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Review

Identification of natural product-based drug combination (NPDC) using artificial intelligence

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ABSTRACT

Natural product-based drug combinations (NPDCs) present distinctive advantages in treating complex diseases. While high-throughput screening (HTS) and conventional computational methods have partially accelerated synergistic drug combination discovery, their applications remain constrained by experimental data fragmentation, high costs, and extensive combinatorial space. Recent developments in artificial intelligence (AI), encompassing traditional machine learning and deep learning algorithms, have been extensively applied in NPDC identification. Through the integration of multi-source heterogeneous data and autonomous feature extraction, prediction accuracy has markedly improved, offering a robust technical approach for novel NPDC discovery. This review comprehensively examines recent advances in AI-driven NPDC prediction, presents relevant data resources and algorithmic frameworks, and evaluates current limitations and future prospects. AI methodologies are anticipated to substantially expedite NPDC discovery and inform experimental validation.

1. Introduction

Single-agent targeted therapies for patients with well-defined molecular characteristics are transforming treatment. However, effective treatments remain elusive for many patients, as the efficacy of even the most advanced medicines is constrained by pre-existing or acquired resistance [1]. Drug combination therapy, utilizing two or more drugs simultaneously, offers several advantages over monotherapy. These combinations enhance efficacy through multi-targeting effects, minimize toxic side effects by enabling lower individual drug doses, and address monotherapy resistance [2, 3]. Combination therapies have emerged as standard clinical management protocols for numerous complex diseases, including cancer, diabetes, and microbial infections [4-7]. Consequently, substantial interest exists in exploring the vast combinatorial space of both approved and investigational agents to identify effective and safe drug combinations for multiple indications [8, 9].

Natural products (NPs), sourced from microorganisms, plants, and animals, exhibit distinctive structural and pharmacological properties particularly beneficial in combination therapies [10, 11]. From 1981 to 2019, NPs served as the source for over 60% of Food and Drug Administration (FDA)-approved small-molecule drugs [12]. NPs provide privileged scaffolds, structural complexity, and enhanced three-dimensionality compared to conventional small molecules, potentially crucial for binding challenging drug targets. The exploration of small molecules with novel molecular scaffolds demonstrating unexpected biological activity significantly benefits from NP-derived insights [13–17]. Their natural origin and evolutionarily optimized structures predispose NPs to interact with multiple targets. These intricate multi-target interactions may prove more effective in addressing complex disease etiologies or drug resistance. Furthermore, unlike conventional synthetic drugs typically comprising single compounds, NPs often contain various physiologically active chemicals. These bioactive components enable synergistic multi-target interactions in combination therapies, reducing resistance risk while enhancing therapeutic efficacy and safety [18–20], presenting promising opportunities for novel combination therapy development. Thus, compared to general drug combinations, natural product-based drug combinations (NPDCs) offer innovative solutions to address therapeutic challenges posed by monotherapy against complex diseases [21, 22].

As potential drug candidates increases rapidly, the number of possible drug combinations grows exponentially, each potentially eliciting different patient responses. Modern high-throughput screening (HTS) alone proves insufficient for comprehensive drug combination assessment. Such experimental screening requires substantial resources and time, rendering it unsuitable for high-throughput NPDC exploration. Furthermore, given the geometric expansion of the experimental parameter space, appropri-

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ate computational methods for drug combination prediction and feature extraction are essential for guiding effective combination discovery and rational experimental design [23, 24]. Contemporary advances in computing technologies and bioinformatics have generated unprecedented data volumes across various omics fields, including transcriptomics, metabolomics, and genomics [25, 26]. Consequently, selecting suitable computational methods for drug combination prediction and meaningful feature extraction is crucial for directing rational experimental design. Recent years have witnessed significant promise in data-driven artificial intelligence (AI) methods within drug combination research. For instance, Tosh et al. [27] developed an active learning-based method for drug combination screening, while Li et al. [28] employed pretrained language models to predict pairwise synergy with high accuracy. Although numerous AI techniques have been implemented for drug combination prediction, their specific effectiveness in predicting synergistic interactions between NPs and drugs remains under active investigation. Therefore, a comprehensive review examining recent advances and future directions in NPDC prediction is essential.

In contrast to previous reviews that broadly address drug combinations with a cursory overview of AI methods, this review presents a comprehensive analysis of the advancements, obstacles, and prospects of AI-driven methodologies in NPDC prediction. The review begins by examining the distinctive features of NPs and small-molecule drugs, emphasizing the benefits and constraints of combination therapies, alongside a discussion of evaluation metrics. Subsequently, it surveys relevant NPDC prediction datasets and explores strategies for multi-source data integration. The review then examines algorithmic frameworks and learning paradigms employed in drug combination research, supported by representative case studies. The final section addresses critical challenges facing AI applications in this domain. This comprehensive review synthesizes recent developments and future trajectories in AI-driven NPDC prediction, serving as an essential reference for researchers in this field.

2. Characteristics and evaluation metrics of NPDCs

In the era of AI-accelerated drug discovery, comprehending combination therapy principles is fundamental for guiding AI-driven identification of novel NPDCs. Through analysis of the distinct characteristics of NPs and small-molecule drugs, researchers can enhance screening workflows and refine evaluation metrics to accurately quantify synergistic effects, thereby facilitating NPDC assessment and validation.

Conventional drug-discovery approaches have emphasized identifying single agents targeting specific disease-associated biomolecules, with novel therapeutic target discovery driving significant advances in drug design. However, diseases such as cancer and cardiovascular disorders frequently involve multiple therapeutic targets, making monotherapies inadequate for meeting clinical efficacy requirements. Moreover, resistance to monotherapy remains a significant challenge, primarily due to the inherent heterogeneity of complex diseases [29]. Furthermore, certain undruggable targets lack clinically approved drugs. Given these limitations, combination therapy has emerged as a viable solution and has become a standard clinical approach for various complex diseases, including multidrug-resistant infections such as tuberculosis and malaria, as well as viral diseases like HIV, hepatitis C, and COVID-19 [30-32]. The FDA defines a drug combination as two or more regulated components, such as drugs, devices, or biologics, that are physically or chemically combined. Reviews of published drug combination studies typically categorize interaction effects into three groups: synergistic, additive, and antagonistic [33, 34]. Additive effects occur when the combined therapeutic outcome equals the sum of individual effects. Synergistic effects manifest when combined action exceeds additive expectations, while antagonistic effects represent the opposite scenario. Synergistic effects have attracted particular attention due to their potential for achieving enhanced therapeutic efficacy at lower doses, thus reducing toxicity and delaying resistance development. Despite increasing clinical adoption of combination therapies, rationally identifying drug combinations that optimize therapeutic efficacy while minimizing adverse effects remains challenging.

Traditional Chinese medicine (TCM) encompasses medicinal materials utilized under traditional theoretical guidance and empirical knowledge, derived from plants, animals, and minerals, predominantly of botanical origin. NPs represent a broader range of specialized metabolites produced by bacteria, fungi, plants, and animals. Excluding certain inorganic mineral constituents and animal-derived macromolecules, most bioactive components in TCM are NPs [35-37]. NPs have historically served as a valuable source of bioactive compounds, providing chemists with structurally novel scaffolds possessing bioactive potential, many evolving into clinically approved drugs [38, 39]. Unlike conventional synthetic agents, NPs feature more complex three-dimensional structures, higher molecular weights, and greater scaffold rigidity, enabling them to function as transporter substrates that facilitate effective drug-target interactions (DTI). Additionally, NPs' intrinsic ability to interact with multiple protein targets grants them substantial potential for combination therapy [37, 40]. NPs demonstrate remarkable structural and functional similarity to endogenous metabolites, combined with excellent biocompatibility and low toxicity, making them ideal candidates for drug combinations addressing persistent challenges in conventional therapies. Based on therapeutic outcomes, NPDCs can enhance drug sensitivity [41, 42], achieve therapeutic synergy [43], reduce toxic side effects [44, 45], and reverse drug resistance [46]. The integration of NPs with small-molecule drugs offers significant potential for overcoming resistance, enhancing therapeutic sensitivity, and enabling safer, more effective clinical treatments. However, challenges including low yields of active constituents, physicochemical instability, and limited solubility continue to hinder comprehensive NP exploration and application [47, 48].

