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Hidden Potential Unlocked: AI-Driven Exploration of Existing Drugs to Fight against Unmet Medical Needs

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Abstract: Drug repurposing (DR), which aims to capitalize on the established safety and efficacy profiles of approved medications, finds new therapeutic uses for existing drugs that were initially created for various purposes. Therefore, avoiding the early phases of medication development is advantageous, as is cutting down on the time and expense involved in introducing novel treatments to the market. Artificial intelligence (AI) offers a potential alternative to conventional experimental methods, which can be expensive and time-consuming, thanks to its lower cost, computational advantages, and ability to identify hidden patterns. The primary topics of this review include the availability of AI algorithms in drug development and their unique and advantageous roles in discovering repurposing methods for current medications, especially when combined with virtual screening. Large-scale datasets are efficiently analyzed by current AI algorithms, which can also identify intricate drug response patterns and predict potential drug repurposing. Building on these findings, there are still challenges in developing efficient AI algorithms and in future research, such as increasing the computational efficiency of AI, extending personalized medicine, and combining drug-related data from other databases for better repurposing. This paper explores the use of AI algorithms in drug research, specifically their role in identifying new uses for approved medications when combined with virtual screening.

Keywords: AI-driven D; machine learning (ML); high-throughput screening (HTS); deep learning (DL); reinforcement learning (RL); transfer learning.

1. Introduction

DR is the process of identifying novel therapeutic uses for medications that were initially developed for other indications. This opens a useful avenue for addressing unmet medical needs and expanding the therapeutic options available to healthcare providers. Off-label clinical investigations can be conducted without requiring additional Good Manufacturing Practices (GMP) production, as the pharmaceuticals are already licensed, reducing trial obstacles. The Food and Drug Administration (FDA) has authorized several successful examples of DR, demonstrating the promise of this approach as an effective way to address unmet medical needs [1]. For instance, thalidomide was taken off the market due to its teratogenic effects when used for morning sickness, but later reintroduced to treat leprosy and multiple myeloma [2]. Furthermore, minoxidil, which was first authorized as an antihypertensive medication, was later used to treat alopecia because of its effects on hair

growth that were seen in clinical trials. Therefore, DR presents a promising method for addressing major gaps in conventional medical care as well as finding possible remedies for illnesses for which there are presently no effective treatments [3]. Figure 1 illustrates AI and how it is used in various drug development and discovery tasks. However, traditional repurposing techniques often rely on time-consuming, narrowly focused manual screening, chance observations, or isolated mechanistic ideas. On the other hand, AI systems can analyze large biomedical datasets, such as transcriptomic, proteomic, genomic, and clinical data, to find hidden patterns, anticipate drug-target interactions (DTIs), and quickly and accurately rank compounds for repurposing. Figure 2 illustrates the performance comparison and the AI-enhanced virtual screening workflow for producing a ranked compound list. Researchers can expedite the drug development process by avoiding numerous trial-and-error phases thanks to these tools. AI technology has helped create intelligent products, including visualization platforms and recommendation systems, which have become game-changing tools with broad applications across sectors such as healthcare and pharmaceuticals [4]. AI-based drug development strategies drastically reduce time, expense, and risk in traditional drug development by leveraging proven safety profiles and offering faster treatment alternatives, making them more economical and effective than conventional methods. By employing multidimensional analysis methodologies and high-throughput data, AI provides robust technology support for DR and fosters advancements in precision medicine and personalized therapies. AI can analyze FDA adverse event records by applying molecular modeling and DL techniques to identify drug side effects that correspond to therapeutic targets for other diseases, thereby exposing the biological causes of these reports [5]. Through virtual screening, similarity comparison, or the discovery of recently reported drug response biomarkers, AI-driven algorithms offer new insights into possible indications for medications whose mechanisms of action are still poorly understood [6]. Furthermore, AI models can help identify similar biochemical pathways and interconnected networks across a variety of therapeutic domains, as the mechanisms of action of many medications extend beyond their initial indications. These developments highlight AI's revolutionary role in DR, extending to target discovery, mechanism elucidation, and side-effect analysis, ultimately speeding the development of novel therapeutic approaches [7,8].

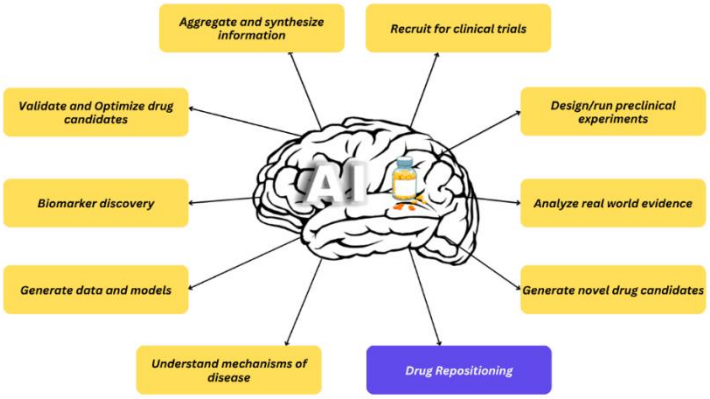

Figure1. Role of Artificial Intelligence (AI) in various stages of drug discovery and development. This image illustrates the activities that AI can perform in the discovery and development of a drug, including drug repositioning.

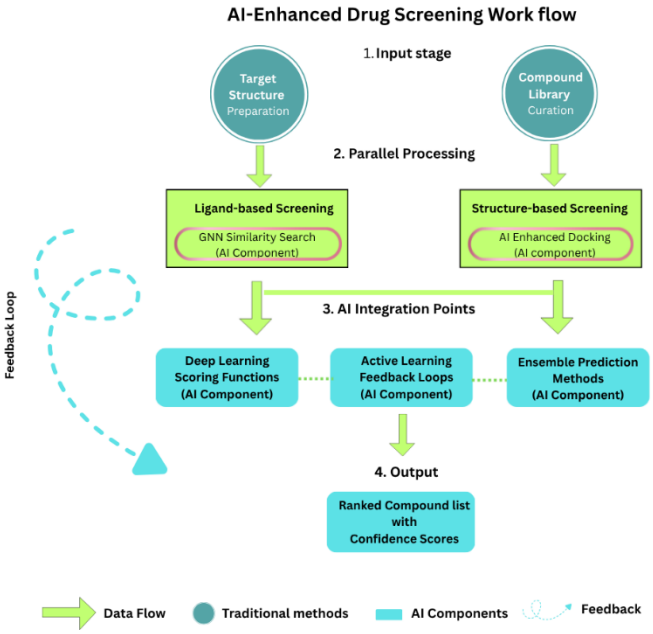

Figure2. Performance comparison and AI-enhanced virtual screening workflow. By displaying the updated procedure with accurate labeling of ligand-based screening and structure-based screening, this image demonstrates how AI techniques enhance both approaches.

2. Historical View of DR

Repurposing medications for new therapeutic uses has historical roots in accidental discoveries and traditional medical practices. Early pharmacological efforts, such as the repurposing of aspirin from an analgesic to an antiplatelet drug, demonstrate the multifunctionality of remedies recognized by traditional healers. Recent advances in ethnopharmacology have revealed various uses of natural compounds in traditional medicine [9,10]. Innovations like the repurposing of sildenafil citrate have emerged from systematic research. Technological advancements, such as HTS and computational modeling, have further expedited DR, making it a cost-efficient method to accelerate treatment development and address unmet medical needs despite obstacles, including regulatory barriers and intellectual property concerns. Interdisciplinary cooperation and technological innovation point to a bright future for DR, enhancing patient care and public health outcomes [11].

3. Drug Repurposing Vs Traditional Drug Discovery

New molecular entities and *de novo* identification are the goals of the traditional drug development approach. Preclinical and discovery research, safety assessment, clinical testing, FDA review, and post-market safety monitoring are the five stages of development. The procedure is expensive, time-consuming, and has little probability of success. In contrast, Figure 3 illustrates the multi-step process of drug development versus drug repositioning; the DR process consists of only four stages: discovering existing compounds, obtaining the compounds, development and testing, and FDA post-market monitoring.

Increased cheminformatics and bioinformatics capabilities, and access to large structural and biological databases, greatly lower failure rates and save time and money in drug development. Databases used for DR are listed in Table 1. AI integration, structure-based drug design (SBDD), and in silico methods have greatly expedited DR in recent years [12,13]. There are several advantages of using DR as opposed to traditional drug discovery techniques. DR

can reduce the traditional 10–16-year timescale for creating a new medicine to 3–12 years. Repositioning may be developed for about $1.6 billion, which is significantly less than the $12 billion average for existing approaches.

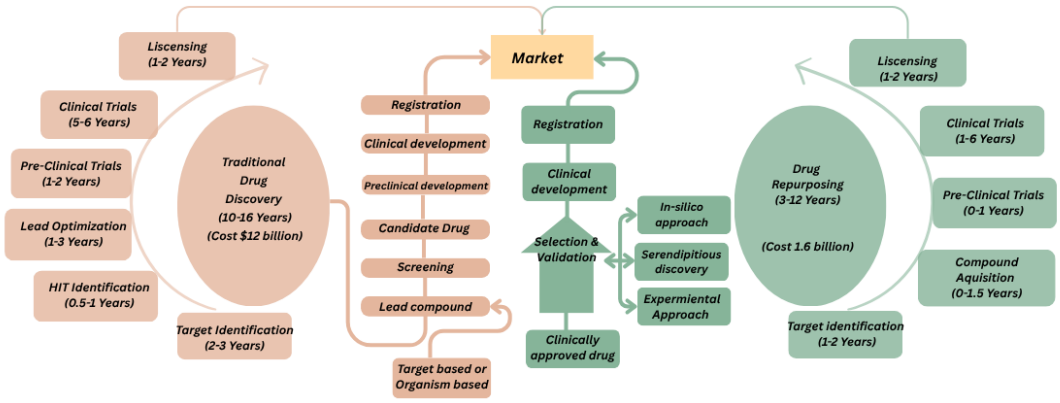

Figure3. Multi-step process of drug development versus drug repositioning. The above illustration shows how traditional drug discovery and traditional drug repurposing differ in terms of the stages of drug development and the amount of time spent on each stage.

Additionally, it typically takes 1–2 years to find new targets for repositioned medications, while it typically takes 8 years to create a new drug from scratch. Repositioned drugs advance through preclinical and clinical trials more quickly by bypassing the first 6–9 years of research required by traditional procedures. As a result, repositioned medications can receive regulatory approvals more quickly and save 50–60% on costs. Repositioned medications, with pre-existing clinical efficacy and safety data, enhance clinical safety, reduce costs, and reduce early-stage failures by leveraging pre-existing data on pharmacokinetics, toxicology, clinical effects, and safety. The stages of DR are illustrated in Figure 4. Furthermore, DR works especially well for diseases that are rapidly changing, reemerging, or neglected, while traditional drug research frequently concentrates on complicated and chronic problems. Targeted repositioning strategies have been enabled by comprehensive omics data, including proteomics, transcriptomics, metabolomics, genomics, bioinformatics, and cheminformatics, for investigating new drug targets and mechanisms of action, identifying related drugs, and discovering novel disease biomarkers [14].

Table 1. Database for drug repurposing applications [11].

