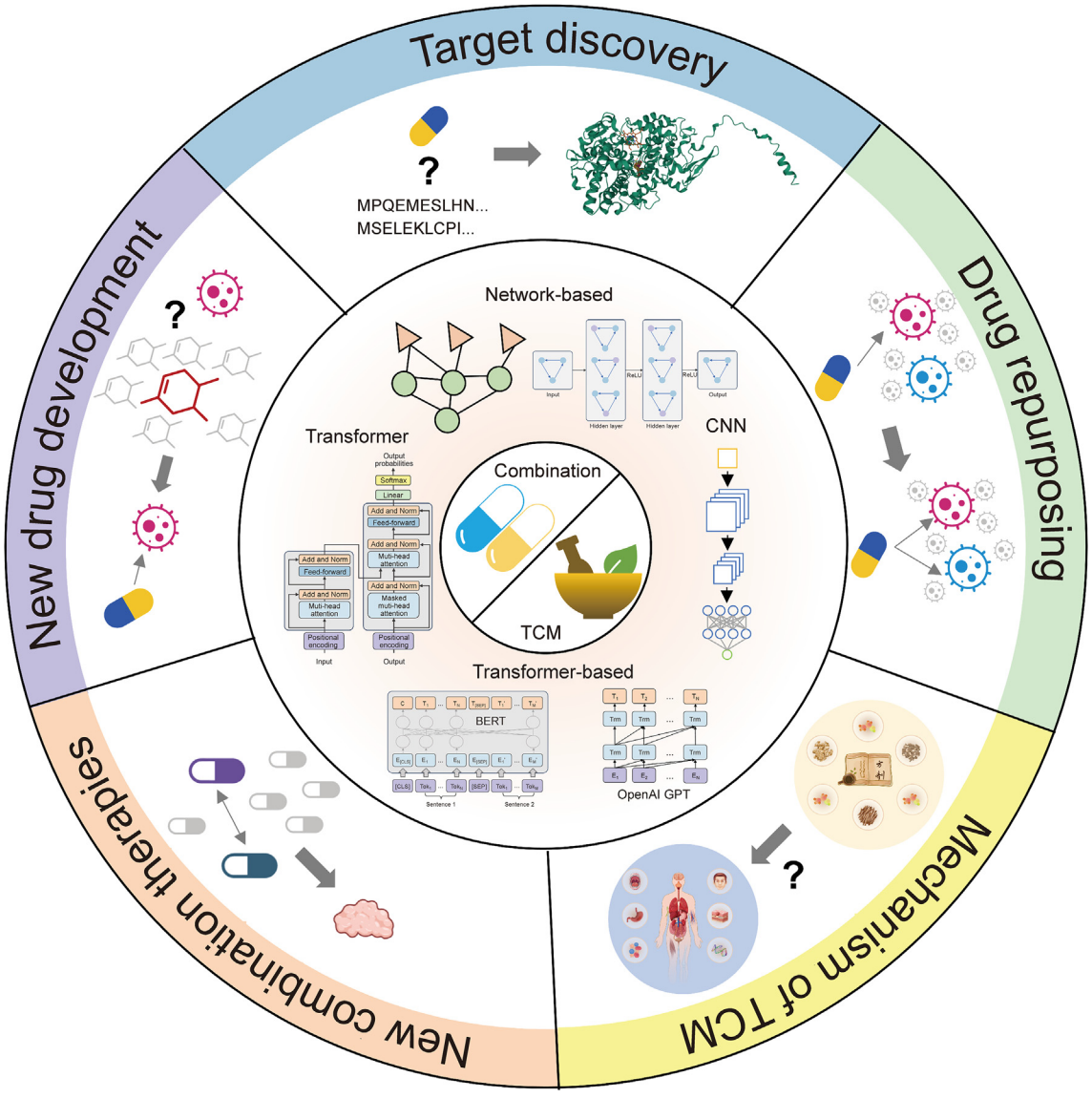

Fig. 2. This comprehensive diagram illustrates the multifaceted approach to artificial intelligence (AI)-driven drug combination development, focusing on the integration of various methodologies for target discovery, drug repurposing, understanding mechanisms of traditional Chinese medicine (TCM), new combination therapies, and new drug development. CNN: convolutional neural network; Add: addition; Norm: normalization; C: contextual representation; T: tokens (Toks) of the input sentences; E: embedding representations; BERT: bidirectional encoder representations from transformers; CLS: classification Tok; SEP: separator Tok; Trm: transformer block; GPT: generative pre-trained transformer.