Drug combination effects are evaluated by comparing observed responses with expected additive effects to identify synergistic interactions. To assess the effectiveness of drug combinations, researchers have developed several reference models. Table 1 summarizes the synergy metrics associated with NPDC. The Loewe additivity model (Loewe) [49] and Bliss independence model (Bliss) [50] represent classical synergy metrics extensively utilized in drug synergy analysis. Both models operate on the principle that compounds within a drug combination do not interact. The Loewe model assumes that the dose-response curves of both compounds exhibit identical shape and slope. Synergistic effects are identified when the observed combined effect surpasses the theoretical additive value, while antagonistic effects occur when the observed effect falls below expectations. The Bliss model, conversely, assumes that the mechanisms of action between drugs operate independently. The Loewe model proves more suitable when drugs target common pathways, while the Bliss model demonstrates greater applicability for drugs targeting distinct pathways. Recent developments have produced new reference models that combine the strengths of these classical approaches. The zero interaction potency (ZIP) [51, 52] score model represents one such advancement, incorporating elements from both Loewe and Bliss models. The ZIP model postulates that the dose-response curve maintains consistency in combination therapy, quantifying synergy on a scale from -1 to 1. Furthermore, the highest single agent model (HSA) [53, 54] evaluates synergy by comparing the maximum effect differential between the drug combination and individual drug components.

Table 1 Comparison of drug synergy evaluation models.

Aspect	Loewe Additivity	Bliss Independence	HSA	ZIP
Mechanism assumption	Same and equivalent dosage	Independent	Neglect	Zero interaction
Target independence	Same or similar	Independent	-	Potency independent
Dose-response curve	Complete curve	Complete curve or data	-	Complete curve
Combination index	$\mathrm{CI}(x)=\frac{D_A}{D_A^*(x)}+\frac{D_B}{D_B^*(x)}$	$E_{Bliss}=\frac{E_A+E_B-E_AE_B}{E_{AB}}$	$E_{HSA}=\frac{E_{AB}}{max\{E_A,E_B\}}$	$E_{ZIP}=\frac{(d_A/m_A)^{\lambda_A}}{1+(d_A/m_A)^{\lambda_A}}+\frac{(d_B/m_B)^{\lambda_B}}{1+(d_B/m_B)^{\lambda_B}}-\frac{(d_A/m_A)^{\lambda_A}}{1+(d_A/m_A)^{\lambda_A}}\times\frac{(d_B/m_B)^{\lambda_B}}{1+(d_B/m_B)^{\lambda_B}}$
Limitations	Stringent curve-fitting requirements	Overestimation of the synergy of low-efficacy drugs	Neglect of dose-dependent information and weak synergistic effects	Computationally intensive and requires high-quality data
Application	Precise quantification of equivalent dose substitution relationships	Preliminary screening by high-throughput screening	Early-stage screening	Large-scale grid experiments with dense two-dimensional dose–response matrices

HSA, highest single agent; ZIP, zero interaction potency; $\mathrm{CI}(x)$, combination index; D_A, D_B, the doses of drug A and drug B, respectively, when used alone to achieve the target effect x; $D_A^*(x), D_B^*(x)$, the doses of drug A and drug B in the combination that actually produce the target effect x when used together; E_{AB}, effect of a drug combination; E_A, effect of a drug A; E_B, effect of a drug B; d_A, d_B, the doses of drug A and drug B; m_A, m_B, the doses that produce the midpoint effect when using drug A at d_A or drug B at d_B individually; λ_A, λ_B, the slopes of the curves induced by the individual drugs.

3. Data sources and fusion overview for model construction

Research has shown that data scale and quality are essential for the successful implementation of AI algorithms in drug discovery [55]. NP databases demonstrate substantial scale and diversity. However, these databases contain fragmented data lacking standardized statistical metrics. Additionally, statistical resources are limited, and integration between different databases remains inadequate [56]. Within general-purpose databases such as PubChem [57] and ChEMBL [58], NP entries often lack explicit annotations, hampering NP-specific data mining and analysis. Although most NP databases contain bioactivity assay data, few include bioassay information for NP extracts and fractions. This limitation in comprehensive and well-annotated data impedes the development of AI-driven models for NPDC prediction. Consequently, establishing a high-quality NPDC database presents a significant challenge.

NPDC prediction datasets can be categorized into two main groups based on data source: experimental data from HTS and knowledge-based data aggregated from heterogeneous databases [24]. Regarding input data requirements for predictive models, datasets fall into four categories: (i) compound data, (ii) NPDC data, (iii) omics data, and (iv) pathway data. Table 2 presents a detailed overview of feature and NPDC datasets. Compound data include molecular fingerprints, chemical structures, and pharmacological properties of NPs and small-molecule drugs, primarily sourced from databases such as DrugBank [59], NPASS [60], TCMBank [61], Super Natural II [62], NPAtlas [63], and COCONUT [64]. NPDC data encompasses experimental datasets characterizing NPDC interactions, with NPCDR [65] serving as a notable example. Table 3 outlines the databases related to omics and pathway data. Omics data encompasses cell-line expression profiles, miRNA expression, genomic mutations, and other molecular profiles essential for understanding combined therapy mechanisms. Relevant databases include CLUE [66], CCLE [67-70], GEO [71], and ENCODE [72]. Pathway data provides information on protein-protein interactions (PPI), DTI, and biological pathways, with major databases including Reactome [73], KEGG [74], IntAct [75], BioGRID [76], and STRING [77].

As of March 2025, NPCDR remains the only comprehensive repository dedicated to NPDC research and applications. NPCDR restricts drug entries to FDA-approved, patented, or clinically relevant compounds. NPs are sourced from high-quality databases including NPACT [78], HERB [79], ETCM [80], SANCDB [81], NANPDB [82], BIOFACQUIM [83], $\mathrm{NuBBE_{DB}}$ [84], and VIETHERB [85], ensuring data quality standards. The database contains 1,172 NPDCs, with 93.5% comprising binary combinations of an NP and a drug. NPCDR provides comprehensive molecular and pathway information for NPDC, alongside validated experimental models, including *in vivo* and *in vitro* systems, cell lines, model organisms, and detailed protocols. This comprehensive resource establishes a solid foundation for predictive modeling. NPCDR content is systematically standardized and integrated with authoritative resources such as UniProt [86], BRENDA [87], TTD [88], Pfam [89], KEGG [74], VARIDT [90], Cellosaurus [91], TCDB [92], and miRBase [93]. Users can access multiple data types through the NPCDR website and incorporate them into models to improve accuracy. Regarding data coverage, general drug combination databases such as DrugCombDB [94] and NCI-ALMANAC [95] demonstrate broader scope compared to NPCDR. DrugCombDB incorporates HTS datasets

Table 2 Public data resources relevant to NPDC prediction.

Category	Database	Description	Website
NP and drug	PubChem	Containing chemical substances, compounds, biological activities, and relevant data for scientific research and pharmaceutical development.	https://pubchem.ncbi.nlm.nih.gov/
	DrugBank	Containing detailed drug and drug-target data, along with extensive pharmacological information, including mechanisms, drug-drug interactions, adverse effects, etc.	https://go.drugbank.com/
	NPASS	Integrating bioactive natural product data with their species sources, physicochemical properties, and bioactivity profiles, plus tools for structure-based and bioactivity-based similarity analysis.	https://bidd.group/NPASS/
	TCMBank	Constructing a comprehensive network with multi-scale relationships, including TCM compounds, their herbal sources, disease associations, and molecular targets, to bridge TCM knowledge and modern pharmacology.	https://tcmbank.cn/
	COCONUT	Curating vast collections of natural products, annotated with chemical structures, taxonomic origins, and key physicochemical properties.	https://coconut.naturalproducts.net/search
	SuperNatural 3.0	Providing structural and physicochemical information about natural products and their derivatives, along with drug-like space predictions for specific diseases.	https://bioinf-applied.charite.de/supernatural_3/index.php
	NPAtlas	Focusing on microbially derived natural products, featuring chemical structures, producing organism taxonomy, and biosynthetic/chemical ontology classification.	https://www.npatlas.org/
NPDC	NPCDR	Compiling extensive data on NPDCs with clinically/experimentally validated therapeutic effects, and providing their disease-specific molecular regulation profiles.	https://npcdr.idrblab.net/

Table 3 The summary of omics and pathway databases related to NPDC prediction.