Database	Type				URL
	Chemical	Biomolecular	Interaction	Disease	
Drug molecular ChEMBL	24,31,025 compounds	15,598 targets	Not available	Not available	https://www.ebi.ac.uk/chembl/
chemDB	5 million small molecules	Not available	Not available	Not available	http://cdb.ics.uci.edu/
Pubchem	115 million compounds	304 million biomolecular targets	Not available	Not available	https://pubchem.ncbi.nlm.nih.gov/
Drug target Binding Database (DB)	4,95,498 small molecules	7,032 protein targets	1,142,124 binding targets	Not available	https://www.bindingdb.org/bind/index.jsp
DrugBank	2,780 proven drugs	5,294 targets	1.3 million drug-drug interactions	Not available	http://www.drugbank.ca/
Drug Target Commons (DTC)	4,276 compounds	1007 targets	Not available	Not available	https://osf.io/qdjup

Database	Type				URL
	Chemical	Biomolecular	Interaction	Disease	
Search Tool for Interacting Chemicals (STITCH)	30,000 compounds	2.6 million targets	Chemical-protein interaction	Not available	http://stitch.embl.de/
Therapeutic Target Database(TTD)	40,000 compounds	3500 targets	Not available	500 therapeutic targets	https://idrblab.org/ttd
Drug response Cancer Cell Line Encyclopedia (CCLE)	24 anticancer drugs	947 cancer cell line	Not available	Cancer	https://sites.broadinstitute.org/ccle/
Comparative Toxicogenomics Database(CTD)	14,923 chemicals	55,359 genes	2,945,493 chemical-gene interactions	3,308 diseases	http://ctdbase.org/
Library of Integrated Network-based Cellular Signatures (L 10000)	40,000 compounds	978 genes	Not available	Not available	http://l1000viewer.bio-complexity.com/
Pharmacogenomics Knowledge Base (PharmGKB)	460 proved drugs	247 pathways	Not available	5,150 clinical annotations	https://www.pharmgkb.org/
Cancer Drug Sensitivity Consortium (CDSC)	621 compounds	1,000 cancer cell lines	5,76,758 dose response curves	Cancer	http://www.cancerrxgene.org/

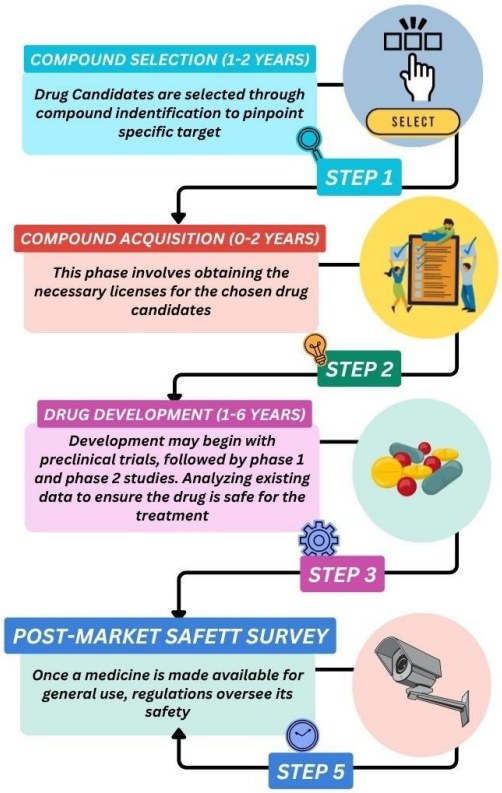

Figure4. Time frame and steps involved in drug repurposing. This image illustrates the condensed stages of drug repurposing along with their activities and required time.

4. Strategies for Repurposing Drugs

DR enhances drug development efficiency by employing accessible medications for various ailments. It utilizes bioinformatics [15,16] for molecular docking and network

pharmacology [17] to analyze drug-disease combinations [18]. Experimental results from animal models support phase II trials that assess safety and efficacy. Multi-omics analysis makes it easier to find new drug-disease correlations, while HTS uses phenotypic analysis to identify effective treatments. Techniques such as natural language processing and DL filter large datasets for healthcare applications. Crowdsourcing and open innovation further cultivate collaborative efforts essential for addressing unmet medical needs, especially in rare diseases [19, 20]. The various approaches to DR include:

4.1. Drug-centric approach.

Drug-based methods for DR emphasize pharmacological characteristics, metabolic processes, and drug targets. Potential repurposing targets can be identified through interactions and metabolic pathways using computational methods and large libraries. Techniques such as molecular docking and network pharmacology are used to predict efficacy and explore multi-target effects. HTS assesses small molecules against disease models, facilitating the identification of treatments for untargeted conditions. ML analyzes data on prescription interactions and clinical outcomes, yet may overlook therapeutic opportunities. This drug-centric focus enhances the development of new medications, particularly for orphan diseases.

4.2. Disease-centric approach.

Finding effective medications for diseases requires knowledge of their pathophysiology and associated characteristics, which makes DR methods possible. Researchers focus on disease-associated genes, signaling pathways, and biological processes to identify existing medications that can produce therapeutic effects. This includes characterizing gene marker expression and using omics platforms such as proteomics, metabolomics, and genomics to build a molecular understanding of diseases. Phenotypic screening techniques evaluate the effectiveness of drugs in disease models, guiding the selection of compounds that promote advantageous phenotypic alterations. Integrating patient clinical data can help identify promising treatments, while AI and ML facilitate the analysis of large datasets to uncover repurposing opportunities for novel diseases. This approach optimizes the DR process by emphasizing disease characteristics over existing medications [21]. Figure 5 illustrates the therapeutic optimization of DR with AI mechanisms.

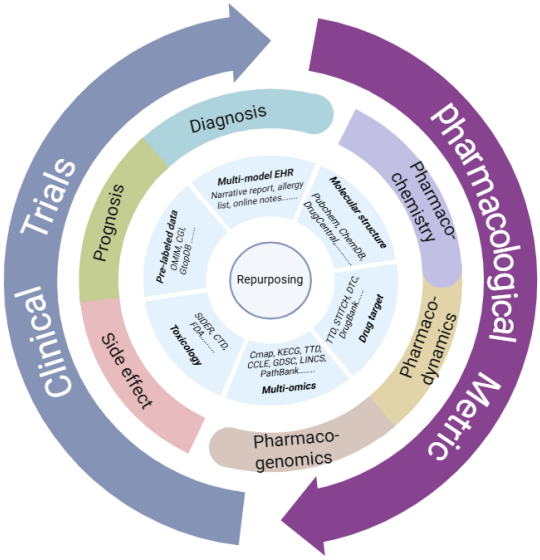

Figure5. Therapeutic optimization of drug repurposing with artificial intelligence mechanisms.

Table 2 lists the medications that have been repurposed. Recently, several drugs have advanced through various phases of clinical trials for repurposing, offering promising opportunities for the treatment of a range of diseases. Examples of medications being studied and the conditions in which they have been repurposed are included in Table 3, and a comparative description of traditional drug repurposing vs. AI-driven repurposing is presented in Table 4.

Table 2. List of repurposed drugs and their indications.

Drug name	Original indication	Potential indication
Aspirin	Analgesic, antipyretic	Antiplatelet*
Hydroxychloroquine	Malaria	Rheumatoid arthritis*, lupus erythematosus
Thalidomide	Sedative	Multiple myeloma*, lepra reaction*, Behcet's disease
Colchicine	Gout	Familial Mediterranean fever*
Tamoxifen	Breast cancer	Prevention of breast cancer in high-risk women*, gynecomastia
Sildenafil	Hypertension, angina	Erectile dysfunction*
Methotrexate	Cancer chemotherapy	Psoriasis*, rheumatoid arthritis*, ectopic pregnancy
Metformin	Type 2 diabetes mellitus	PCOS, anticancer, psoriasis
Disulfiram	Alcohol dependence	Cocaine dependence
Ivermectin	Antiparasitic	Antiviral (COVID-19), scabies
Naltrexone	Alcohol dependence, opioid dependence	Fibromyalgia
Clozapine	Schizophrenia	Treatment-resistant bipolar disorder
Topiramate	Epilepsy, migraine prophylaxis	Obesity* alcohol dependence, and bipolar disorder
Ezetimibe	Hypercholesterolemia	NAFLD
Olanzapine	Schizophrenia, bipolar disorder	Chemotherapy-induced nausea and vomiting, anorexia nervosa
Minoxidil	Hypertension	Androgenic, alopecia*
Acetylcysteine	Acetaminophen overdose antidote	Contrast-induced nephropathy
Bupropion	Depression, smoking cessation	SAD, obesity, ADHD
Dapsone	Leprosy	PJP
Cimetidine	Peptic Ulcer	Prevention of gastric cancer recurrence
Pioglitazone	Type 2 diabetes mellitus	NASH, Prevention of cardiovascular events in high-risk patients
Aripiprazole	Schizophrenia, bipolar disorder	Tourette syndrome*, augmentation therapy for depression*
Celecoxib	NSAID	FAP*
Propranolol	Hypertension, angina	Migraine prophylaxi*, anxiety
Minocycline	Antibiotic	Leprosy, Rheumatoid arthritis
Amantadine	Parkinson's disease	Fatigue in multiple sclerosis
Chlorpromazine	Antipsychotic	Intractable hiccups*, nausea, and vomiting
Misoprostol	Gastric ulcer	Medical abortion, induction of labor
Semaglutide	Type 2 diabetes mellitus	Obesity*

*Approved by the FDA, PCOS: Polycystic ovary syndrome; NAFLD: Non-alcoholic fatty liver disease; SAD: Seasonal affective disorder; ADHD: Attention deficit hyperactivity disorder; PJP: Pneumocystis Jirovecii pneumonia; NASH: Non-alcoholic steatohepatitis; FAP: Familial adenomatous polyposis; NSAID: Nonsteroidal anti-inflammatory drug [22].

Table3. List of repurposed drugs under research and their indications.

Drugs	Repurposed indications
Nitroglycerin	Wound healing and tissue repair
Baclofen	Alcohol use disorder
Doxycycline	Parkinson's disease
Metformin	PCOS
Amitriptyline	Fibromyalgia
Rapamycin	Neurodegenerative disease, cancer chemotherapy
Ezetimibe	NAFLD
Cimetidine	Cancer chemotherapy
Diclofenac	Actinic keratosis
Mefloquine	Glioblastoma multiforme
Metformin	Cancer, prevention of cardiovascular disease
Losartan	Parkinson's disease

Drugs	Repurposed indications
Atorvastatin	Alzheimer's disease
Pioglitazone	Parkinson's disease
Disulfiram	Glioblastoma multiforme
Propranolol	Infantile hemangioma
Allopurinol	Heart failure
Gabapentin	Hot flashes in menopausal women
Bisphosphonates	Reducing the risk of breast cancer
Minocycline	Multiple sclerosis, amyotrophic lateral sclerosis

NAFLD: Non-alcoholic fatty liver disease; PCOS: Polycystic ovary syndrome [22].

Table 4. Comparative description of traditional drug repurposing vs. AI-driven drug repurposing approaches: [11, 23].

Aspects	AI-driven Drug Repurposing	Traditional Drug Repurposing
Drug discovery method	Network pharmacology, deep learning, and machine learning	Clinical observation, serendipity, and literature review
Discovery speed	Quickly, as a result of computational screening and automation	slow and dependent on accidental observation or manual research
Time required	Weeks to months	Several years to decades
Data dependency	High and dependent on biological data, both organized and unstructured	Low, depends on human judgment and chance
Cost-effectiveness	cost-effective because of less laboratory work and in-silico prediction	Expensive because of the need for clinical trials and thorough wet-lab testing
Scalability	High scalability over thousands of indications and compounds	Scalability is limited because of the manual method.
Validation needs	Strong prediction models are beneficial, but clinical validation is still needed.	Has a greater failure rate and needs complete validation.
Success rate	Growing with improved datasets and algorithms	Moderate; in late-stage trials, many leads fail
Limitation	Model bias, interoperability requirements, and issues with data quality	Time-consuming, unpredictable, and limited scope

6. AI-Driven DR Techniques

AI-based methods are sophisticated computational methods that can identify new therapeutic applications for approved medications through repositioning in the drug development process, making them more affordable, faster, and more effective.

6.1. Classification of learning paradigms.

6.1.1. Supervised learning.

DR uses supervised learning, as the models are trained on labeled data that incorporates existing knowledge about the drug's target, pharmacological properties, and bioactivities. Support vector machines (SVMs), random forests (RFs), and neural networks are therefore suitable for forecasting potential interactions when current medications are combined with novel targets. This ensures that medications with comparable pharmacological classifications or chemical characteristics are identified for the treatment of various illnesses [24]. To facilitate the use of these AI techniques, a number of open-source tools and frameworks have been developed, including Scikit-learn, PyTorch, and Keras. These packages give users access to a variety of drug discovery methods. In drug discovery, regression analysis techniques are essential, especially for predicting the physicochemical characteristics of molecules. By finding compounds with desired qualities and reducing testing time and expense, these algorithms can help optimize the drug development process [25].