Table 2
Studies for drug combination-target prediction.

Model	Name	Input	Refs.
Biological network-based	NIMS	Agent and candidate agents	[71]
	DMIM	Candidate herbal formulae and herb pairs	[72]
	comCIPHER	Protein interaction, drugs and their targets, drug-disease associations, and chemical-drug associations	[73]
	_	Drug A, drug B, disease, and protein	[74]
	SRWR	TCM	[75]
	_	Protein-metabolite network	[76]
	MatchMaker	Gene expression profile and drug chemical structure	[77]
	SynPathy	Drug feature based on pathway, chemical structure, and cell line feature	[78]
CNN and GCN-based	CNN-DDI	Drug categories, targets, pathways, and enzymes	[85]
	CNN-Siam	Chemical substructures, targets, and enzymes	[86]
	_	Patient records	[87]
	DRSPRING	Chemical structure, genetic interactions, drug-target information, and gene expression profiles of cell lines	[88]
	MK-GNN	Medical records (diagnosis, treatment procedure, medications, and drug network)	[89]
	GCN-BMP	Canonical SMILES strings	[90]
Transformer-based	SynergyX	Drug substructure and multiomics cell features	[91]
	SynergyGTN	SMILES and cell-line gene expression profiles	[92]
	DeepPSE	Polypharmacy side effects, mono side effects information, and drug-protein interactions	[93]
	MDF-SA-DDI	Substructures, targets, and enzymes	[94]
	LaGAT	Knowledge graph	[95]
	EGFI	Each sentence has a pair of drugs with an annotated relation (advise, effect, mechanism, int, and negative)	[96]
	CancerGPT	Drug pair synergy data	[97]

−: model without name. NIMS: network target-based identification of multicomponent synergy; DMIM: distance-based mutual information model; CIPHER: correlating protein interaction network and phenotype network to predict disease genes; SRWR: signed random walk with restart; TCM: traditional Chinese medicine; CNN: convolutional neural network; GCN: graph convolutional network; DDI: drug–drug interaction; DRSPRING: drug synergy prediction by integrated GCN; MK: medical-knowledge-based; GNN: graph neural network; BMP: bond-aware message propagation; SMILES: simplified molecular input line entry system; MDF: multi-source drug fusion, multi-source feature fusion; SA: self-attention; LaGAT: link-aware graph attention; EGFI: extraction and generation with fusion of enriched entity and sentence information; int: DDIs are provided without any information.

accuracy of the prediction of drug combinations. From a network perspective, Li et al. [72] developed the distance-based mutual information model (DMIM) to identify significant relationships among herbs in various herbal formulae. DMIM combines mutual information entropy with “between-herb-distance” to score herb interactions and construct an herb network. The effectiveness of the model has been validated on a case study of the Liu-Wei-Di-Huang formula. The comCIPHER [73] algorithm introduces a novel representation of drug-gene-disease relationships called a “comodule”, which characterizes closely related drugs, diseases, and genes. The method begins by defining a network-based gene closeness profile to establish connections between drugs and diseases. A Bayesian partition method was subsequently developed to identify these drug-gene-disease comodules on the basis of gene closeness data. Finally, the comodules established through comCIPHER can be used for new drug applications.