Category	Database	Description	Website
Omics databases	CLUE	Generating and cataloging gene expression profiles induced by perturbagens across diverse cell lines, doses, and time points, enabling analysis of drug actions, drug-drug synergies and pathway-level insights.	https://clue.io/
	CCLE	Characterizing and integrating multi-omics resources, including genomic, proteomic, transcriptomic, metabolomic, and pharmacologic profiles of over 1,000 cancer cell lines.	https://sites.broadinstitute.org/ccle/
	GEO	Archiving and disseminating high-throughput gene expression, epigenomics, and functional genomics datasets submitted by researchers, while also providing standardized storage, search and analytical tools.	https://www.ncbi.nlm.nih.gov/geo/
	ENCODE	Serving as an encyclopedia of functional elements in genome by integrating multi-omics experimental data and providing structured annotations.	https://www.encodeproject.org/
Pathway databases	TTD	Documenting known and explored therapeutic targets, along with their associated diseases, pathways, and corresponding drugs.	http://db.idrblab.net/ttd/
	HIT 2.0	Elucidating targets of herbal ingredients by capturing direct/indirect interactions and gene regulation events, with evidence curated from PubMed literature.	http://hit2.badd-cao.net/
	KEGG	Providing signaling pathway data on metabolism, disease, pharmacology, etc. in the form of hand-drawn diagrams, while also supporting gene regulatory network predictions from expression profiles.	https://www.genome.jp/kegg/
	Reactome	Containing detailed information on signaling and metabolic molecules and the biological pathways they constitute across a wide range of human physiological and pathological processes.	https://reactome.org/
	BioGRID	Curating and Archiving protein, genetic and chemical interaction across multiple species, while also documenting post-translational modifications and annotating genome-wide CRISPR/Cas9-based screens that report gene-phenotype and gene-gene relationships.	https://thebiogrid.org/
	STRING	Offering known and predicted protein-protein interaction, including direct physical associations and indirect functional linkages.	https://cn.string-db.org/

like NCI-ALMANAC and collects data from multiple sources including the AstraZeneca-Sanger drug combination dataset, DCDB2.0 [96], and DrugBank. Analysis indicates that while these comprehensive databases contain some NPDCs, they do not include all combinations documented in NPCDR. Regarding NPDC specificity, NPCDR demonstrates superior performance. In terms of data depth, beyond basic information on drugs, cell lines, and dose-response provided by comprehensive databases, NPCDR offers detailed insights into molecular pathways regulated by NPDCs and their regulatory characteristics. This aspect proves crucial for enhancing predictive model accuracy. All databases enable data access through official websites designed for viewing, evaluation, and downloading purposes. NPCDR provides a comprehensive compilation of NPDCs with disease-specific molecular regulatory data.

While individual data modalities offer valuable insights, their isolated application often fails to capture the complex interdependencies inherent in drug interactions. For example, molecular-level features may not account for cellular context, while omics data might lack mechanistic detail. Multimodal data delivers complementary perspectives on drug combinations, enabling a comprehensive understanding of complex biological mechanisms [97]. Multimodal data fusion forms the foundation of this process, involving the extraction and integration of information from multiple modalities for predictive tasks, thereby enhancing the predictive capability and generalizability of AI-driven models [98]. Current multimodal data fusion approaches fall into three categories: early fusion, late fusion, and intermediate fusion [99]. Early fusion integrates raw data or low-level features from different modalities during initial model processing. This integration typically employs vector concatenation, element-wise summation, and element-wise multiplication [100]. However, this approach requires a single model to process all modalities, presenting challenges when handling complex multimodal biological data. Late fusion, conversely, trains separate models for each modality and combines their predictions using methods such as averaging, majority voting, and learned models like multilayer perceptron (MLP). While suitable for unaligned multimodal data, late fusion neglects interactions between modality-specific models, limiting its capacity to capture cross-modal dependencies [101]. Intermediate fusion addresses these limitations by integrating intermediate- or high-level feature representations at specific model layers, facilitating the learning of cross-modal dependencies. State-of-the-art implementations include attention-based fusion and contrastive learning-based fusion. For instance, the MMGCSyn model introduced by Zhang et al. [102] integrated drug molecular graph features extracted by graph attention network (GAT), drug fingerprint features extracted by deformable convolutional network, and cell line features extracted by MLP. These modality-specific features were subsequently fused using a self-attention mechanism to capture drug-drug-cell interactions and generate a joint feature representation for synergy prediction. Similarly, the HGCLSynergy model developed by Xue et al. [103] utilized a neighbor-view encoder and a meta-path-view encoder to extract topological and semantic features from a heterogeneous graph comprising drugs, cell lines, and proteins. By employing contrastive learning to maintain consistency in the embedding space, the model performed indirect feature fusion through concatenation, significantly improving prediction accuracy and robustness. These innovative approaches present promising technical pathways for multimodal data integration and establish new directions for drug synergy prediction research.

4. AI-based methods for drug combination prediction

4.1. Algorithmic frameworks used in drug combination

As shown in Fig. 1, extensive research into general drug combination prediction has employed a wide spectrum of AI algorithms. The approaches established in AI-driven general drug combination research are highly relevant to NPDC prediction. Although general drug combinations and NPDCs differ in chemical and pharmacological properties, their underlying computational workflows, including feature representation, interaction modeling, and network-based data integration, share fundamental similarities. Therefore, AI algorithms validated on general datasets can serve as methodological references and provide effective starting points for developing NP-specific predictive models. These established computational strategies can assist researchers in overcoming data limitations, facilitating cross-domain knowledge transfer, and enhancing predictive accuracy in NPDC research. The input data type and other information of each method reviewed in this manuscript are listed in Table 4. There exists substantial detail and variation within the general datatypes, and specific details should be verified from the original articles. This section provides a concise overview of the theoretical foundations underlying the principal algorithms used in both general and NPDC prediction. Prediction tasks for drug combination therapies can be broadly categorized into classification and regression. The classification task aims to predict labels indicating whether a drug combination is synergistic or non-synergistic. However, this task faces challenges such as imbalanced data, inconsistent label definitions across experimental conditions, and data heterogeneity, which complicate the determination of an appropriate classification threshold. The regression task focuses on