6.1.2. Unsupervised learning.

In complex biological data, where the optimum categories are difficult to identify, unsupervised learning is ideal for clustering and pattern recognition. Clustering and dimensionality reduction (PCA) are two techniques that reveal relationships between medications, illnesses, and genes that would not otherwise be apparent. One medication may be used in combination with another that behaves similarly, either therapeutically or molecularly, as researchers do not need to know the molecular targets of these treatments [26]. Using the t-distributed stochastic neighbor embedding (t-SNE) method, some researchers have employed ML to map compound activity across the kinome. Sammon mapping is a tool developed to simplify the application of AI techniques [27].

6.1.3. Semi-supervised learning (SSL).

When labeled data is scarce, SSL combines labeled and unlabeled data to achieve greater accuracy. Given the abundance of unlabeled biological and chemical data in DR, the SSL method is particularly advantageous. Models will be able to generate more accurate predictions and more generalizable assumptions about data that may contain only a small percentage of positively labeled drug–target interactions when SSL is applied. Graph-based techniques have attracted significant interest lately and have proven effective at anticipating potential DTIs. Nevertheless, these approaches have the drawback that the available DTIs are extremely scarce and costly to obtain, thereby reducing the systems' capacity for generalization. As a result, the self-supervised heterogeneous graph contrastive learning for drug–target interaction (SHGCL-DTI) prediction framework has been proposed for DTI prediction, which adds an additional graph contrastive learning module to the traditional semi-supervised DTI prediction task [28].

6.1.4. Reinforcement learning.

Artificial neural networks (ANNs) and deep RL architectures are combined in RL approaches, which are AI algorithms that use a dynamic approach to solve decision problems. The foundation of these methods is the analysis and estimation of the statistical relationship between each possible course of action and its outcomes. The program then looks for the best possible result. The RL for structural evolution (ReLEASE) software (v. 1.0) has been used to optimize the construction of chemical libraries for de novo drug development and screening [29]. A multilayer ANN is typically used as the generative model in reinforcement learning approaches, with inputs such as molecular graphs or Simplified Molecular Input Line Entry System (SMILES) strings. Through iterative learning and decision-making processes, the model is then trained using data from known bioactive chemicals. Finally, it creates new outputs and evaluates their responses for optimization. In this way, it functions as a virtual agent that, with neural network instruction, alters molecules to maximize their attributes. The creation of models using reinforcement learning to generate chemicals projected to actively combat a biological target, or analogous to a query structure, is an example of this methodology [30].

6.1.5. Transfer learning.

This article covers the use of deep transfer learning for drug response prediction, emphasizing the benefits of using models from one disease or drug class to improve learning

in other diseases with less data. It describes how deep neural networks (DNNs) work in this situation, with lower layers that can be adjusted or retrained and upper layers that serve as feature extractors. The DNN technique extracts significant features across domains while predicting medication response as a regression issue using mean squared error as the loss function. It also explains how LightGBM efficiently constructs decision trees to improve predictions via boosting, and it goes into detail on Ensemble Transfer Learning (ETL) using traditional and ensemble cross-validation with models like DNN and LightGBM [31].

6.2. Methodological/functional categorization.

ML serves as an intelligent data mining technology to generate prediction models. By analyzing large volumes of existing biological data, ML systems can detect and extract meaningful, usable information. For drug discovery, ML algorithms were divided into four categories: those based on DL, matrix complementation and decomposition, network propagation, and conventional ML models. These categories are illustrated in Figure 6.

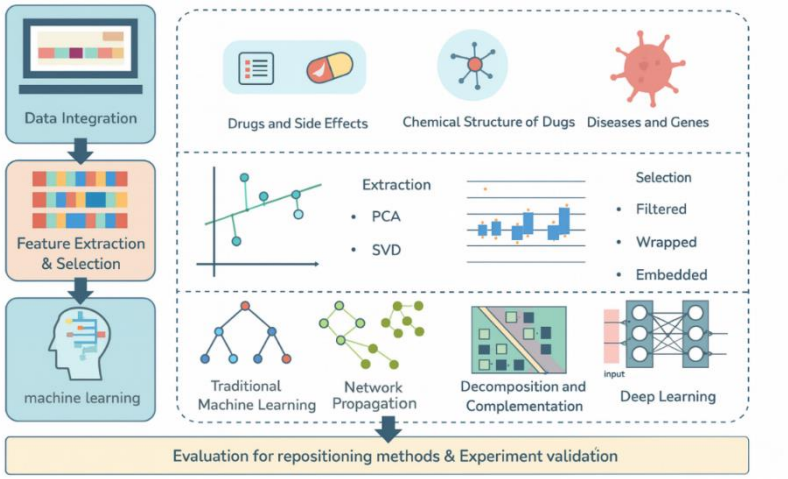

Figure6. Flow chart of the machine learning algorithms for drug repurposing.

Various algorithm approaches have been developed for drug repositioning. These algorithms are generally classified into: Conventional ML models; Models based on network transmission [32]; Models based on matrix completion (MC) and matrix factorization; Models based on DL.

6.2.1. Conventional ML models for drug repositioning.

Traditional ML starts with some labeled or observed samples and looks for patterns that principled analysis is unable to find. To uncover disease targets with similar pharmaceutical effects, traditional ML in drug repositioning often uses genes, drug targets, and disease manifestations as features. This process creates a dichotomous network of connections between features and medications [33]. Table 5 presents an analysis of the approaches discussed below, including the methodologies, biological networks, and evaluation criteria.

Table 5. List of traditional machine learning-based methods.

Name	Methods	Biological network used	Evaluation criteria
KronRLS-MKL [34]	MKL, KronRLS, BLM	DTI	AUPR
PUDTI [35]	SVM, PU	DTI	AUC, precision, recall, F-measure

Name	Methods	Biological network used	Evaluation criteria
FRMSL [36]	KronRLS, SymNMF	DTI	AUC, ROC
iPPI-Emsl [37]	RF, DWT	PPI	ACC, MCC, SE, SP
GTB-PPI [38]	L1-RLR, decision tree	PPI	ROC, PR, AUPRC
	SVM, BLM, integration of multiple similarities	CPI, PPI	AUC, PR
DDR [39]	RF, Label propagation	DTI	Precision, Recall, SP, AUPR
PUDT [40]	SVM, Heat kernel diffusion	DTI	AUC, ROC, AUPR
LRF-DTI [41]	RF, SMOTE, LDR	DTI	AUC, SE, SP, ACC
Bigram-PSSM [42]	SVM, PSSM	DTI	AUC, AUPR, SE, SP, Precision
DTIGBDT [43]	GBDT, KNN	DTI	AUC, ROC, AUPR

MKL: Multiple kernel learning; KronRLS: Kronecker regularized least squares; BLM: Bipartite local model; SVM: Support vector machine; PU: Positive–unlabeled learning; SymNMF: Symmetric non-negative matrix factorization; RF: Random forest; L1-RLR: L1-Regularized logistic regression; DWT: Discrete wavelet transform; SMOTE: Synthetic minority oversampling technique; LDR: Lasso dimensionality reduction; PSSM: Position-specific scoring matrix; GBDT: Gradient boosting decision tree; KNN: K-nearest neighbors; CPI: Compound-protein interactions; MCC: Matthew's correlation coefficient; DTI: Drug–target interaction; PPI: Protein–protein interaction; AUPR: Area under the precision–recall curve; AUC: Area under the curve; ROC: Receiver operating characteristic curve; PR: Precision–recall curve; SE: Sensitivity; SP: Specificity; ACC: Accuracy.

6.2.1.1. Methods based on logistic regression and linear regression.

To address the issue of large drug-protein spaces [34], the drug-target interaction problem was formulated as a linkage prediction task on a bi-directional network using the Kronecker regularized least squares (Kronecker RLS) [36]. The technique can handle large drug-target interaction matrices without requiring additional network sampling. The drug repositioning task was first formulated as a two-layer heterogeneous network comprising drug and disease nodes, along with known drug-disease associations, with the Kronecker RLS integrating multiple heterogeneous data sources to predict drug-disease associations. Later, a novel prediction pipeline based on protein-protein interactions (PPI) was proposed, which utilized L1-regularized logistic regression (L1-RLR) to reduce redundant features [38].

6.2.1.2. Methods based on SVMs.

Proteins with distinct targets for a given molecule are unlikely to be targeted by the compound, according to a novel notion described in [44]. Negative interactions were used to train SVM classifiers to identify new therapeutic targets [40]. Different biological data for target proteins were integrated, and a framework for predicting DTIs was proposed based on positive-unlabeled learning, classifying unlabeled samples into reliable negative and probable negative classes based on target similarity information, and using a weighted SVM. SVMs were used as pattern-classification engines to predict DTIs, with binary syntactic features derived from the protein's position-specific scoring matrix. Negative selection strategies were also investigated for prediction effectiveness [42]. For a new drug design called Positive-unlabeled drug–target interaction (PUDTI), an efficient pre-filtering screening framework, fuzzy sample probabilities belonging to positive and negative classes, and an SVM-based optimization model to infer current drugs and new drug repositioning prospects for targets were presented [35].

6.2.1.3. Methods based on random forest.

An integrated classifier was developed by merging seven distinct RFs to predict PPI [37]. A DTI heterogeneous graph was created by combining drug and target similarities with pre-existing DTI, and a DTI prediction approach was established using RFs and heterogeneous graphs [39]. A prediction method based on the RF classifier and Lasso dimensionality reduction was proposed, using DTI information from the recovered features to create positive and negative samples. The RF classifier was fed the processed ideal feature vector in order to forecast DTI [41].

6.2.1.4. Methods based on a decision tree.

A decision tree can show how cases are categorized according to their characteristics. Drug–target interaction gradient boosting decision tree (DTIGBDT) is a unique computational technique that was presented to increase the accuracy of DTI predictions and mitigate the effects of class imbalance. Drug-target interaction (DTI) scores were computed to assess the potential DTI, using gradient-boosted decision trees and the gathered features. Although several solutions have been developed using classical ML, they have disadvantages. For example, some procedures typically require negative samples to be processed by selecting unlabelled samples, yet these unlabelled samples may contain undetected positive samples. In this case, a positive sample shows the existence of the substance of interest in the measured sample, whereas a negative sample indicates its absence. Some strategies apply exclusively to marketed medications with detailed side effect information. However, many irrelevant keywords must still be filtered when establishing similarity, and there may be a relationship between the hierarchies of related keywords or medical phrases [43].

6.2.2. Models based on network transmission for drug repositioning.

The guilt-by-association presumption theory, which holds that drugs with similar structures and functions are linked to illnesses with comparable etiologies and symptoms, and vice versa, is the fundamental foundation of network-based approaches. The explicitly analyzed methods are listed in Table 6.

Table 6. List of network transmission-based methods.

Name	Methods	Biological network used	Evaluation criteria
CLDISMMA [45]	Within layer topology	Small molecule- miRNA interactions	ROC, AUC
NEDTP [46]	Network embedding, random walk	DTI, PPI	AUROC, AUPR
PPDTS [47]	Collaborative Filtering	DTI	AUC, AUPR

ROC: Receiver operating characteristic curve; AUC: Area under the curve; AUROC: Area under the receiver operating characteristic curve; AUPR: Area under the precision–recall curve; DTI: Drug–target interaction; PPI: Protein–protein interaction; miRNA: microRNA.

6.2.2.1. Methods based on drug-disease similarities.

The network proximity metric was used to assess the link between pharmacological targets inside a PPI network. This method identifies probable pathways for new drug-disease indications, side effects, and the impacts of established medications, thereby addressing critical challenges in drug development and care [48]. A systems pharmacology-based network medicine platform was used to characterize the relationships between the human coronavirus–

host (HCoV-host) interactome and therapeutic targets in the protein-protein interaction network. The method utilizes the integrated interactome network, focusing on sub-networks containing proteins that influence viral infections. A novel network-based similarity metric quantifies interactions between drug targets and disease-associated proteins, enabling the prediction of drug-disease associations [49]. The novel similarity metric is a network-based tool that assesses the interaction of drug targets and disease-associated proteins in the human interactome. It especially rewards drug-disease correlations that occur in the same network neighborhoods [50].