Many algorithms based on the attributes of biological networks for drug combinations have also been developed. Cheng et al. [74] proposed a network-based methodology to identify clinically effective drug combinations for treating complex diseases, addressing the challenge of combinatorial explosion due to numerous drug pairs and dosage combinations. The methodology quantifies the network-based relationships between drug targets and disease-related proteins within the human protein-protein interactome. Their analysis revealed six distinct classes of drug-drug-disease combinations. Among these classes, only one is correlated with therapeutic effects: when the targets of both drugs hit the disease module but target separate neighborhoods. In addition, to understand the molecular mechanisms of herbal medicines used in TCM for treating complex diseases, a novel computational systems pharmacology approach was proposed by Zhao et al. [75]. This approach includes transcriptome profiling, data collection, statistical analysis, network algorithms, bioinformatics analysis, and pharmacological validation. Central to this method is the network algorithm called signed random walk with restart (SRWR), which simulates the propagation of drug effects on networks. SRWR identifies proteins as either positively or negatively regulated (activated or inhibited) by drugs within human signaling networks. Casas et al. [76] proposed a mechanism-based disease definition within the framework of network pharmacology. This method begins by identifying a primary causal target and extends to a secondary target via guilt-by-association analysis. Predictions have been validated and explored for synergy through *in vitro* and *in vivo* mouse models. MatchMaker [77], a deep learning framework for drug combination prediction, consists of two drug-specific networks and a synergy prediction network. Drug-specific networks are designed to extract the hidden biological information between drug chemical structures and cell line gene expression profiles so that the prediction network can precisely predict and present novel drug combinations. Tang and Gottlieb [78] proposed a biological network-based deep learning model named SynPathy, which utilizes pathway-level drug features and cell line molecular data as inputs to suggest potential strategies for drug combination therapy. By testing the DrugComb benchmark, SynPathy performs better than existing methods do and provides explainable pathways for synergy prediction.

The numerous applications of network pharmacology methods in drug discovery demonstrate the potential of AI to address specific challenges. For example, do Valle et al. [79] developed a network medicine framework to understand how polyphenols influence health by analyzing interactions between polyphenol protein targets and disease-associated proteins. Their study revealed that these targets cluster in specific regions of the human interactome, with their proximity to disease proteins predicative of known therapeutic effects, which highlights AI’s ability to integrate complex biological data and predict therapeutic outcomes that traditional methods might miss [79]. In addition, in complex drug combinations or TCM fields, network target theory and techniques have also been applied in drug development and repositioning [80,81]. For example, AI revealed that Weifuchun and Moluodan, both of which are used for treating chronic atrophic gastritis, have distinct mechanisms of action: Weifuchun primarily modulates immune responses, whereas Moluodan affects lipid metabolism [82,83]. These findings underscore the role of AI in refining

therapeutic strategies. Additionally, in biomarker prediction, AI combines network analysis with clinical trials and animal studies to identify key biological modules regulated by the Yiqi Tongqiao pill. This analysis revealed pathways related to immune regulation, epithelial barrier disorders, and cell adhesion, centered on biomarkers such as interleukin 4 (IL-4), interferon gamma (IFN-γ), TNF-α, and IL-13 [84], and demonstrated AI's capacity to predict clinically relevant biomarkers and guide therapeutic development.

4.2. CNN- and GCN-based association algorithms for drug combination target prediction

Unlike most network-based pharmacological approaches, some studies utilize advanced deep learning methods to extract drug-related features and apply these features to tasks such as combination drug therapies, drug synergy score predictions, and IC_{50} predictions for drug combinations. CNNs and GCNs are commonly used to extract both the global and local features of drugs, demonstrating their strengths, particularly in drug-drug interaction (DDI) prediction tasks (Table 2) [85–90].

The CNN-DDI method [85] incorporates multiple drug-related features, such as drug categories, targets, pathways, and enzymes, and then uses a CNN to extract features for DDI prediction. The fusion of diverse features of this method and the use of the Jaccard similarity have been validated to improve the prediction ability in the drug-drug-interaction events predicted by a multimodal deep learning framework (DDIMDL) task. The CNN-Siam model [86], which employs a Siamese network architecture, is recognized for its effective prediction of DDIs via multimodal drug data. This model leverages twin convolutional networks and sophisticated optimization algorithms, achieving significant accuracy improvements over the state-of-the-art methods. Although many studies have focused mainly on drug synergistic effects or the prediction of DDIs, Küçükosmanoglu et al. [87] proposed an innovative method for analyzing adverse events in combination therapies by using real-world data from the U.S. FDA's reporting system. By employing a CNN autoencoder to visualize complex adverse event patterns from millions of patient records, this research provided novel insights into the predominantly additive nature of drug interactions. This approach not only enhances understanding but also supports safer implementation of combination therapies in clinical settings, marking a significant advancement in predictive health care analytics.