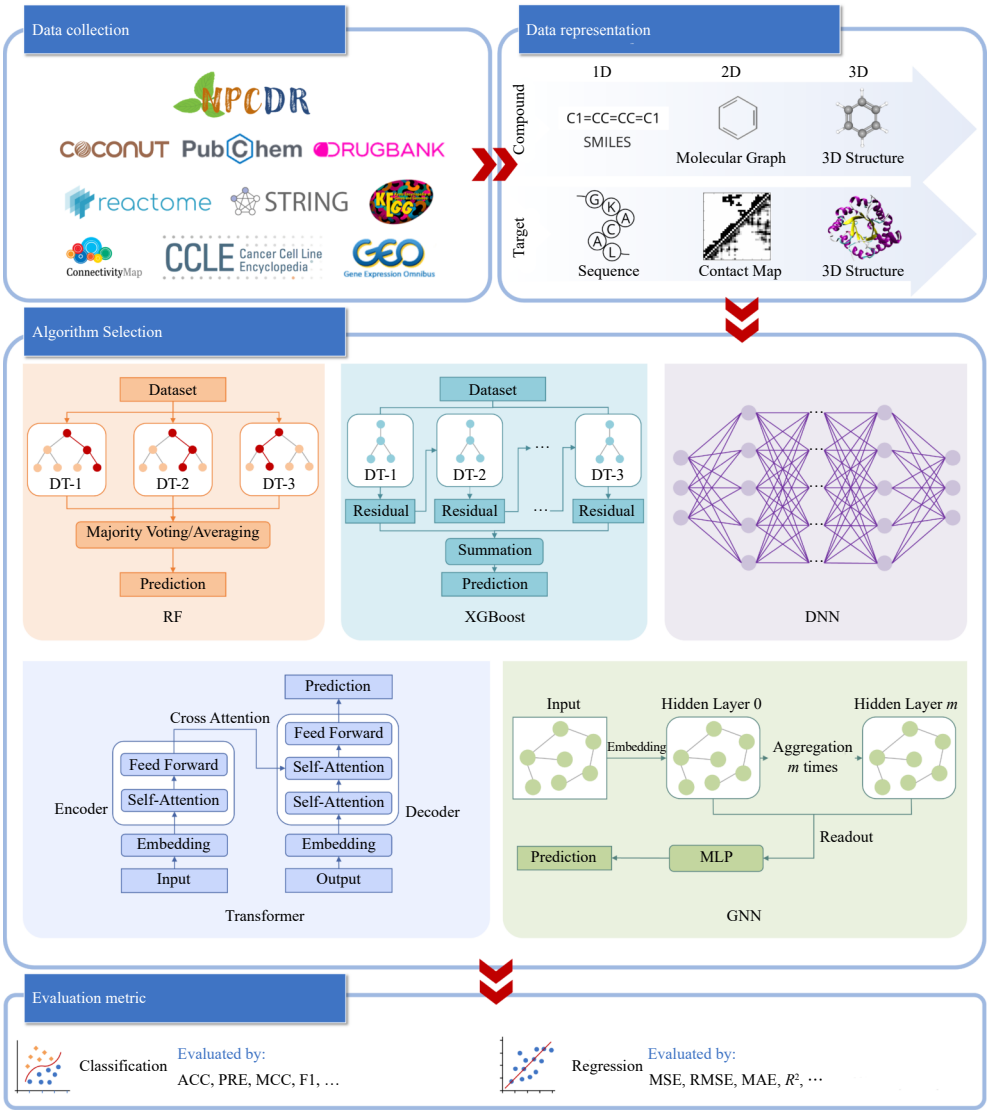

Fig. 1 A brief workflow of AI-driven drug combination prediction. First, comprehensive data from diverse chemical and biomedical database is curated. Then, the collected data can be represented at multiple dimensions (e.g., small molecules can be encoded using 1D structures (SMILES) strings, 2D molecular graphs, and 3D structure). Next, appropriate AI algorithm framework must be selected for modeling. These include traditional machine learning such as random forest (RF) and XGBoost, as well as deep learning like deep neural networks (DNNs), Transformer, graph neural networks (GNNs). Finally, the predictive performance is quantified using suitable evaluation metrics, providing guidance for model optimization and ensuring reliability.

quantitatively measuring synergy in drug combinations by providing continuous synergy scores to predict the level of synergy. We reviewed the advances of AI models in drug combination prediction.

4.1.1. Random Forest (RF)

RF demonstrates widespread adoption due to its effectiveness in both classification and regression tasks [104]. RF constructs an ensemble of decision trees (DTs) through bootstrap sampling and random feature subsampling, fostering diversity among the base learners [105, 106]. For classification tasks, predictions are determined through majority voting, while regression tasks utilize averaged predictions across all trees. In the AZ-DREAM challenge, RF-based models exhibited exceptional performance, attributable to three key characteristics: (i) RF efficiently identifies and leverages informative features in high-dimensional datasets without explicit dimensionality reduction, utilizing intrinsic feature importance metrics to enhance predictive relevance; (ii) sample-level bootstrapping and feature subsampling at each node, reducing model variance and mitigating overfitting; and (iii) the progressive increase in the number of trees reduces variance asymptotically without increasing bias [107].

Gayvert et al. [108] developed a methodology based on feature vectors derived from single-drug efficacy data to predict drug synergy. The half-maximal inhibitory concentration (GI_{50}) values across 27 melanoma cell lines served as features, with the feature set enhanced by calculating the average GI_{50} value and GI_{50} difference between drug pairs. The method's efficacy was demonstrated through experimental validation of seven drugs in the BRAF-mutant MALME-3M cell line. However, this approach indicated that while drug response provides valuable input features, focusing solely on GI_{50} neglected important pharmacological parameters such as maximum tolerated doses, and the feature engineering process simplified the complex mechanisms of drug synergy. Moreover, the evaluation metrics' limitation to area under the receiver operating characteristic curve (AUROC) and accuracy restricted model interpretability and comprehensive performance assessment. To enhance drug synergy prediction, Liu et al. [109] introduced TAIJI, a software tool integrating pharmacological parameters including the half-maximal inhibitory concentration (IC_{50}) and maximum inhibition rate, alongside cell-specific molecular features. TAIJI employed RF as its core predictive model. Testing across 85 cancer cell lines and 1089 drug combinations, TAIJI achieved an average Pearson correlation of 0.53 and

Table 4 Summary of studies involved in this manuscript.

Method	Data sources	Input data types	Model type	Synergy Scores
Sun et al. [110]	DrugCombDB, DrugBank, TCMSP	Compound similarity, gene expression, PPI	RF	Classification
Chen et.al. [120]	DILIrank and LiverTox	SMILES	DBN	Classification
Gayvert et al. [108]	Held et al. dataset	Drug response	RF	Combination Index
TAIJI [109]	AstraZeneca	Drug response, CLE	RF	Loewe
NEXGB [114]	Oncology-Screen, DrugCombDB, CCLE	PPI, DPA, Pathway	XGBoost, struc2vec	Classification
He et al. [115]	HERCULES Project	Drug Response, Genomic and transcriptomic profiles	XGBoost	HSA
SynPredict [118]	ONEIL, NCI-ALMAMAC, CCLE	FP, physicochemical descriptors, toxicophoric descriptors, CLE	DNN	Loewe, Bliss, HSA, S-score, ZIP, CSS
MARSY [119]	CCLE, CellMiner, LINCS; DrugCombDB	CLE, LINCS drug-induced signatures	DNN	ZIP, S-score
DualSyn [149]	ONEIL, NCI-ALMANAC, AstraZeneca, DrugBank, CCLE, LINCS	CLE, molecular graph	GNN, Attention mechanism, MLP	Classification
DTSyn [131]	ONEIL, AstraZeneca, FLOBAK, NCI-ALMANAC, FORCINA, YOHE, CCLE, LINCS	CLE, SMILES, PPI	GNN, Node2vec, Transformer encoder, MLP	Classification
HANSynergy [130]	DrugCombDB, PubChem, UniProt, CCLE, PubChem, DrugBank	SMILES, Protein sequence, CLE, Tissue-specific features	GNN, Attention, MLP	Classification
AttenSyn [135]	ONEIL, DrugBank, CCLE	SMILES, CLE	GNN, LSTM, Attention, MLP	Classification
HCPGraph [136]	TCMSP, RCSB PDB, Zhang-lab predicted protein structure dataset	ADME, CPA	GNN, VGA	Cosine Similarity
DrugSK [142]	DrugCombDB, PubChem, DrugBank, ChEMBL	SMILES	Ensemble, SMILES-BERT	Classification
DDSBC [143]	BC-specific drug-drug synergy study, CCLE, LINCS	molecular descriptor, CLE	Ensemble	Classification
CancerGPT [28]	DrugComb	Drug pair, cell line, tissue, drug sensitivity	Attention	Loewe
BAITSAO [132]	DrugComb, DrugCombDB, DeepDDs. DeepSynergy, MARSY	Cell line, drug name, gene expression	Attention	HSA, Bliss, Loewe, ZIP
MMGCSyn [102]	DrugCombDB, DrugComb, ONEIL, CCLE, LINCS	SMILES, FP, CLE	GNN, CNN, Attention mechanism, MLP	Classification
HGCLSynergy [103]	DrugCombDB, DrugComb, Cheng et al. dataset, CCLE, DrugBank	SMILES, Protein sequence, CLE	GNN, Contrastive learning, MLP	Classification

PPI, Protein–protein interaction networks; CLE, Cell line expression profiles; DPA, Drug-Protein associations; FP, fingerprints; CPA, compound-protein binding affinity.

accuracy of 0.56, approximating experimental replicate reproducibility. The tool demonstrated remarkable computational efficiency, processing predictions for individual drug combinations in under one second.

As shown in Fig. 2, we redrew the experimental workflow originally proposed by Sun et al. [110] to provide a clearer and more comprehensive illustration of the method. The workflow initiated with FDA-approved drug combination data and associated cheminformatics collection from DrugCombDB [94] and DrugBank databases, followed by a 7 : 3 training and internal validation set division. The study constructed 16 feature variables based on molecular fingerprint similarity, small-molecule ADME similarity, small-molecule target sequence similarity, small-molecule target Gene Ontology (GO) functional similarity, small-molecule target pathway similarity, and distances between small-molecule targets within the human PPI network. Statistical independence evaluation of the initial 16 features utilized *t*-tests and Mann-Whitney U tests, followed by recursive feature elimination (RFE) identifying eight discriminative features: $S_{Pathway}$, S_{GOmin}, S_{GOmax}, S_{Seqmin}, S_{Seqmax}, $S_{Seqmean}$, $S_{PPImean}$, and S_{np}. The research gathered 41 active TCM compounds for rheumatoid arthritis (RA) treatment from TCMSP database, alongside 10 clinically used anti-RA Western drugs from DrugBank. All possible TCM-WMCs generated a prediction set of 410 pairs. Five ML models underwent training through three iterations of 10-fold cross-validation, with validation set performance evaluated using accuracy, precision, F1 score, AUROC, and area under the precision-recall curve (AUC-PR). The RF model demonstrated superior performance compared to alternatives. The study identified 15 promising therapeutic pairs, with experimental CI analysis confirming significant synergistic effects in five pairs. To address training set imbalance between positive and negative samples, the method implemented 1000 random samplings of negative samples to create 1000 independent training sets, enhancing model training stability. Notably, the model's training utilized exclusively FDA-approved Western drug combination data, excluding active NP components, potentially introducing bias in NPDC prediction that may not fully capture NP diversity.