6.2.2.2. Reasoning based on network similarity.

A recommendation strategy was developed to implement two network-topology-based inference methods aimed at predicting drug-disease correlations [51, 52]. The strategy involved constructing multi-layer heterogeneous networks derived from known small molecule-microRNA (miRNA) interactions, utilizing intra-layer topology and established cross-layer associations for the prediction of small molecule-miRNA interactions. Latent feature matrices are obtained for each layer using the block coordinate descent approach. The small molecule-miRNA association score matrix is then constructed using the small molecule and miRNA layer feature matrices [45]. A network embedding framework for the mulTiPlex network was presented to predict DTI, featuring a new negative sampling model for handling positive-negative sample imbalances. The collaborative filtering approach was initially used in recommendation systems to provide users with personalized recommendations [46]. To produce similarity scores, a linear combination of drug-target and target-drug similarity models was proposed, using collaborative filtering methods in conjunction with known drug-target topological information. Similarity-based approaches are effective at distinguishing between known drug-illness pairs and unknown drug-disease pairs, but they rely on prior knowledge of drugs and diseases and are susceptible to overfitting. However, these approaches are only applicable when drug-target interactions are known, limiting their ability to predict new drug targets [47].

6.2.3. Models based on MC and matrix factorization.

Matrix decomposition methods are also utilized to discover novel drug-disease interactions. Typically, one input matrix is used, and two correlation matrices are generated as outputs, then multiplied to produce an approximation of the actual input matrix. Table 6 lists the specially analyzed methods.

Table7. Matrix completion and matrix decomposition-based methods.

Name	Methods	Biological network used	Evaluation criteria
DLGRMC [53]	MC	DTI	AUPR, PR
symLMF [54]	symLMF	PPI	prediction accuracy, recall, precision, MCC
MLMC [55]	MC, ML	DTI	ROC, AUC, AUPR, precision
SPLCMF [56]	CMF, RLS	DTI	RMSE, MAE, AUCPR, AUC
NRLMF β [57]	RLMF	DTI	AUC, AUPR
SRCMF [58]	CMF	DTI	AUPR
DDAPRED [59]	RLMF	DTI	AUROC, AUPRC
L2,1-GRMF [60]	GRMF	DTI	AUPR, AUC
OMC [61]	MC	Drug-disease associations	ROC, PR
DLGrLMF [62]	RMF	DTI	AUPR, PR

Name	Methods	Biological network used	Evaluation criteria
BNNR [63]	ADMM, MC	DDI, Drug-disease associations	ROC, AUC, PR, precision

MC: Matrix completion; ML: multi-view learning; symLMF: symmetric logistic matrix factorization; CMF: collective matrix factorization; RLS: regularized least squares; RLMF: regularized logistic matrix factorization; GRFM: graph regularized matrix factorization; RMSE: root-mean square error; MAE: mean absolute error; ADMM: alternating direction method of multipliers; DTI: drug–target interaction network; PPI: protein–protein interaction network; AUPR: area under the precision–recall curve; AUROC: area under the receiver operating characteristic curve; ROC: receiver operating characteristic curve; AUC: area under the curve; PR: precision–recall curve.

6.2.3.1. Methods based on MC.

MC tries to discover novel indications by populating the drug-target or drug-disease relationship matrix with unknown elements. A Laplacian-regularized Monte Carlo model was proposed for drug-target interaction (DTI) prediction, reformulating the prediction task as a Monte Carlo problem that estimates probable interactions based on matrix prediction scores obtained after the completion procedure [53, 64, 65]. Studies have demonstrated that combining heterogeneous, multisource data can significantly enhance prediction accuracy. The drug-disease matrix was constructed using bounded kernel norm regularization under the low-rank assumption and enhanced with the alternating direction multiplier method to identify unknown connections between drugs and diseases [63]. Additionally, prior information was incorporated into two- and three-layer networks to predict scores for unobserved drug-disease combinations and complete missing elements in the matrices [61]. To achieve multi-view learning with Laplacian graph regularization, a matrix complementation strategy was introduced. This led to the inference of potential pharmacological indications and two integrated similarity matrices [55].

6.2.3.2. Methods based on logistic matrix factorization (LMF).

A neighborhood regularized (NR) LMF, based on rescoring using the Bernoulli distribution, was developed to improve the prediction accuracy of drug–target combinations with limited interaction information [57]. By combining multiple drug-disease similarities, regularized logistic matrix decomposition was used to identify new therapeutic correlations between drugs and disorders in the training set [59]. The symmetric LMF algorithm was used to predict protein–protein associations and can be applied to PPI datasets for specific organs or disorders [54].

6.2.3.3. Methods based on collaborative matrix factorization (CMF).

A self-paced learning method based on weighted low-rank approximation (SPLCMF) was proposed for collaborative matrix decomposition. When the drug and target are projected into a shared low-rank feature space, RLS incorporates several networks associated with the drug and target [56]. In contrast to typical collaborative matrix decomposition, this approach aims to achieve a low-rank feature representation of drug-target similarity by employing soft regularization terms. These terms constrain the approximation of drug-target similarity features to potential features in drug-target interaction (DTI) analysis [58].

6.2.3.4. Methods based on regularized matrix factorization (RMF).

An enhanced graph regularization matrix decomposition was proposed to learn these flow patterns, as datasets are typically distributed on or near low-dimensional nonlinear manifolds. Using stream learning, medications and targets were represented in a low-dimensional space using a bipartite graph regularization matrix decomposition approach to predict DTIs [60]. Additionally, a sparse procedure was used to remove unnecessary data from medication pairs and target pairs. Drug pairwise chemical structure similarity and target gene pairwise genomic sequence similarity were used to address the matrix decomposition problem by employing pairwise Laplacian regularization terms to overcome challenging drug-feature and target-feature selection. Potential factor vectors of the breakdown matrix are represented by similarities between drug and target neighbors, and possible interactions are inferred from likelihood scores using logistic functions. The primary benefit of matrix decomposition is that it does not require information on physicochemical and structural characteristics or functional annotations; instead, it infers top-level interactions solely from the known interaction patterns of each protein/target. Nevertheless, scenarios in which expected values fall outside the [0, 1] range, such as when there is a lot of noise and missing data, cannot be avoided by matrix decomposition and complementation techniques. Additionally, complementation techniques are prone to inadequate local minima. It is difficult to construct a single metric to accurately describe the similarity between a drug and a disease when the drug–target interaction pair has little information about the interaction [62].

6.2.4. Models based on DL for drug repositioning.

Large chemical databases have become more accessible for medication research and discovery.

Table 8. Matrix completion and matrix decomposition-based methods.

Name	Methods	Biological network used	Evaluation criteria
MSDF-CNN [66]	CNN	drug-LProt association	ACC, AUROC, AUPR sensitivity, specificity
HNet-DNN [67]	DNN	DDI, drug-disease associations	Accuracy, precision, recall, F1, AUC, AUPR
DeepAffinity [68]	RNN	CPI	pIC_{50}
Graph-CNN [69]	GCN	Protein-ligand interactions	AUC, RE
DNN-DTIs [70]	XGBoost, DNN	DTI	ACC, GPCR, CI, NR
GCAN [71]	RNN, random walk	Rare diseases	MRR
LAGCN [72]	GCN, layer attention	Drug-disease associations, Disease-diseases similarities	Recall, specificity, ACC, precision, F1
SKCNN [73]	Sigmoid Kernel, CNN	DTI	ACC, Precision, F1, recall
DRHGCN [74]	GCN, layer attention	Drug-disease associations, Disease-diseases similarities	AUROC
SimCNN-DTA [75]	CNN	DTI	MSE, CI, AUPR, r^2m

CNN: Convolutional Neural Network; DNN: Deep Neural Network; RNN: Recurrent Neural Network; GCN: Graph Convolutional Network; WL: Weisfeiler-Lehman is well-known because of its graph isomorphism test; XGBoost: eXtreme gradient boosting: LProt: PD-associated proteins; DDI: Drug–Drug Interaction; CPI: Compound–Protein Interaction; DTI: Drug–Target Interaction; F1: F1-measure; AUC: Area Under the Curve; AUPR: Area Under the Precision–Recall Curve; pIC_{50}: Negative Logarithm of IC50 CI: Concordance Index; RE: Relative Error; ACC: Accuracy; GPCR: G-Protein-Coupled Receptor; NR: Nuclear Receptors; r^2m: modified squared correlation coefficient; MRR: mean reciprocal rank; AUROC: Area Under the Receiver Operating Characteristic Curve.

DL has the advantage of being able to learn intricate correlations between input attributes and output decisions from massive amounts of data. Although it is still in its infancy, its application in molecular informatics and medication repositioning has shown a lot of promise. Several popular deep architectures have yielded more substantial advances in drug-related research as compared to traditional ML methods. Table 8 lists the methods specifically analyzed.

6.2.4.1. Methods based on DNNs.

A supervised learning approach was put out to anticipate DTIs. For every drug-target pair sample, subgraphs are recovered, the similarity between nodes and subgraphs is measured using graph labeling techniques, and DNNs are utilized to extract complex patterns and non-linear topological properties from the closed subgraphs [76]. To train the DNN model, a drug-disease heterogeneous network was constructed by incorporating known drug-disease associations [67]. Topological properties were then retrieved from the heterogeneous network. Because of its broad versatility, the compound structure can be employed in conjunction with a variety of data, including molecular characteristics, transcriptomes, bioassays, and functional class fingerprints [77, 78]. DNN was created using a layer-by-layer learning strategy with functional class fingerprints for compounding and an MLP with four hidden layers for DTI prediction. The DTI model is built utilizing the best parameters from each component after different feature extraction algorithms, feature selection techniques, and classifier algorithms have been optimized [70].

6.2.4.2. Methods based on convolutional neural networks (CNNs).

Sigmoid kernels and CNNs are used in the suggested method, which uses feature descriptors as input to an RF classifier to predict each drug's connection with every ailment [73]. A similarity-based model was proposed that predicts drug–target binding affinity by applying a 2D CNN (2DCNN) to the outer product of the column vectors of two similarity matrices for a drug and a target [75]. To find possible medications linked to Parkinson's disease, a DR strategy based on CNNs and multi-source data integration was proposed. Low-dimensional features were used as inputs to the CNN model after diffusion component analysis reduced the dimensionality of the drug and LProt (Linked Protein) feature vectors [66].

6.2.4.3. Methods based on recurrent neural networks (RNNs).

A new, understandable DL method was introduced to extract representations of long-term nonlinear interactions between atoms in compounds by pre-training bidirectional RNNs as part of an autoencoder using a large amount of rich, unlabeled data [68]. Cao *et al*. employed a model based on the Gated Recurrent Unit network, an RNN-based variant, and focused on rare-illness nodes with hierarchical linkages and nodes within two hops to achieve information-limited medication relocation for rare diseases [71].

6.2.4.4. Methods based on Graph convolutional networks (GCNs).

An unsupervised GCN was constructed to learn a fixed-size representation of protein pockets from a representative selection of druggable protein binding sites. Without using target-ligand complexes, the framework performed better or on par with existing structure-based techniques [69]. An end-to-end DL method based on graphs was proposed. It learns

embeddings for medications and illnesses using graph convolution techniques. Embeddings from several graph convolution layers are combined using attention methods [72]. Based on the integrated embeddings, the model assigns a score to unobserved drug-disease relationships. To provide more representative medication and illness embeddings, inter- and intra-domain feature extraction modules were created by applying graph convolutional operations within the network, rather than simply merging three networks into a single heterogeneous network [74].

6.2.4.5. Methods based on ANNs.

Based on a revolutionary optimization method, a groundbreaking ML technique dubbed Trader was suggested. A multi-layer ANN was created and trained using this technique to predict DTIs precisely. Neural networks have great potential in this area of research for precisely predicting drug-target affinity values. Neural networks' ability to combine drug and target features changes the current situation, where they are concatenated or tensor products. Compared to classical ML, DL uses deeper neural network architectures with more hidden layers, enabling it to process large datasets and learn intricate patterns. Neural networks, however, take longer to execute than classification or ranking algorithms for the same reason. Overfitting may happen when the medication and target features have a high dimensionality [79].

6.3. Knowledge graph-based AI techniques.

By using databases of DTIs, graph-based methods offer a thorough understanding of DTIs. Many recent DR findings have relied heavily on the creation and analysis of these networks [80]. A network-based DL model (DeepDR) was developed to integrate networks, such as drug–disease and drug–target networks, and learn high-level drug properties using a random walk approach. Integrating multi-omics data and genome-wide association studies (GWASs) into network-based AI techniques is another practical tactic [81]. For example, the network topology-based DL framework (NETTAG) uses an interpretable AI model based on multi-omics data to identify repurposable drugs by integrating disease-associated genes into the human PPI network [82].