In addition to network pharmacology methods, research on drug combination prediction also encompasses numerous studies leveraging GCNs. These studies employ GCNs to extract structural features of compounds and network-related features of drugs, which include associations among drugs, cells, genes, and pathways. By utilizing GCNs, these approaches can effectively capture the intricate relationships and interactions within biological networks, thereby enhancing the accuracy and comprehensiveness of drug combination predictions. By incorporating a GCN to integrate chemical structures, genetic interactions, and drug-target information, a deep-learning model called drug synergy prediction by integrated GCN (DRSPRING) [88] was established to predict drug synergy effects by innovatively utilizing pharmacogenomic profiles alongside molecular properties. The model has demonstrated good performance on the DrugComb database and can be extended to arbitrary drug pairs and cell lines. The medical-knowledge-based (MK)-GNN model [89] effectively integrates patient representations derived from historical medical records with essential medical knowledge, including prior knowledge and medication knowledge, to enhance medication combination prediction (MCP). Finally, the researchers performed a case study to show the application value of the MK-GNN. In addition to research on drug combinations, GCNs are also suitable for predicting DDIs. The GCN-BMP method [90] for predicting DDIs uses GCNs with a focus on bond-aware message propagation. Unlike several methods that consider various drug-related features that may cause noise, this model addresses this limitation by employing an end-to-end graph representation learning technique and achieves superior performance.

4.3. Transformer-based association algorithms for drug combination target prediction

While CNNs/GCNs have significantly advanced research, such as DDI prediction, the field of drug combination research is looking toward more sophisticated models, such as transformers (Table 2) [91–97].

SynergyX [91] has emerged as a groundbreaking tool in the domain of antitumor drug synergy prediction. This model is trained on features of drug substructures and multiomics data and uses a multimodality mutual attention network to capture information on intricate biological interactions, which excels in DrugComb task testing. The SynergyGTN [92] model represents a significant advancement in predicting synergistic drug combinations for cancer treatment. By leveraging graph transformer networks and integrating comprehensive drug and cell line features, SynergyGTN achieves notable improvements, with a receiver operating characteristic curve improvement of 5% over the state-of-the-art methods in terms of five-fold cross-validation. DeepPSE [93] presents a novel deep learning method to predict polypharmacy side effects by integrating multiple neural network types and a transformer encoder block for feature extraction. The model then applies feed-forward layers to predict polypharmacy side effects of drug pairs. Transformers also play an important role in the field of DDI prediction. The multi-source drug fusion, multi-source feature fusion (MDF)-self-attention (SA)-DDI model [94] introduces a sophisticated approach for predicting DDI events by employing a combination of multisource drug fusion and feature fusion with a transformer self-attention mechanism. This method distinguishes itself by not only predicting whether drugs interact but also detailing the nature of those interactions, providing a deeper understanding of drug interaction mechanisms. LaGAT [95] introduces a novel approach for DDI prediction by utilizing a link-aware graph attention mechanism that customizes attention pathways on the basis of different drug pair links. This method enhances the model's ability to capture meaningful semantic relationships between drugs, leading to improved performance and interpretability over both traditional and contemporary models.

The emergence of large-scale deep learning models has revolutionized various fields, including pharmacology. Following the development of BERT, the advent of generative pretrained transformers (GPTs) and other LLMs has significantly propelled research in drug combination studies. These models, which leverage vast textual descriptions, offer novel insights and methodologies for predicting effective drug synergies, thus enhancing the potential for breakthroughs in personalized drug and treatment strategies. Huang et al. [96] proposed an innovative approach using the extraction and generation with fusion of enriched entity and sentence information (EGFI) model, which integrates BioBERT and BioGPT-2 to enhance DDI extraction from the biomedical literature. This framework significantly improves DDI prediction by fusing enriched entity and sentence information, demonstrating its utility in identifying unrecorded drug interactions and potential novel relationships and providing a valuable tool for biomedical research. Li et al. [97] explored a novel application of LLMs to predict drug pair synergy in rare cancerous tissue with limited data. Leveraging the advanced capabilities of LLMs for few-shot learning, the study demonstrates that CancerGPT, a model tailored for this specific task, significantly enhances prediction accuracy compared with

traditional data-driven models, especially in contexts where data are scarce. This approach opens new avenues for the use of AI in personalized medicine and highlights the potential of LLMs in biomedical applications.