4.1.2. XGBoost

XGBoost advances the traditional gradient boosting framework by incorporating a regularization term into its loss function, effectively controlling model complexity [111-113]. The training process consists of three primary phases. Initially, sequential tree fitting occurs, where each subsequent weak learner is trained to minimize a second-order Taylor approximation of the loss relative to ensemble residuals. Subsequently, regularization is applied, introducing a penalty term that combines L1 and L2 norms on leaf weights and tree structure to mitigate overfitting by limiting complex splits. Finally, prediction aggregation takes place: for regression tasks, individual tree outputs are combined additively, while for classification tasks, class probabilities are integrated to generate the final prediction. Additionally, by utilizing both gradient and Hessian information during each iteration, XGBoost achieves accelerated convergence and enhanced generalization on high-dimensional datasets.

Meng et al. [114] developed the NEXGB method, which utilized the struc2vec algorithm to derive topological features from protein nodes within a PPI network. These features were integrated with target protein information from drugs and cancer cell lines to generate multidimensional feature vectors. XGBoost was then applied to predict synergistic effects of anti-cancer drug combinations. NEXGB exhibited robust performance on Oncology-Screen and DrugCombDB datasets, achieving significant scores in accuracy, recall, AUROC, AUC-PR, and F1 score. Nevertheless, the model failed to address consistency challenges in heterogeneous data

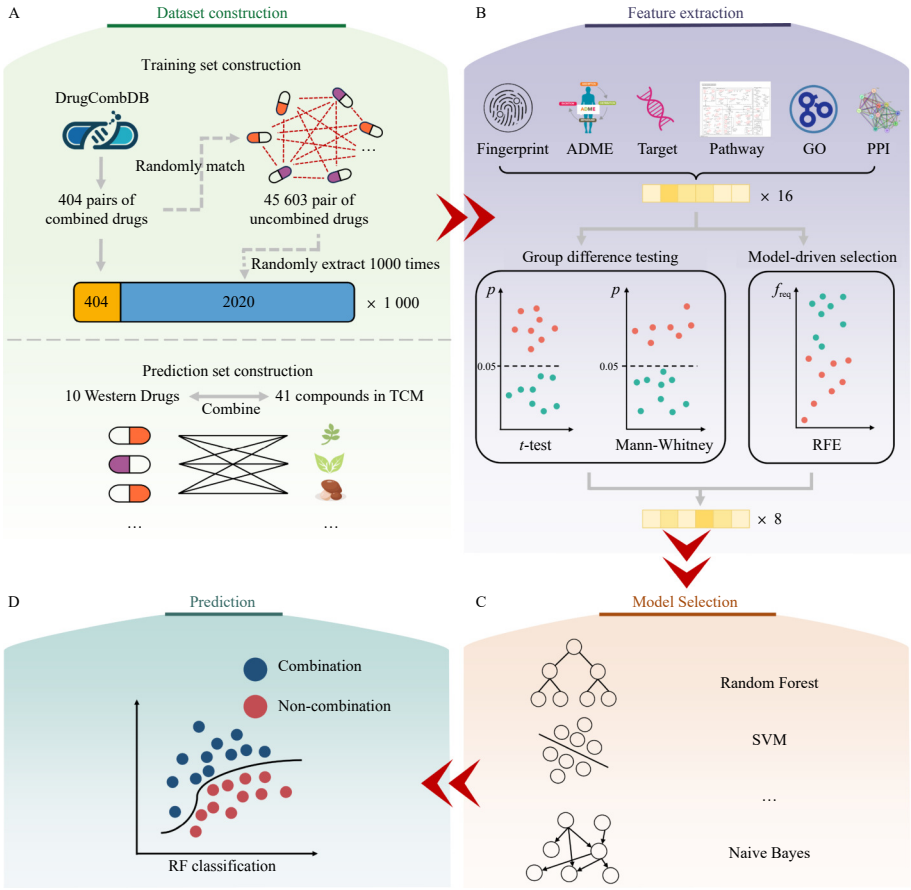

Fig. 2 The workflow of the predictive model proposed by Sun et al. for identifying combinations of Western and TCM. A. Schematic diagram of dataset construction procedures. 1000 training sets were generated by random sampling from the negative samples, and the prediction set included all pairwise combinations of 41 small-molecule TCM compounds and 10 Western drugs. B. Schematic diagram of feature extraction process. Eight feature variables, namely $S_{Pathway}$, S_{GOmin}, S_{GOmax}, S_{Seqmin}, S_{Seqmax}, $S_{Seqmean}$, $S_{PPImean}$, and S_{np}, were finally selected through frequency ranking based on *t*-test, Mann-Whitney test, and recursive feature elimination. C. The generalization performance metrics of different models were compared, and the RF model exhibited the best performance. D. RF was applied to carry out the classification analysis. TCM, traditional Chinese medicine. PPI, protein-protein interaction. SVM, support vector machine. freq, frequency. RFE, recursive feature elimination.

formats, potentially impacting feature quality and model stability, and lacked independent experimental validation. He et al. [115] implemented multiple analytical approaches, including single-cell imaging cytometry, whole-genome transcriptomics, and genetic analyses, to conduct single-cell resolution analysis of drug responses. Their investigation identified differential gene expression patterns across various cellular subpopulations. These findings informed the development of an XGBoost model for drug combination prediction, utilizing multimodal data with combinations ranked by HSA synergy scores. The results, validated through 10-fold cross-validation and Spearman correlation analysis, demonstrated XGBoost's exceptional capability in processing few-shot, high-dimensional data.

4.1.3. Deep Neural Network (DNN)

DNN represents a core DL architecture for drug synergy prediction [116-118]. Leveraging the rapid expansion of high-throughput omics data, DNN improves predictive capabilities through its multi-layered structure. The varied connectivity patterns between these layers enable the development of numerous DNN architectures, offering substantial modeling flexibility. This architectural adaptability provides the essential framework for various models commonly implemented in drug synergy prediction. DNNs are distinguished by their hierarchical structure and end-to-end learning approach. Through multiple stacked hidden layers, they extract essential features directly from raw input data, eliminating the need for predetermined feature engineering. The network produces quantitative predictions of drug synergistic efficacy through output layer projections.

Alsherbiny et al. [118] developed SynPredict, a multimodal fusion method based on DNN that integrated multimodal data and multiple synergy metrics. The model incorporated extended-connectivity fingerprints (ECFPs) of drug molecules, physicochemical properties, toxicity data, and gene expression profiles of cancer cells, concatenating them into high-dimensional input vectors. The architecture implemented three fully connected layers for each drug to extract chemical features, while a separate fully connected layer encodes cellular gene expression data, utilizing dropout regularization to prevent overfitting. The model integrated six synergy metrics, including Loewe, Bliss, HSA, ZIP, S score, and the combination sensitivity score (CSS), through logistic regression (LR) fusion to generate comprehensive synergy predictions. This method pioneered the introduction of the Combination Sensitivity Score, enabling a thorough assessment that incorporates both synergistic effect and synergy efficacy, thus providing a more comprehensive framework for drug synergy evaluation. Khili et al. [119] developed the MARSY method, based on a multitask DL architecture designed to address the limitations of conventional DNN models in drug synergy prediction. The model processed differential gene expression data from the LINCS database and baseline gene expression profiles from the CCLE database. The architecture employed a dual-encoder system to independently learn interaction features of drug pairs and tripartite features encompassing drug pairs and cell line characteristics. The model employed three distinct activation functions to generate results for three prediction tasks: the drug combination synergy score and the inhibitory effects of two single drugs. Through hierarchical encoders, the model effectively combined synergistic

patterns between drug pairs with cellular microenvironment influences on synergy effects, creating complementary embeddings. The incorporation of single-drug inhibitory effect data addressed synergy data sparsity, enhancing model generalization and biological interpretability. Chen et al. [120] demonstrated DL's effectiveness in screening hepatotoxicity risks for TCM-WMC therapies. The research collected hepatotoxicity-related data on TCM and Western medicine from literature and public databases including DILIrank [121] and LiverTox [122]. The datasets were split into training and test sets at a 3 : 1 ratio, maintaining the same ratio for positive and negative sample balance. The study evaluated nine ML models and one DL model using accuracy, F1 score, and recall metrics. The deep belief network (DBN) achieved 82.2% accuracy on the test set, substantially outperforming traditional ML models [123]. The study assessed hepatotoxicity solely for individual compounds in TCM-WMC, without evaluating potential pharmacodynamic or pharmacokinetic interaction effects during combined use. This research established a preliminary screening framework for TCM-WMC therapy hepatotoxicity and provided groundwork for future studies incorporating drug interaction analysis and metabolite toxicity assessment.