7. Role of AI in Mitigating the Drawbacks of DR

Compared to the traditional method of drug development, which has several limitations, DR appears to be more efficient and initially less expensive. The repurposed medications may then be less effective, less target-specific, and more likely to cause side effects. Additionally, there may be a limit to the variety of molecules that can be targeted, and repurposed medications may require additional refinement to serve a new role [83]. Furthermore, challenges include intellectual property rights issues and the need for additional trials. AI algorithms can be advantageous in addressing these imperatives, even though they can pose some serious issues. AI can analyze massive daily streams of chemical and biological data and uncover previously undiscovered connections between medications, targets, and possible therapeutic applications [84]. This results in various benefits for AI; Figure 7 illustrates the role of AI in mitigating the drawbacks of DR.

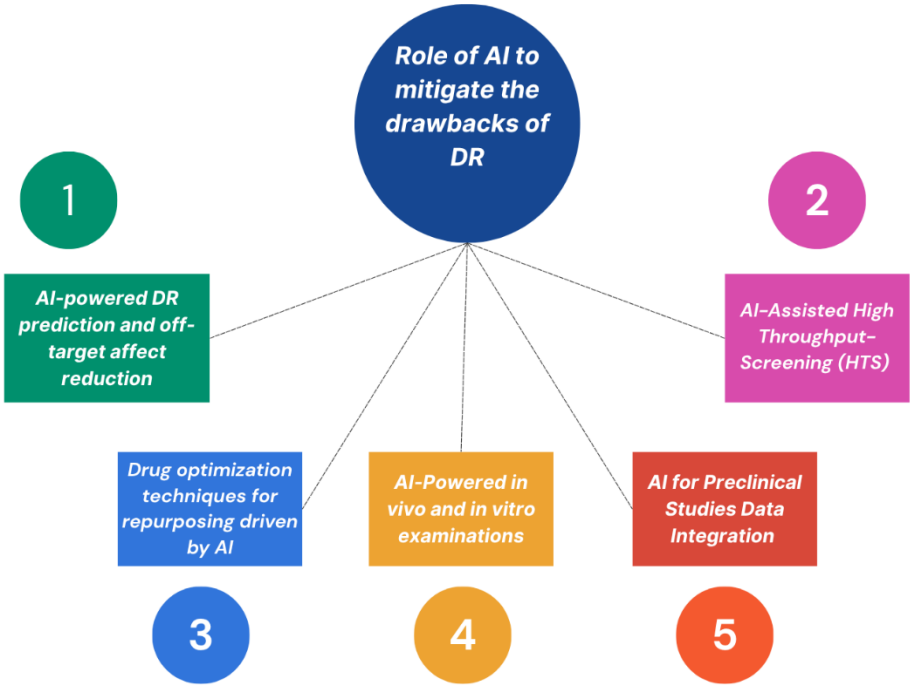

Figure7. Role of Artificial Intelligence to mitigate the drawbacks of drug repurposing. This picture demonstrates the strategies used to mitigate the drawbacks of conventional drug repurposing.

7.1. AI-powered DR prediction and off-target effect reduction.

The usage of well-known medications for various conditions, or DR, is one tactic for the quick reapproval of drug discoveries. However, there are still serious concerns about the safety of reusing medications in the planned new use. Side effects may occur if the provided molecule interacts with molecules other than the intended target, leading to off-target effects. AI shows up here in a big and positive way as a helpful tool for forecasting and preventing undesirable side effects. However, AI systems can work with large amounts of data, including protein structures and drug-target connections.

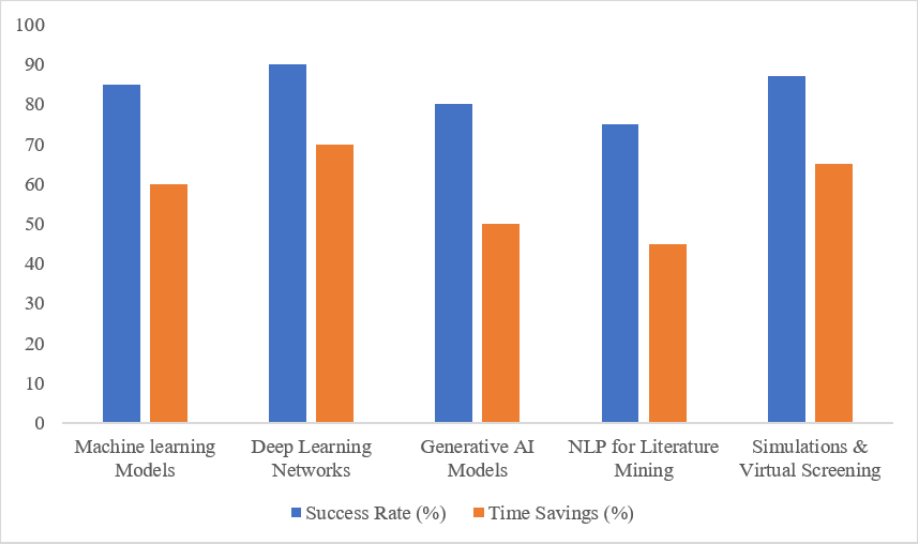

Figure 8. AI-powered DR prediction and off-target effect reduction.

AI helps clinical trial safety and efficiency by enabling the new DR to describe potential off-target effects for a particular medicine [85]. For example, baricitinib, which was first used to treat rheumatoid arthritis, may be utilized to treat coronavirus disease (COVID-19) due to

its anti-inflammatory and antiviral properties. The second example is the human immunodeficiency virus (HIV) medication lopinavir/ritonavir, which was studied as a potential therapeutic alternative because of its capacity to block a crucial severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) protein (protease). AI analysis determined its efficacy by identifying adverse impacts on liver function. AI eliminates the issues associated with using medications originally developed for other purposes and paves the way for the development of novel, more specific inhibitors for SARS-CoV-2 [86,87]. Figure 8 illustrates the mitigation of off-target effects and AI-powered prediction in DR.

The success rate and time savings for various AI techniques are displayed in the bar graph in Figure 8. However, no data were provided to compute the standard deviation or standard error, which are crucial indicators of data variability and the dependability of the stated percentages. The information at hand shows a single representative estimate. Consequently, error bars are not feasible.

7.2. AI-assisted HTS.

HTS is a resource-intensive process that often involves evaluating hundreds of compounds to identify potential medicinal candidates. By evaluating chemical libraries and forecasting compound activity, AI-powered models like CNNs optimize this process and rank candidates with the greatest therapeutic promise first. For instance, protein structure prediction has greatly improved thanks to the AlphaFold technique mentioned above, which enables scientists to identify previously elusive chemical interactions. This has revolutionized the early phases of drug development by enabling the development of more focused and cost-effective screening methods [88].

7.3. Drug optimization techniques for repurposing driven by AI.

AI is revolutionizing pharmacology and personalized medicine in DR, ensuring that side effects are prevented and that medication effectiveness and comfort are enhanced. By using ML algorithms on large datasets of molecular interactions, AI might discover novel off-target interactions that traditional approaches might miss. These models use structural and functional data to determine probable biological targets that the medication can modify to reduce the likelihood of adverse effects. CNNs and RNNs are the most accurate DL approaches for examining drug-protein interactions. These networks have the ability to identify complex patterns in chemical structures and rule out or clarify the effects of drugs on unexpected targets. Deep generative models, such as Variational Autoencoders (VAEs) and Generative Adversarial Networks (GANs), facilitate the development of modifications to current treatments that lessen side effects without sacrificing their effectiveness. Medical literature, clinical trial data, and pharmacological databases are mined using natural language processing (NLP) models. Thus, NLP assists in prioritizing possible medications for repurposing to reduce adverse effects through the extraction of drug target relations [89]. AI is used in computational molecular docking to determine how a medication will connect with several targets. Data mining, prediction, and virtual screening are used to identify drug-like compounds with fewer potential adverse effects. Because AI requires less laboratory work, it speeds up the identification and repurposing of medications. It is particularly important to work at this speed when dealing with serious health issues (like COVID-19). Patient compliance and higher survival rates can be attained in complex conditions like cancer and neurological disorders

because repurposed medications have fewer negative effects. AI can align prescription medications with patient characteristics and repurpose them, recommending them based on environmental factors, molecular markers, and genetics. Some AI models rely heavily on diversity and high-quality data, whereas a lack of comparable datasets may hamper their performance. Open-access databases must be created and shared immediately. There should always be transparency into the algorithms used, as AI decision-making in DR should entail a high degree of accountability. AI-predicted clinical trial designs and real-time impact monitoring are equally crucial for advancing and validating these technologies. AI's predictive and analytical capabilities help overcome DR invariance, making it more efficient, focused, and safe for organisms. This opens the way to more adaptable and responsive models of pharmaceutical manufacturing [90].

7.4. AI-powered in vivo and in vitro examinations.

AI also assists with in vitro and in vivo testing, where predictive models help design experiments and lessen the need for time-consuming techniques. For example, before conventional testing begins, GANs provide preliminary information on safety and efficacy by simulating biological responses to novel chemicals. Additionally, multi-omics AI models combine proteomic, transcriptomic, and genomic data to predict potential interactions between medication candidates and biological pathways specific to each patient. In addition to improving the accuracy of experimental tests, these integrated methods make it easier to create individualized treatment plans [91].

7.5. AI for preclinical studies data integration.

Last but not least, AI has been incredibly helpful in incorporating various datasets into preclinical research. By simultaneously analyzing omics datasets, imaging data, and physiological measurements, AI models can identify biomarkers and therapeutic targets that might otherwise have gone undetected. For example, DL algorithms have been used to analyze gene expression profiles and histological images, revealing novel insights into drug interactions and tumor microenvironments. Adopting a comprehensive approach increases the translational potential of preclinical research, paving the way for more successful clinical application [92].

8. Applications of AI at Various Phases of DR

AI applications undoubtedly enhance several DR phases, such as linking diseases to novel bioinformatics targets identified through genomics. ML categorization and regression leverage DL and network pharmacology for virtual screening, enhancing HTS, and predicting binding affinities by utilizing existing databases for drug-target interaction predictions. Real-world evidence and natural language processing are examples of clinical data analysis based on AI and ML that uncover new patterns and new uses for currently available medications. AI is essential to clinical trials because it enhances patient and risk profiling, thereby improving trial design and outcomes. Additionally, to help identify alternative therapy applications, it tracks post-marketing reports of any adverse consequences, thereby strengthening and advancing the frameworks that govern medical care and solutions. AI speeds up the identification and approval of medications by even tailoring them to each person, making it a groundbreaking tool in modern medical research [93, 94].

9. Case Studies that Elucidate the Application of AI Technologies In Real-World DR Projects

9.1. Case study 1: Baricitinib to treat COVID-19.

An AI study supports the idea of repurposing baricitinib, an oral Janus kinase (JAK) inhibitor that was once authorized for the treatment of rheumatoid arthritis, to treat COVID-19. Benevolent AI researchers identified baricitinib's ability to inhibit cyclin G-associated kinase (GAK) and AP2-associated protein kinase 1 (AAK1), both of which are involved in viral entrance and propagation, using DL and knowledge graph technologies. Preclinical evaluations and clinical research that followed this AI-driven prediction demonstrated baricitinib's efficacy in reducing inflammatory responses in COVID-19 patients. The FDA's 2020 emergency use authorization for the drug marked a significant turning point in demonstrating how AI may be used to repurpose already-approved drugs. It became a key part of treatment protocols worldwide, highlighting the impact of AI in rapidly addressing global health crises [95].

9.2. Case study 2: Ketamine to treat cocaine use disorder.

Ketamine for Addiction to Cocaine: An AI-based prediction model identified ketamine, which is commonly used as an anesthetic and more recently for its antidepressant properties, as a potential repurposing option for cocaine use disorder (CUD). To verify ketamine's potential effectiveness in treating CUD, the study used electronic health records, clinical trial databases, and drug-target prediction algorithms. Clinical reports of decreased cocaine cravings and relapse corroborated AI's identification of NMDA receptor regulation as a crucial mechanism. Low-dose ketamine infusions can dramatically lower cocaine usage in treatment-resistant people, according to further pilot studies, supporting the model's prediction and illustrating how AI might guide repurposing choices in substance use disorders [96].