5. Conclusion

Drug-target interactions are crucial in AI-assisted drug development. By leveraging advanced deep learning techniques such as CNNs, GCNs, and transformers, along with network-based models and traditional ML methods, these approaches have significantly improved prediction accuracy and broadened the generalization capabilities of models. These advancements are particularly useful for identifying single drug-target interactions and understanding the complex dynamics of drug combination–target interactions. As a result, they accelerate the drug discovery process and contribute to the development of more effective and personalized therapies. The significance of these advancements lies in their ability to process and learn from vast amounts of biological data, overcoming the limitations of traditional methods that often struggle with the complexity of molecular interactions. For example, CNNs excel at identifying spatial patterns and structural features of molecules, which are critical for predicting potential drug-target interactions. GCNs offer a detailed representation of molecular structures and their related data, providing a comprehensive understanding of how individual drugs interact with specific targets. Owing to their powerful attention mechanisms, transformers further increase prediction accuracy by capturing intricate dependencies within biological sequences. Network-based models add to this predictive framework by offering a systems-level perspective, integrating various data sources to reveal complex biological interactions. Traditional ML techniques complement these approaches by efficiently handling large datasets and extracting relevant features, thereby increasing overall predictive accuracy and reliability.

Predicting drug combination-target interactions presents additional challenges owing to the increased complexity of multidrug interactions. Deep learning methods, such as CNNs, GCNs, and transformers, have shown promise in addressing these challenges by modeling the combined effects of multiple drugs on biological targets. GCNs, in particular, excel at representing and analyzing the relational data inherent in drug combinations, providing insights into synergistic and antagonistic effects. The ability of transformers to handle complex sequential data is instrumental in predicting the outcomes of drug combinations on specific targets. Network-based models offer a holistic approach, which is crucial for understanding the broader implications of drug combinations within biological systems, enabling the identification of multitarget strategies and potential side effects. The integration of molecular collision models further enhances these predictions by simulating the physical interactions between drug combinations and targets, offering detailed insights into binding affinities and specificities.

However, the application of AI in drug development is not without its limitations. Despite the promise shown by these techniques, challenges remain in ensuring the interpretability of AI models, especially when dealing with the complex nature of biological systems. The “black-box” nature of deep learning models can obscure the mechanistic understanding of how predictions are made, which is critical for regulatory approval and clinical adoption. Additionally, the quality and diversity of the training data significantly influence the performance of AI models. Biases in the data can lead to inaccurate predictions, potentially resulting in serious implications for drug development. In the context of drug combination-target interactions, this increased complexity presents additional challenges. While deep learning methods such as GCNs and transformers have shown promise in modeling the combined effects of multiple drugs, the potential for unforeseen interactions and side effects remains a significant concern. Moreover, the ability of these models to predict synergistic and antagonistic effects is still limited by the availability of comprehensive training datasets that capture the full range of possible drug interactions.

Despite these challenges, the integration of deep learning, network-based models, and traditional ML provides a robust framework for advancing drug discovery. These approaches not only accelerate the identification of promising drug candidates but also have the potential to revolutionize the development of personalized therapies. As these technologies continue to evolve, their impact on drug development is likely to grow, offering new possibilities for the treatment of complex diseases. However, addressing current limitations, such as improving model interpretability, enhancing data quality, and ensuring the ethical use of AI, will be essential to fully comprehend the potential of AI in drug development and clinical applications.

CRediT authorship contribution statement

Boyang Wang: Writing – review & editing, Writing – original draft, Visualization, Data curation. **Tingyu Zhang:** Writing – original draft, Visualization, Data curation. **Qingyuan Liu:** Writing – original draft, Visualization, Data curation. **Chayanis Sutcharitchan:** Writing – original draft, Data curation. **Ziyi Zhou:** Writing – original draft, Data curation. **Dingfan Zhang:** Data curation. **Shao Li:** Writing – review & editing, Project administration, Conceptualization.

Declaration of competing interest

The authors declare that there are no conflicts of interest.

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