4.1.4. Attention

Attention mechanisms represent a fundamental component in encoder and decoder architectures, where encoders extract latent features from input data and decoders generate outputs based on these features [124]. The Transformer architecture introduced an innovative application of attention mechanisms in DL and established the architectural foundation for large language models (LLMs) such as GPT [125–126]. The Transformer differs substantially from conventional sequential models like recurrent neural network (RNN) and long short-term memory (LSTM) networks. It utilizes parallel attention mechanisms to process sequences simultaneously, significantly enhancing training efficiency. While LSTMs can capture long-range dependencies, they frequently encounter gradient vanishing or exploding issues [127]. The Transformer demonstrates enhanced stability and efficiency under these conditions. In drug discovery, representations such as SMILES for chemical structures and protein sequences contain essential semantic and syntactic information about underlying biological mechanisms [128]. The Transformer's capacity to capture long-range dependencies and contextual relationships proves particularly valuable for modeling molecular or atomic interactions in drug discovery. Advancing Transformer developments, BERT introduced innovations in pre-training and fine-tuning approaches [129]. Through training on extensive text corpora to learn general semantic representations, BERT establishes a fundamental understanding of language structures. Subsequent fine-tuning on smaller task-specific datasets enables adaptation to various applications. Additionally, hybrid architectures, including generative adversarial network (GAN) and autoencoder (AE), within Transformer architecture have gained increasing application in drug combination prediction. These multimodal fusion strategies combine the advantages of distinct architectures, addressing limitations of single-model approaches.

Chen et al. [149] developed DualSyn, a dual-level feature interaction framework integrating graph neural networks (GNNs) and transformers. The feature extraction layer employed a graph transformer to process drug molecular graphs, capturing global dependencies among drug atoms through a multi-head attention mechanism. The feature interaction layer comprised two parallel modules: a high-order relationship module constructing a ternary attention matrix for drug-drug-cell line interactions, and a global information module preserving gene expression profile details through sequential feature concatenation. These modules achieved cross-scale information complementarity, attaining an AUC value of 0.95 on the Merck-2016 dataset. Hu et al. [131] introduced DTSyn, utilizing a dual-branch transformer encoder for drug synergy prediction through a multi-granularity attention mechanism. The model incorporated a fine-grained transformer encoder for drug target-gene associations and a coarse-grained transformer encoder for global chemical entity interactions and chemical-cell line relationships. This architecture enhanced interpretability by focusing on drug combination synergistic mechanisms in specific cellular contexts. The model integrates multimodal data, including chemical SMILES, gene expression profiles (from CCLE/LINCS), and PPI data, enhancing predictive performance. Li et al. [132] developed CancerGPT, a few-shot learning framework utilizing LLM for cancer drug sensitivity prediction. This approach transformed structured data into text-based inputs compatible with LLMs. The architecture implemented a two-stage transfer learning strategy: initial pre-fine-tuning on common tissue datasets followed by fine-tuning on rare tissue subtypes. Notably, CancerGPT surpassed the large-parameter GPT-3 model in most tasks, demonstrating that targeted pre-training optimization enables small-parameter LLMs to achieve comparable or superior performance in specialized biomedical applications. Liu et al. [28] introduced BAITSAO, a multi-task learning framework incorporating LLM contextual embeddings for drug synergy prediction. The model generated textual descriptions of drugs and cell lines *via* GPT with customized prompts, converting these into vector embeddings. The pre-training phase implements three tasks: Loewe score regression, single-drug inhibition regression, and synergy binary classification. BAITSAO demonstrated superior performance compared to baseline models, attributed to LLMs addressing traditional feature space limitations and multi-task learning enhancing predictive capabilities.

4.1.5. GNNs

GNNs [133–134] function through iterative message-passing, aggregating node feature information while maintaining input graph structural integrity. This mechanism facilitates the extraction of high-dimensional, non-linear interactions inherent in molecular architectures and biological networks. This framework has led to various model variants, including graph convolutional network (GCN) utilizing convolution operations, GAT employing attention mechanisms, graph sample and aggregate (GraphSAGE) implementing sampling strategies, and graph autoencoders (GAEs) based on AE frameworks. Each variant provides unique perspectives on drug networks, collectively advancing drug combination discovery. GNNs have increasingly demonstrated effectiveness in drug synergy prediction, frequently matching or exceeding other ML algorithms in performance and impact.

Cheng et al. [130] created HANSynergy, combining heterogeneous GATs with multi-source data fusion, utilizing virtual nodes and a dual-layer attention mechanism to enhance prediction accuracy and model interpretability. The heterogeneous graph construction incorporated virtual nodes for each drug node. Initial feature representations derive from ECFPs computed *via* RDKit, while SimCSE-extracted semantic embeddings characterize primary drug nodes. The model implemented a multi-head attention mechanism to integrate features from drugs, virtual nodes, and cell lines. This integration approach demonstrated exceptional performance in local feature selection and global semantic information fusion. Wang et al. [135] developed AttenSyn, employing graph-based drug embedding modules. The model utilized GCNs for atom-level structural feature extraction and LSTM networks for hierarchical molecular feature capture, preserving both structural and sequential information for enhanced interpretability. An attention pooling module identified critical chemical substructures within molecules, with final synergistic effect predictions generated through MLP. These innovative designs enabled AttenSyn to achieve high performance and interpretability.

As shown in Fig. 3, Yang et al. [136] developed the HCPGraph

method to recommend herb combinations targeting SARS-CoV-2, integrating heterogeneous graph embedding (HCP-DGE) with variational graph autoencoder (VGAE). A "Herb-Compound-Protein" heterogeneous graph was constructed using "Herb-Compound" associations filtered by ADME criteria and "Compound-Protein" associations identified through QVina molecular docking. HCP-DGE, based on the structural deep network embedding (SDNE) model, incorporated Laplacian eigenmaps for local structure preservation and deep autoencoders for global structure retention, generating low-dimensional embeddings. For screening herb combination candidates, clustering identified the top 10 herbs for each protein, producing 24 × Top-10 signaled herb sets. Based on TCM theory and clinical data, 20 herb combination candidates were selected from these sets. VGAE recommended herb combinations with potential therapeutic efficacy by comparing their reconstructed graph with clinically validated TCM formulations. This approach demonstrated an innovative strategy for repurposing TCM against SARS-CoV-2, utilizing network pharmacology and deep learning to connect herbal mechanisms with pathophysiological targets.

4.2. Learning paradigms employed in drug combination

Model performance depends not only on architecture but also significantly on the chosen learning paradigm. Learning paradigms encompass supervised learning, unsupervised learning, semi-supervised learning, active learning, reinforcement learning, transfer learning, and ensemble learning. These paradigms employ various algorithms for tasks such as classification or clustering. In drug combination prediction, the intricate interaction mechanisms and limited annotated data present substantial challenges for conventional data-driven learning methods. Consequently, learning paradigms designed for low-data scenarios offer viable solutions. Ensemble learning [137] has become particularly prominent among these approaches due to its robust generalization capabilities in few-shot scenarios.

Ensemble learning integrates multiple models to reduce individual biases through diversity, enhancing predictive accuracy and generalization performance. It comprises homogeneous ensembles which combine identical base learners, and heterogeneous ensembles which integrate diverse model architectures [138–139]. Stacking represents a notable heterogeneous framework where base models train on identical datasets, with their predictions serving as input features for a meta-learner. This meta-learner then refines the final prediction. Stacked ensembles reduce overfitting and bias while improving generalization performance and model interpretability [140–141]. These advantages have led to stacking's widespread adoption in drug combination prediction.