9.3. Case study 3: Efavirenz to treat Parkinson's disease.

Based on AI-driven discovery methods, efavirenz, an antiviral medication that was first authorized as a non-nucleoside reverse transcriptase inhibitor (NNRTI) to treat HIV/AIDS, was repurposed for Parkinson's disease. FDA-approved drugs were screened against targets involved in α-synuclein propagation, a hallmark of Parkinson's pathogenesis, using a computational drug repositioning model. It was discovered that efavirenz activates CYP46A1, improving the brain's metabolism of cholesterol and lowering the build-up of α-synuclein. Efavirenz may have a neuroprotective impact, according to this mechanistic insight uncovered by AI and validated by preclinical research. In addition to demonstrating AI's predictive capacity, this repositioning creates new therapeutic options for the treatment of neurodegenerative illnesses [97].

9.4. Case study 4: Repurposing drugs to prevent cataracts in diabetes.

Researchers sought medications that could reduce the risk of cataract extraction in individuals with diabetes in a novel AI-based repurposing study. A number of potential medicines, such as angiotensin receptor blockers and certain anti-inflammatory drugs, were found after ML algorithms examined extensive clinical data to forecast drug-disease interactions. These predictions were validated using retrospective clinical records, which

showed a strong association between certain medications and a reduced incidence of cataract surgery. The study demonstrated how AI can be used to mine real-world data to identify preventive treatments, offering potential methods for managing diabetes complications [98].

9.5. Case study 5: Vandetanib and everolimus to treat diffuse intrinsic pontine glioma (DIPG).

Diffuse intrinsic pontine glioma (DIPG), a highly aggressive and deadly pediatric brain tumor, was treated with a combination of vandetanib, which was first approved as a tyrosine kinase inhibitor targeting vascular endothelial growth factor receptor (VEGFR), rearranged during transfection (RET), and EGFR for medullary thyroid carcinoma, and everolimus, a mechanistic (or mammalian) target of rapamycin (mTOR) inhibitor used in various cancers and organ transplant rejection. Drugs effective against Activin A Receptor Type 1 (ACVR1)-mutant DIPG, which accounts for around 25% of all DIPG patients, were found using an AI-driven platform. According to the investigation, vandetanib decreases the viability of DIPG cells by targeting ACVR1 (K_d = 150 nmol/L).

However, because of its limited brain penetration, vandetanib distribution across the blood-brain barrier is improved when combined with everolimus, which blocks P-glycoprotein (P-gp) and Breast Cancer Resistance Protein (BCRP) drug efflux transporters. This has shown potential in orthotopic xenograft models and guided early clinical translation in pediatric patients. The study demonstrates how AI can combine pharmacological data and genetic analysis to identify logical and practical repurposing strategies for rare disorders such as DIPG [99].

9.6. Case study 6: DREAM-RD project: fragile X syndrome (FXS).

DREAM-RD Project FXS is a rare genetic disorder characterized by intellectual disability and behavioral challenges, with no FDA-approved targeted treatments currently available. Researchers used AI/ML approaches in the DREAM-RD effort to find possible repurposed medications for FXS. Numerous potential compounds were shortlisted by the study using a hybrid strategy that included transcriptome analysis, gene-expression signature matching, and ML classifiers. This approach offered a targeted, data-driven path to therapeutic repurposing by leveraging drug perturbation profiles to reverse disease-specific gene expression patterns. The AI-based pipeline identified interesting candidates that require further clinical research, even though it is still in its early phases. This work represents an emerging trend in the use of AI for rare illness therapies, although it is noteworthy that it is based on a preprint and has not yet received peer review [100].

Table 9. Summary of AI-based drug repurposing: Case study examples and success stories from recent literature.

Drug	Original use	AI method used	Data used	Repurposed use	Clinical phase	Outcome
Ketamine [92]	Anaesthetic	Machine learning, EHR	Not available	Cocaine use disorder	Ongoing clinical trials	Clinical trials were started, and the results showed promise in lowering cocaine consumption
Raloxifene [96]	Osteoporosis and breast	Deep learning	Genetic data	Fragile X syndrome (FXS)	Early phase trials	Early trials revealed improvements in

Drug	Original use	AI method used	Data used	Repurposed use	Clinical phase	Outcome
	cancer prevention					FXS's behavioral and cognitive symptoms
Vendetanib+ Everolimus [95]	Cancer (Thyroid)	AI- based drug repurposing	Not available	Diffuse intrinsic pontine glioma (DIPG)	Phase 1	Preclinical research revealed possible advantages in ongoing trials to evaluate efficacy in DIPG.
Efavirenz [93]	Antiretroviral for HIV	Deep learning	Genomic data	Parkinson's disease	Phase 2	Proven ability to lower α-synuclein aggregation, with potential benefits for Parkinson's disease
Baricitinib [91]	Rheumatoid Arthritis	Machine learning EHR	Clinical 1 data	COVID 19	Phase 3	successfully enhanced COVID-19 patient outcomes; FDA-approved for emergency use

10. AI-Driven Drug Discovery: Challenges and Considerations

While ML offers tremendous speed and efficacy improvements in drug discovery, it also poses unique questions and concerns. The main obstacles are as follows:

10.1. Quality and accessibility of data.

It is clear that AI models rely heavily on data as an input for both training and validation. However, there may be a lack of substantial datasets, particularly for orphan diseases, and even quantitative data may be of poor quality. A number of problems lead to inaccurate projections, including bias in previous data and inconsistent data presentation. AI's ability to comprehend complex algorithmic decision-making relationships can make some ML techniques opaque, making it challenging for stakeholders to understand AI-generated predictions and obtain regulatory approval. AI developments can be incorporated into current drug discovery procedures. Life science companies (LISCs) must ensure that AI tools work with older technologies, which requires significant organizational system changes and personnel training. Adoption of AI in drug research is still a very new area of regulation. Given the widespread use of AI today, especially in pharmaceutical development, regulatory organizations should establish appropriate norms and procedures. These ought to consist of adequately safe and accurate validation processes and performance measures [101].

10.2. Concerns about privacy, consent, and regulatory compliance.

The utilization of health data for AI training raises questions about consent and privacy. Businesses and healthcare organizations face significant challenges in complying with data protection regulations and ensuring the reasonable handling of patient data [102].

10.3. Robustness and generalizability.

Adapting AI models to diverse demographics and situations is challenging, especially in drug discovery. Obtaining robust, solid models for multiple applications is crucial. Data scientists, biologists, pharmacologists, and doctors must work together to develop transdisciplinary AI solutions to improve problem-solving, enabling AI to be applied effectively in drug discovery [103].

10.4. Cost and allocation of resources.

AI is not a low-cost activity; it requires significant resources, including capital investment for system implementation and human capital for the actual implementation of AI technology. Executives in organizations must therefore consider the possible benefits and the resources required to develop AI-based projects. The development of AI must effectively address these significant concerns to unleash the capabilities necessary for novel drug discovery, as well as for safety, effectiveness, and ethical reasons [104].

10.5. Ethical intricacies.

Currently, ethical norms worldwide are being refined, and the ethical challenges of AI in therapeutic applications are being thoroughly investigated. The potential for cyberattacks on AI systems and the ensuing data security breach, access to private and sensitive information, the lack of explainability and transparency as a defining feature of AI-based decision-making and recommendations (i.e., how the output is being derived from the input—the "black-box issue"), and an excessive reliance on the output from AI-driven technologies (also known as "automation bias") are a few examples of ethical issues [105]. The ideals of "transparency," "justice, fairness, and equity," "non-maleficence," "responsibility and accountability," and "privacy" were found to be common throughout international recommendations on ethical AI [106].

10.6. Human-centered considerations.

Additionally, despite their inherent drawbacks and controversies, such as language bias, regional divide, environmental impact, and—most importantly—compromise on publication ethics, chatbots (such as ChatGPT and its successor GPT-4) have recently become the buzzwords in various health-related applications, from academic writing to passing medical licensing exams [107]. Although ML-based healthcare solutions may not always be able to duplicate the fundamental values of love, empathy, and compassion, the medical industry nonetheless operates on these foundations. Additionally, making unjustified predictions about future health issues could put the person at risk for increased anxiety, mental strain, and emotional suffering, as well as the stigmatization that follows. Thus, another area under investigation is the addition of an emotional component to all AI applications, including chatbots [108].

11. AI-Driven DR: Revolutionizing Drug Development and Discovery

More thoughtful, data-driven approaches to finding repurposing prospects are now available thanks to developments in data mining and AI [109]. AI has already been used to repurpose medications in areas including neurology, cardiology, cancer, and infectious

illnesses, as illustrated in Figure 9. These techniques enable a more logical and effective repurposing approach by analyzing intricate genomic and clinical information to identify common disease causes or therapeutic targets.

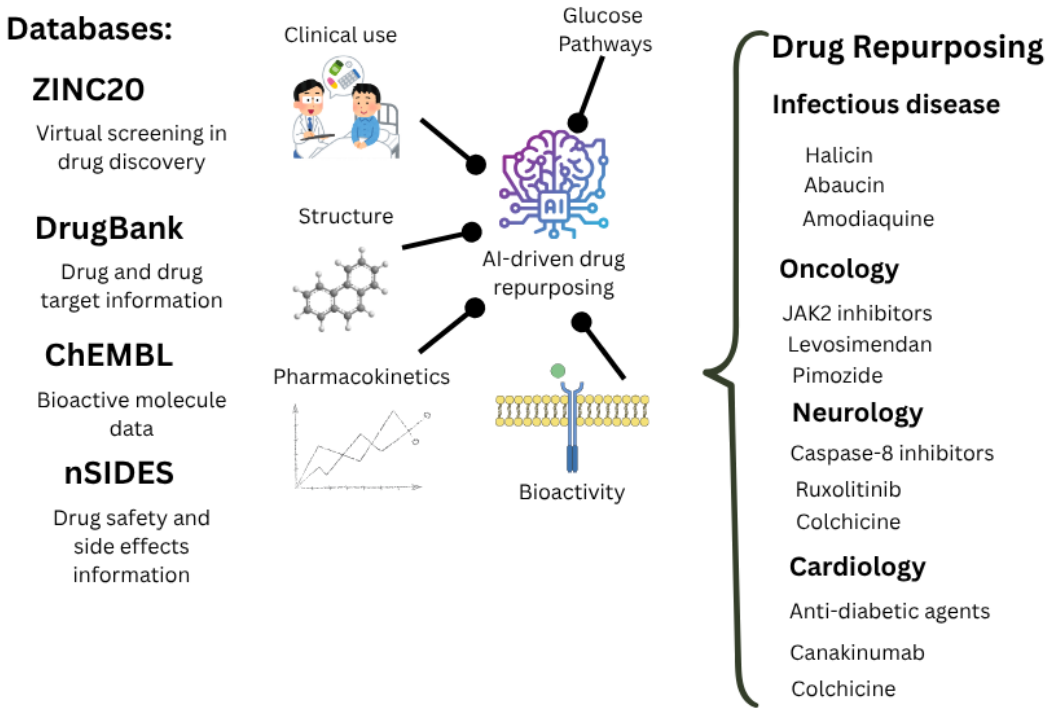

Figure 9. AI speeds up the repurposing of drugs in many therapeutic domains. Using structural, pharmacological, and adverse effect data from databases like DrugBank, ChEMBL, ZINC20, and nSIDES, advances in AI and XAI techniques have made it possible to find repurposing candidates in a methodical manner. For instance, medications like canakinumab and colchicine show potential in cardiology, whereas JAK2 inhibitors and pimozide have been repurposed in oncology. Ruxolitinib and caspase-8 inhibitors have become viable options in neurology, while medications like halicin and abaucin have been found in infectious disorders. AI stands for AI; XAI for explainable AI; and JAK2 for Janus kinase 2.

11.1. AI-powered DR for cancer.

Kinases are excellent targets for therapeutic intervention because they are essential to many pathological processes, especially cancer. The discovery and development of small-molecule kinase inhibitors has also received a great deal of interest. VEGFR1, hematopoietic cell kinase (HCK), mitogen- and stress-activated kinase 1 (MSK1), and epidermal growth factor receptor (EGFR) are important kinases implicated in cancer development [110]. For instance, 19 small-molecule inhibitors of these kinases have been found using a computational platform called VirtualKinomeProfile to profile compound-kinase interactions and predict the inhibitory activity of repurposed drugs. Another ML-based attempt employing the (eXtreme Gradient Boosting) XGBoost method identified promising JAK2 inhibitors from the ZINC database. Of these, 13 compounds underwent experimental validation, and 6 showed IC50 values < 100 nM [111]. Levosimendan, a phosphodiesterase (PDE) inhibitor effective in heart failure, also shows activity against multiple cancers, including lymphoma, through direct inhibition of Right Open Reading Frame Kinase 1 (RIOK1) and other kinases. This further broadens the scope by repurposing existing drugs for dual cancer indications through a one-drug, multi-target approach. Kinase inhibitors are not the only drugs that have been repurposed. Pimozide, an anti-dyskinesia medication used to manage the symptoms of Tourette's illness, was found to be a promising treatment option for non-small cell lung cancer via a DL-driven

pipeline that integrated transcriptome data and chemical structures [112]. Furthermore, candidates that inhibit the RET receptor—a crucial component in ligand-independent kinase activation and carcinogenesis—were identified using an ML-based in silico screening method applied to FDA-approved drugs from DrugBank. When combined, these computational techniques highlight the promise of DR for both finding powerful kinase inhibitors and uncovering novel anticancer uses for currently available treatments [113].

11.2. AI-powered DR in neurology.

In the context of Alzheimer's disease (AD), researchers have increasingly used ML-based methods to find viable candidates for therapeutic repurposing. For example, Rodriguez *et al*. screened 80 FDA-approved drugs to produce a ranked list of repurposing candidates, using computational models to link illness severity with underlying molecular pathways. Ruxolitinib, a JAK1/2 inhibitor originally developed as a targeted treatment for myeloproliferative neoplasms, became a top hit among them, demonstrating the potential of data-driven pipelines to identify existing medications with novel therapeutic uses for AD. Furthermore, by incorporating dynamic molecular descriptors from molecular dynamics simulations into ML models, caspase-8-targeting medications were identified [114].

Other strategies have demonstrated comparable potential. Graph CNNs have enabled the detection of minute structural details that conventional descriptors can miss in discovering inhibitors of the beta-secretase enzyme 1 (BACE1), a crucial component in the formation of amyloid-beta. In the end, these methods guided the selection of promising medication candidates for experimental validation by improving candidate prioritization [115]. Other approaches have used extended connectivity fingerprints and Bayesian ML models to systematically search for inhibitors of glycogen synthase kinase 3β (GSK3β), an enzyme essential to tau phosphorylation in AD, across large collections of bioactive compounds, including FDA-approved medications from databases such as ChEMBL. Ruboxistaurin, which was initially studied for various purposes, became a potent GSK3β inhibitor with an IC50 of 97.3 nM as a result of this work. These findings reinforce the utility of computational methods for identifying new therapeutic applications of existing drugs, thereby streamlining the pathway to effective AD interventions [116].

11.3. AI-powered DR for viral illnesses.

DR has become a more appealing approach in the field of infectious illnesses due to the emergence of drug-resistant organisms, weak market incentives, and declining returns on investment in new drug research. Over 107 million molecules were virtually screened using DL models trained on data from 2,335 compounds with their activity against Escherichia coli compounds. This resulted in the discovery of halicin, a compound initially studied for the treatment of diabetes, as a powerful antibacterial agent [117]. Halicin showed broad-spectrum action, including effectiveness against *Acinetobacter baumannii* in mouse models and low minimum inhibitory doses. Similar to this, abaucin was found to be a narrow-spectrum antibacterial candidate that targeted A. baumannii using an AI-driven screening of about 7,500 compounds. This drug likewise successfully reduced infection in mouse models [118].

To tackle antibiotic resistance, there is growing interest in developing combination therapies using authorized medications in addition to single-agent therapy. Chemogenomics data have been incorporated into ML frameworks to forecast whether antibiotic combinations

would interact antagonistically or synergistically to stop the growth of *E. coli*. To find synergistic medication pairings of repurposed medicines against Mycobacterium tuberculosis, transcriptomic data analysis has been utilized [119]. Further advancements have taken into account temporal and sequence-dependent factors that influence the effects of drug combinations. In a recent study, a transparent ML approach was used to assess the synergistic activity of all FDA-approved drugs with existing antibiotics against *E. coli*. This study identified fasudil, a cerebrovascular medication, as a possible antibiotic synergizer and revealed mechanisms of synergy [120].

These developments demonstrate the increasing complexity and potential of computer approaches for the optimization of combination therapy design. During the COVID-19 pandemic, a similar trend in DR surfaced. Using knowledge-graph-based methods, it was discovered that baricitinib, first developed to treat rheumatoid arthritis, could potentially treat COVID-19 by blocking JAK1, JAK2, adaptor-associated kinase 1 (AAK1), and cyclin G-associated kinase [121]. Cloperastine and clemastine, two σ1 and σ2 receptor modulators, were found to exhibit antiviral activity against SARS-CoV-2 in another investigation that employed cheminformatics and protein interaction studies. Ritonavir and rifampicin were identified as possible repurposed medicines for COVID-19 using ML frameworks, using drug-target and protein-protein interaction data [122].

Additionally, amodiaquine, zuclopenthixol, and nebivolol were identified as effective in vitro agents against SARS-CoV-2 in Vero E6 cells via virtual screening, using hydroxychloroquine as a template and comparing structural similarities with nearly 4,000 licensed medications. When taken as a whole, these initiatives highlight the importance of computational and ML approaches in accelerating DR and the development of combination therapies, offering viable alternatives for treating new diseases and drug-resistant infections [123].

11.4. AI-powered DR in cardiology and its applications.

The efficacy of antidiabetic medications in reducing Major Adverse Cardiovascular Events (MACE) and cardiovascular mortality has gained popularity, highlighting growing interest in using metabolic medicines for cardiovascular benefit [124]. The growing understanding of inflammation as a key driver of cardiovascular disease (CVD), beyond metabolic control, has spurred research into repurposing anti-inflammatory drugs as cardioprotective agents. For example, individuals with a history of myocardial infarction (MI) and elevated C-reactive protein levels were evaluated for canakinumab, a monoclonal antibody targeting interleukin-1β, originally developed to treat autoinflammatory diseases. After 48 months of treatment, improvements in cardiovascular outcomes and reductions in inflammatory biomarkers showed the potential of an anti-inflammatory approach.

Colchicine, a medication commonly used to treat gout attacks, had similar results. Colchicine medication significantly decreased cardiovascular events in people with chronic coronary disease and decreased the risk of recurrent ischemic events when given soon after MI. When taken as a whole, these trials highlight the potential of repurposed anti-inflammatory drugs to treat the inflammatory causes of CVD. Despite its success in other areas, such as neurology and oncology, the application of AI approaches in cardiovascular DR is still in its infancy. AI-driven frameworks could effectively identify new drug-disease associations, predict therapeutic responses, and optimize dosage regimens by combining ML algorithms with extensive clinical, genomic, and proteomic data. These features promise to speed up the

drug development process and cut expenses and time. Using AI-enhanced bioinformatics for DR may accelerate the conversion of preclinical discoveries into safe, efficient cardiovascular treatments as research continues to clarify the complex interactions between metabolic and inflammatory pathways in CVD [125].

12. Conclusion

AI in drug discovery has the potential to drastically accelerate the growth of the pharmaceutical industry by rapidly advancing novel therapeutic approaches. By analyzing massive data and applying algorithms to make better judgments, AI technology can significantly reduce costs and increase the success rate of medication candidates. However, to reap these advantages, the sector needs to address important issues such as data quality, the comprehensibility of applied AI models, and legal and ethical compliance. Increased optimism for the application of AI in drug research, as well as reliable, enhanced AI architectures with features that provide clear explanations to improve comprehension of their outcomes, are examples of future developments in AI for drug discovery. Pharmaceutical corporations, academics, and regulatory bodies will need to create new laws and regulations to develop a set of best practices standards to apply AI ethics and efficiency in drug discovery. Additionally, new safeguards in the distribution of big data resources and public-private partnerships may make data heterogeneous, thereby improving model creation and assessment. To deliver more customized treatments, the future of AI in drug discovery will also bring greater convergence of proteomics, genomics, and real-world evidence analytics, alongside other AI techniques. As AI develops, its application in drug repurposing and the creation of novel medications will become more sophisticated. It has the potential to significantly alter the direction of medicine and produce treatments that can close gaps and improve the quality of life for patients everywhere. Thus, the key conclusion is that, for AI to demonstrate its potential in medical search in the near future, a pragmatic approach that supports innovation, safety, and ethical standards is necessary.

Author Contributions

Conceptualization, K.V.R. and L.P.N.; methodology, K.V.R. and A.S.; investigation, K.V.R. and A.S.; resources, L.P.N.; writing—original draft preparation, K.V.R. and A.S.; writing—review and editing, L.P.N.; visualization, K.V.R. and A.S.; supervision, L.P.N.; project administration, L.P.N. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

References

1. Gan, J.-h.; Liu, J.-x.; Liu, Y.; Chen, S.-w.; Dai, W.-t.; Xiao, Z.-X.; Cao, Y. DrugRep: an automatic virtual screening server for drug repurposing. *Acta Pharmacol. Sin.* **2023**, *44*, 888-896, https://doi.org/10.1038/s41401-022-00996-2.
2. Langarizadeh, M.A.; Salary, A.; Tavakoli, M.R.; Nejad, B.G.; Fadaei, S.; Jahani, Z.; Forootanfar, H. An overview of the history, current strategies, and potential future treatment approaches in erectile dysfunction: a comprehensive review. *Sex. Med. Rev.* **2023**, *11*, 253-267, https://doi.org/10.1093/sxmrev/qead014.
3. Wang, H.; Fu, T.; Du, Y.; Gao, W.; Huang, K.; Liu, Z.; Chandak, P.; Liu, S.; Van Katwyk, P.; Deac, A. Scientific discovery in the age of artificial intelligence. *Nature* **2023**, *620*, 47-60, https://doi.org/10.1038/s41586-023-06221-2.
4. Rathore, A.S.; Nikita, S.; Thakur, G.; Mishra, S. Artificial intelligence and machine learning applications in biopharmaceutical manufacturing. *Trends Biotechnol.* **2023**, *41*, 497–510, https://doi.org/10.1016/j.tibtech.2022.08.007.
5. Jeong, J.; Choi, J. Artificial intelligence-based toxicity prediction of environmental chemicals: Future directions for chemical management applications. *Environ. Sci. Technol.* **2022**, *56*, 7532–7543, https://doi.org/10.1021/acs.est.1c07413.
6. Wang, W.; Tan, J.; Wu, J.; Huang, S.; Huang, Y.; Xie, F.; Sun, X. Use of real world data to improve drug coverage decisions in China. *bmj* **2023**, *381*, e068911, https://doi.org/10.1136/bmj-2021-068911.
7. You, Y.; Lai, X.; Pan, Y.; Zheng, H.; Vera, J.; Liu, S.; Deng, S.; Zhang, L. Artificial intelligence in cancer target identification and drug discovery. *Signal Transduct. Target. Ther.* **2022**, *7*, 156, https://doi.org/10.1038/s41392-022-00994-0.
8. Liu, Z.; Chen, X.; Carter, W.; Moruf, A.; Komatsu, T.E.; Pahwa, S.; Chan-Tack, K.; Snyder, K.; Petrick, N.; Cha, K.; Lal-Nag, M.; Hatim, Q.; Thakkar, S.; Lin, Y.; Huang, R.; Wang, D.; Patterson, T.A.; Tong, W. 1.10 - AI-powered drug repurposing for developing COVID-19 treatments. In Comprehensive Precision Medicine (First Edition), Ramos, K.S., Ed.; Elsevier: Oxford, **2024**; pp. 144-154, https://doi.org/10.1016/B978-0-12-824010-6.00005-8.
9. Niazi, S.K. Artificial intelligence in small-molecule drug discovery: A critical review of methods, applications, and real-world outcomes. *Pharmaceuticals* **2025**, *18*, 1271, https://doi.org/10.3390/ph18091271.
10. Patrono, C.; Rocca, B. Aspirin at 120: Retiring, recombining, or repurposing? *Res. Pract. Thromb. Haemost.* **2021**, *5*, e12516, https://doi.org/10.1002/rth2.12516.
11. Wan, Z.; Sun, X.; Li, Y.; Chu, T.; Hao, X.; Cao, Y.; Zhang, P. Applications of artificial intelligence in drug repurposing. *Adv. Sci.* **2025**, *12*, 2411325, https://doi.org/10.1002/advs.202411325.
12. Singh, A. Artificial intelligence for drug repurposing against infectious diseases. *Artif. Intell. Chem.* **2024**, *2*, 100071, https://doi.org/10.1016/j.aichem.2024.100071.
13. Chang, Y.; Hawkins, B.A.; Du, J.J.; Groundwater, P.W.; Hibbs, D.E.; Lai, F. A guide to in silico drug design. *Pharmaceutics* **2023**, *15*, 49, https://doi.org/10.3390/pharmaceutics15010049.
14. Spreafico, R.; Soriaga, L.B.; Grosse, J.; Virgin, H.W.; Telenti, A. Advances in genomics for drug development. *Genes* **2020**, *11*, 942, https://doi.org/10.3390/genes11080942.
15. Nori, L.P.; Priya, A.S.; Raju, K.V. The Drug Reboot: Finding New Life in Old Formulations. *Biointerface Res. Appl. Chem.* **2025**, *15*, 5, https://doi.org/10.33263/briac151.005.