Chen et al. [142] developed DrugSK, implementing a two-stage training process. The first stage combined RF, support vector machine (SVM), and XGBoost in an ensemble model to extract drug data features and generate initial predictions. The second stage employed an LR model for weighted fusion of primary learners' output to produce final predictions. DrugSK utilized SMILES-BERT to extract structural features directly from molecular SMILES strings, eliminating the need for multi-source data common in traditional methods. This approach leveraged multiple ML models to analyze chemical information from different perspectives: RF effectively handled high-dimensional sparse data; SVM performed well with limited data; XGBoost optimized complex feature interactions; and LR mitigated overfitting risks. Similarly, Mehmood et al. [143] introduced DDSBC, employing a two-stage stacking ensemble architecture. Its primary learners included AdaBoost, which iteratively adjusted sample weights to minimize bias, and RF, which enhanced generalization through DT en-

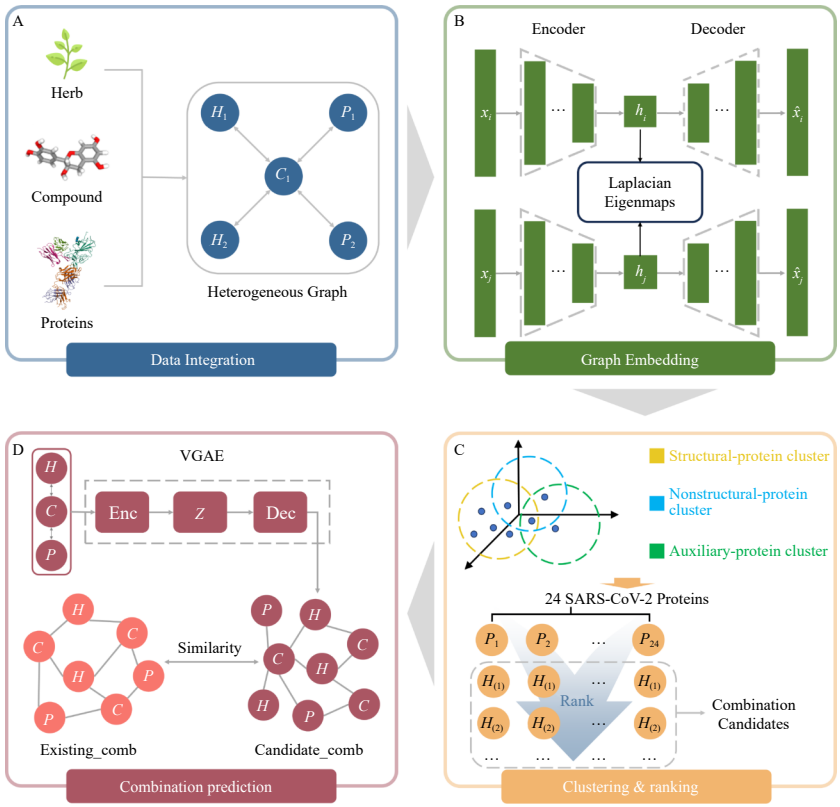

Fig. 3 The workflow of HCPGraph method for recommending herb combinations against COVID-19. A. Data integration. Herb (H), compound (C) and Protein (P) data were used to construct heterogeneous graphs. B. Graph Embedding. The HCP-DGE model (similar to the SDNE model) was used to extract feature vectors from heterogeneous graphs, which considered both global and local structures of the graph. C. Clustering and Ranking. Cluster analysis identified the top 10 herbs with close relationships to each of 24 SARS-CoV-2 proteins, which were used to construct drug combinations. D. Combination prediction. Variational graph autoencoder (VGAE) assessed the similarity between combination candidates and existing combinations by reconstructing the graph structure of these combinations.

sembles. These models complemented each other in balancing model bias and variance, while LR filtered noise through linear combinations to improve model robustness.

4.3. Comparison of model performance in drug combination

Model evaluation metrics are classified into two categories based on prediction tasks. For regression tasks, the Pearson correlation coefficient (PCC) and mean absolute error (MAE) measure the linear relationship strength and average prediction error magnitude, respectively. Classification task performance is assessed through multiple metrics that evaluate distinct model characteristics. The AUROC measures discriminative capability by integrating true positive rate (TPR) and false positive rate (FPR) across classification thresholds. The AUC-PR aggregates classifier precision and recall across these thresholds. Additional performance metrics, including accuracy, balanced accuracy (BACC), precision, Kappa coefficient, and F1 score, are typically used together to provide comprehensive evaluation.

As shown in Table 5, Chen et al. and Sun et al. compared various classical ML models with a DBN in NPDC prediction studies. In a dataset of approximately 2000 samples, RF demonstrated superior performance among classical ML models across AUC, accuracy, F1 score, and precision metrics, with only marginally lower recall than SVM. The DBN, however, achieved higher accuracy than all ML models. The DBN architecture, comprising stacked restricted Boltzmann machines (RBMs), enabled unsupervised pretraining to automatically extract hierarchical abstract features, followed by supervised backpropagation. Given NP data's high dimensionality and structural complexity, the DBN extracted structure-related abstract representations directly from raw molecular descriptors or SMILES strings without manual feature engineering. Additionally, DBN effectively modeled the complex, hierarchical interactions characteristic of NPs' multi-target properties. While RF handled high-dimensional data effectively and demonstrated resilience to noise and missing values, it had limitations in modeling complex non-linear relationships, particularly those arising from multi-target effects. Other traditional ML models, such as SVM, are heavily dependent on kernel selection, presenting challenges for complex NP datasets. Similarly, k-nearest neighbors (k-NN) showed limitations in capturing complex non-linear relationships and sensitivity to noise and outliers. The performance difference between DBN and traditional ML models exceeded 0.1 on average, becoming more pronounced when comparing DBN with less effective ML methods. DL enabled automatic feature extraction and typically surpassed traditional ML methods requiring manual feature engineering. Its non-linear transformation capabilities facilitated effective modeling of complex drug combination mechanisms. Furthermore, DL enabled multi-source data integration by compressing heterogeneous information into low-dimensional representations. The tabulated results demonstrated DL models' superior performance over traditional ML models, confirming findings from previous systematic benchmarking analysis [144].

4.4. Model interpretability in drug combination

As AI applications in NPDC expand, model interpretability has become increasingly crucial. DL models, often characterized as "black boxes", present inherent complexity and opacity, making their decision-making processes challenging to trace and verify. To address this limitation, interpretability techniques such as attention weight visualization in transformer or GNN-based explanation methods have gained prominence. Zhang et al. [102] developed MMGCSyn, implementing GAT to learn atom-level attention weights. This approach identified key chemical substructures through higher-weighted atoms, visualized using PyMOL to verify alignment with binding sites, thus validating the biological relevance of the model's focus areas. The transformer's self-attention mechanism during feature fusion revealed different features' contributions to final predictions, enhancing interpretability. Similarly, Liu et al. [145] developed SDSynergy, utilizing a multi-layer substructure information propagation network (SIPN) for adaptive multi-scale substructure extraction from drug molecular graphs. The model incorporated a drug-cell line attention mechanism to identify cancer cell line-specific relevant substruc-

Table 5 Comparison of generalization ability across different models.

Case	Data size	Method	AUC	Accuracy	F1 score	Precision	Recall	AUPR
Chen et al. [121]	2035	SGD	0.627	0.682	0.694	0.712	0.682	-
		k-NN	0.574	0.745	0.636	0.555	0.745	-
		SVM	0.669	0.747	0.712	0.71	0.747	-
		DT	0.544	0.68	0.679	0.678	0.68	-
		RF	0.739	0.767	0.731	0.739	0.767	-
		AdaBoost	0.614	0.708	0.707	0.707	0.708	-
		ANN	0.647	0.694	0.696	0.697	0.694	-
		LR	0.656	0.733	0.694	0.688	0.733	-
		NB	0.598	0.675	0.648	0.705	0.675	-
		DBN	-	0.822	-	-	-	-
Sun et al. [110]	2424	k-NN	0.651 ± 0.024	0.827 ± 0.012	0.903 ± 0.008	0.848 ± 0.012	0.965 ± 0.013	0.309 ± 0.033
		NB	0.617 ± 0.026	0.813 ± 0.014	0.894 ± 0.009	0.845 ± 0.012	0.949 ± 0.013	0.269 ± 0.031
		SVM	0.657 ± 0.027	0.834 ± 0.011	0.909 ± 0.007	0.838 ± 0.012	0.992 ± 0.006	0.330 ± 0.038
		RF	0.739 ± 0.024	0.849 ± 0.012	0.915 ± 0.007	0.861 ± 0.012	0.977 ± 0.008	0.460 ± 0.039
		AdaBoost	0.667 ± 0.027	0.833 ± 0.011	0.909 ± 0.007	0.834 ± 0.012	0.998 ± 0.004	0.317 ± 0.038

The results reported by Chen et al. are based on the test set from a single data split, whereas Sun et al. report the average of three repetitions of 10-fold cross-validation. LR, Logistic regression; RF, Random forest; SVM, Support vector machine; k-NN, k-nearest neighbor; DT, Decision tree; NB, Naive bayes; ANN, Artificial neural network; SGD, Stochastic gradient descent.

tures. The substructure-pair attention mechanism examined interactions between drug combination substructures, providing molecular-level insights into synergy prediction.

5. Challenges and perspectives

Despite substantial advances in AI-driven drug combination prediction, AI-based NPDC prediction faces several ongoing challenges, as depicted in Fig. 4.

The predictive performance of AI models for drug combination effects significantly depends on the quality and quantity of training data. While widely utilized drug combination databases such as DrugCombDB [94] and NCI-ALMANAC [95] incorporate NP information, they lack specificity regarding the intrinsic compound-specific pharmacological properties and mechanistic distinctiveness of NPDC. Notably, NPCDR, currently the most comprehensive database for NPDCs, contains merely approximately 1000 NPDC entries. Comparative analyses of NPDC prediction under few-shot conditions demonstrate that RF generally surpasses other traditional ML models across multiple evaluation metrics. However, DBN exhibits the highest accuracy and has consequently been adopted as the preferred predictive model in related research. These findings suggest that DL shows substantial potential in this field. Transfer learning presents a viable solution to address data scarcity. The process initiates with pretraining models on large -scale drug combination databases. After parameter learning, the model undergoes an adaptation phase where the learned representations transfer to NPDC prediction tasks. Subsequently, the model undergoes fine-tuning using NPDC datasets. This methodology not only enhances model generalization but also addresses the limitations imposed by sparse NP-specific data in existing databases. Active learning offers another solution, involving the selection of informative samples from a large pool of unlabeled data for labeling. This approach aims to maximize the representativeness of information within the small labeled dataset relative to the entire unlabeled data space, enabling comprehensive data analysis despite limited labeled data. Through the integration of ML models with experimental or computational methods, active learning facilitates bidirectional optimization of both data and models.

Approximately 20% of drug candidates fail in the early stages of development due to safety concerns, and over 50% fail because of inadequate efficacy. However, most existing models focus solely on the synergistic effects of drug combinations as the key factor in their combined application, while neglecting the toxicity and overall efficacy. Drug combinations are also closely associated with dose-dependent responses. Synergy manifests within specific concentration ranges, whereas antagonism may occur beyond this range. Therefore, future research should evaluate how dosage influences model accuracy. To enhance both prediction accuracy and biological plausibility, researchers should adopt multimodal data integration and augmentation strategies that incorporate toxicity and dosage features of combinations into their models. Expert knowledge regarding drug combinations can also enhance the predictive performance of such models. Taking TCM as an example, integrating core TCM theories into predictive models can bridge the gap between theoretical foundations and computational frameworks. One widely adopted approach is the representation of TCM expertise through knowledge graphs and GNN. The construction of a TCM knowledge graph depends on the identification and standardization of terminology within TCM theory. By collecting information on TCM terms, herb properties, prescriptions, chemical components, targets, and diseases, semantic mapping can establish standardized associations between TCM and Western medical concepts. This process builds semantic relationships among entities. In this graph structure, herbs, their properties, and prescriptions are represented as distinct entity nodes. Given that a single herb may possess multiple properties and a property may correspond to multiple herbs, herbal combinations in prescriptions can be defined as hyperedges, directly connecting the involved herb nodes and revealing the synergistic mechanisms underlying TCM formulations. Based on this structure, GNNs can explore the synergistic mechanisms of TCM herbs. To further enhance model interpretability, the classical TCM compatibility rule "Jun-Chen-Zuo-Shi" (sovereign-minister-assistant-messenger) can be transformed into prior weights within the graph model. For instance, sovereign herbs receive higher weights than minister, assistant, and messenger herbs in descending order. These prior rules can serve as constraints within an attention mechanism, facilitating interpretable analysis of herbal compatibility and improving predictive accuracy. For example, Taneja et al. [146] proposed an NP-drug interaction knowledge graph that systematically captures inter-drug interactions and associated toxicity risks. Moreover, with the growing clinical demand for cancer and other complex diseases, general binary drug combinations no longer suffice in practice. Consequently, combinations of three or more drugs require novel computational methods to accurately evaluate their therapeutic efficacy.

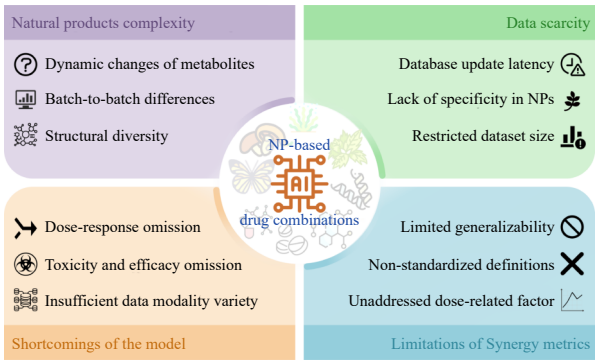

Fig. 4 Current challenges in the field of AI-based NPDC prediction.

Synergy metrics such as HSA, Bliss, and Loewe generate divergent interpretations of synergy due to their different assumptions regarding the independence of synergistic effects [147]. For instance, the HSA model posits that the effect of a drug combination should not exceed the maximum effect of its individual components, potentially leading to underestimation of synergistic interaction when drugs approach their maximal effect concentrations. Conversely, the Bliss model's assumption of independent drug action results in greater sensitivity in capturing subtle synergistic variations. The selection among these metrics depends on multiple factors, including *in vivo* experimental design, biological context, and molecular data availability. Currently, no definitive consensus exists on the optimal metric for quantifying drug synergy, highlighting the ongoing need for new synergy metrics. In recent years, certain AI methods have directly predicted the actual response values of drug combinations at specific concentrations, enabling the simultaneous quantification of synergy, antagonism, and other interaction types. Compared to classical metrics, this approach enables more flexible and accurate quantification of underlying combination effects [148].

Combination therapies incorporating NPs and drugs have an established history in treating complex diseases, including cancer and autoimmune disorders. However, their research and development face significant challenges. NPs demonstrate inherent complexity due to dynamic metabolite changes, structural diversity, and batch-to-batch variability, which complicates their purification and formulation. Furthermore, NP chemical compositions fluctuate with environmental conditions and temporal factors, hindering standardized production for clinical applications. While extensive literature and experimental data exist,

most remain unstructured and underutilized. AI driven by data has created new opportunities for NPDC research, though its progress is primarily constrained by insufficient large-scale, high-quality NPDC datasets [150]. While strategies including transfer learning, active learning, multi-task learning, and data augmentation have been proposed to address data insufficiency, their practical effectiveness remains limited. Improvements in model performance largely depend on the correlation between dataset size and model complexity. The field's databases remain highly fragmented. Emerging technologies present promising solutions to these challenges. Explainable AI addresses data scarcity by enhancing model interpretability, facilitating the identification of crucial molecular features and biological pathways. This approach reduces dependence on extensive labeled datasets while directing experimental validation in resource-limited contexts. Knowledge graphs resolve database fragmentation by integrating structured and unstructured data, establishing semantic relationships that reveal hidden cross-domain associations. Multimodal data fusion addresses data heterogeneity by combining genomic and proteomic data into unified representations, enhancing prediction robustness in few-shot scenarios. Future efforts should prioritize establishing a globally collaborative NPDC database with consistent maintenance and regular updates. This database should implement standardized protocols for essential data, including experimental conditions and bioassay information. It should also systematically investigate domains such as chemical structure space and bioactive space, extracting valuable information to expand usable data volume. Additionally, AI methods frequently encounter difficulties in predicting novel chemical entities or mechanisms of action, emphasizing the ongoing importance of fundamental biochemical research.

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Declaration of Interest Statement

The authors declare no competing interests.

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