16. Ye, H.; Wei, J.; Tang, K.; Feuers, R.; Hong, H. Drug repositioning through network pharmacology. *Curr. Top. Med. Chem.* **2016**, *16*, 3646–3656, https://doi.org/10.2174/1568026616666160530181328.
17. Zhang, J.; Lin, Z.; Zhang, Y.; Gu, H.; Li, W. Bioinformatics-based drug repositioning and prediction of the main active ingredients and potential mechanisms of action for the efficacy of Dan-Lou tablet. *Sci. Rep.* **2024**, *14*, 23297, https://doi.org/10.1038/s41598-024-74243-5.
18. Rapicavoli, Rosaria V.; Alaimo, S.; Ferro, A.; Pulvirenti, A. Computational Methods for Drug Repurposing. In Computational Methods for Precision Oncology, Laganà, A., Ed.; Springer International Publishing: Cham, **2022**; pp. 119-141, https://doi.org/10.1007/978-3-030-91836-1_7.
19. Liu, R.; Wei, L.; Zhang, P. A deep learning framework for drug repurposing via emulating clinical trials on real-world patient data. *Nat. Mach. Intell.* **2021**, *3*, 68–75, https://doi.org/10.1038/s42256-020-00276-w.
20. Urbina, F.; Puhl, A.C.; Ekins, S. Recent advances in drug repurposing using machine learning. *Curr. Opin. Chem. Biol.* **2021**, *65*, 74–84, https://doi.org/10.1016/j.cbpa.2021.06.001.
21. Jarada, T.N.; Rokne, J.G.; Alhajj, R. A review of computational drug repositioning: Strategies, approaches, opportunities, challenges, and directions. *J. Cheminform.* **2020**, *12*, 46, https://doi.org/10.1186/s13321-020-00450-7.
22. Saranraj, K.; Kiran, P.U. Drug repurposing: Clinical practices and regulatory pathways. *Perspect. Clin. Res.* **2025**, *16*, 61–68, https://doi.org/10.4103/picr.picr_70_24.
23. Selvaraj, N.; Swaroop, A.K.; Nidamanuri, B.S.S.; Kumar, R.R.; Natarajan, J.; Selvaraj, J. Network-based drug repurposing: A critical review. *Curr. Drug Res. Rev.* **2022**, *14*, 116–131, https://doi.org/10.2174/2589977514666220214120403.
24. Issa, N.T.; Stathias, V.; Schürer, S.; Dakshanamurthy, S. Machine and deep learning approaches for cancer drug repurposing. *Semin. Cancer Biol.* **2021**, *68*, 132–142, https://doi.org/10.1016/j.semcancer.2019.12.011.
25. Priya, S.; Tripathi, G.; Singh, D.B.; Jain, P.; Kumar, A. Machine learning approaches and their applications in drug discovery and design. *Chem. Biol. Drug Des.* **2022**, *100*, 136–153, https://doi.org/10.1111/cbdd.14057.
26. Han, R.; Yoon, H.; Kim, G.; Lee, H.; Lee, Y. Revolutionizing medicinal chemistry: The application of artificial intelligence (AI) in early drug discovery. *Pharmaceuticals* **2023**, *16*, 1259, https://doi.org/10.3390/ph16091259.
27. Hu, J.; Allen, B.K.; Stathias, V.; Ayad, N.G.; Schürer, S.C. Kinome-wide virtual screening by multi-task deep learning. *Int. J. Mol. Sci.* **2024**, *25*, 2538, https://doi.org/10.3390/ijms25052538.
28. Yao, K.; Wang, X.; Li, W.; Zhu, H.; Jiang, Y.; Li, Y.; Tian, T.; Yang, Z.; Liu, Q.; Liu, Q. Semi-supervised heterogeneous graph contrastive learning for drug–target interaction prediction. *Comput. Biol. Med.* **2023**, *163*, 107199, https://doi.org/10.1016/j.compbiomed.2023.107199.
29. Pereira, T.O.; Abbasi, M.; Arrais, J.P. Enhancing reinforcement learning for de novo molecular design applying self-attention mechanisms. *Brief. Bioinform.* **2023**, *24*, bbad368, https://doi.org/10.1093/bib/bbad368.
30. Mouchlis, V.D.; Afantitis, A.; Serra, A.; Fratello, M.; Papadiamantis, A.G.; Aidinis, V.; Lynch, I.; Greco, D.; Melagraki, G. Advances in de novo drug design: from conventional to machine learning methods. *Int. J. Mol. Sci.* **2021**, *22*, 1676, https://doi.org/10.3390/ijms22041676.
31. Hajihosseinlou, M.; Maghsoudi, A.; Ghezelbash, R. A novel scheme for mapping of MVT-type Pb–Zn prospectivity: LightGBM, a highly efficient gradient boosting decision tree machine learning algorithm. *Nat. Resour. Res.* **2023**, *32*, 2417–2438, https://doi.org/10.1007/s11053-023-10249-6.
32. Cai, L.; Chu, J.; Xu, J.; Meng, Y.; Lu, C.; Tang, X.; Wang, G.; Tian, G.; Yang, J. Machine learning for drug repositioning: Recent advances and challenges. *Curr. Res. Chem. Biol.* **2023**, *3*, 100042, https://doi.org/10.1016/j.crchbi.2023.100042.
33. Zhao, K.; So, H.-C. Drug repositioning for schizophrenia and depression/anxiety disorders: A machine learning approach leveraging expression data. *IEEE J. Biomed. Health Inform.* **2019**, *23*, 1304–1315, https://doi.org/10.1109/jbhi.2018.2856535.
34. Nascimento, A.C.A.; Prudêncio, R.B.C.; Costa, I.G. A multiple kernel learning algorithm for drug-target interaction prediction. *BMC Bioinform.* **2016**, *17*, 46, https://doi.org/10.1186/s12859-016-0890-3.
35. Peng, L.; Zhu, W.; Liao, B.; Duan, Y.; Chen, M.; Chen, Y.; Yang, J. Screening drug-target interactions with positive-unlabeled learning. *Sci. Rep.* **2017**, *7*, 8087, https://doi.org/10.1038/s41598-017-08079-7.

36. Elisei-Iliescu, C.; Dogariu, L.-M.; Paleologu, C.; Benesty, J.; Enescu, A.-A.; Ciochină, S. A recursive least-squares algorithm for the identification of trilinear forms. *Algorithms* **2020**, *13*, 135, https://doi.org/10.3390/a13060135.
37. Jia, J.; Liu, Z.; Xiao, X.; Liu, B.; Chou, K.-C. iPPI-Esml: An ensemble classifier for identifying the interactions of proteins by incorporating their physicochemical properties and wavelet transforms into PseAAC. *J. Theor. Biol.* **2015**, *377*, 47–56, https://doi.org/10.1016/j.jtbi.2015.04.011.
38. Yu, B.; Chen, C.; Zhou, H.; Liu, B.; Ma, Q. GTB-PPI: Predict protein-protein interactions based on L1-regularized logistic regression and gradient tree boosting. *Genomics Proteomics Bioinform.* **2020**, *18*, 582–592, https://doi.org/10.1016/j.gpb.2021.01.001.
39. Olayan, R.S.; Ashoor, H.; Bajic, V.B. DDR: Efficient computational method to predict drug-target interactions using graph mining and machine learning approaches. *Bioinformatics* **2018**, *34*, 1164–1173, https://doi.org/10.1093/bioinformatics/btx731.
40. Lan, W.; Wang, J.; Li, M.; Liu, J.; Li, Y.; Wu, F.-X.; Pan, Y. Predicting drug–target interaction using positive-unlabeled learning. *Neurocomputing* **2016**, *206*, 50-57, https://doi.org/10.1016/j.neucom.2016.03.080.
41. Shi, H.; Liu, S.; Chen, J.; Li, X.; Ma, Q.; Yu, B. Predicting drug-target interactions using Lasso with random forest based on evolutionary information and chemical structure. *Genomics* **2019**, *111*, 1839–1852, https://doi.org/10.1016/j.ygeno.2018.12.007.
42. Mousavian, Z.; Khakabimamaghani, S.; Kavousi, K.; Masoudi-Nejad, A. Drug-target interaction prediction from PSSM based evolutionary information. *J. Pharmacol. Toxicol. Methods* **2016**, *78*, 42–51. https://doi.org/10.1016/j.vascn.2015.11.002.
43. Xuan, P.; Sun, C.; Zhang, T.; Ye, Y.; Shen, T.; Dong, Y. Gradient boosting decision tree-based method for predicting interactions between target genes and drugs. *Front. Genet.* **2019**, *10*, 459, https://doi.org/10.3389/fgene.2019.00459.
44. Liu, H.; Sun, J.; Guan, J.; Zheng, J.; Zhou, S. Improving compound-protein interaction prediction by building up highly credible negative samples. *Bioinformatics* **2015**, *31*, i221–i229, https://doi.org/10.1093/bioinformatics/btv256.
45. Wang, C.-C.; Chen, X. A unified framework for the prediction of small molecule-MicroRNA association based on cross-layer dependency inference on multilayered networks. *J. Chem. Inf. Model.* **2019**, *59*, 5281–5293, https://doi.org/10.1021/acs.jcim.9b00667.
46. An, Q.; Yu, L. A heterogeneous network embedding framework for predicting similarity-based drug-target interactions. *Brief. Bioinform.* **2021**, *22*, bbab275, https://doi.org/10.1093/bib/bbab275.
47. Wang, W.; Wang, Y.; Zhang, Y.; Liu, D.; Zhang, H.; Wang, X. PPDTS: Predicting potential drug-target interactions based on network similarity. *IET Syst. Biol.* **2022**, *16*, 18–27, https://doi.org/10.1049/syb2.12037.
48. Cheng, F.; Desai, R.J.; Handy, D.E.; Wang, R.; Schneeweiss, S.; Barabási, A.-L.; Loscalzo, J. Network-based approach to prediction and population-based validation of in silico drug repurposing. *Nat. Commun.* **2018**, *9*, 2691, https://doi.org/10.1038/s41467-018-05116-5.
49. Zhou, Y.; Hou, Y.; Shen, J.; Huang, Y.; Martin, W.; Cheng, F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov.* **2020**, *6*, 14, https://doi.org/10.1038/s41421-020-0153-3.
50. Sibilio, P.; Bini, S.; Fiscon, G.; Sponziello, M.; Conte, F.; Pecce, V.; Durante, C.; Paci, P.; Falcone, R.; Norata, G.D. In silico drug repurposing in COVID-19: A network-based analysis. *Biomed. Pharmacother.* **2021**, *142*, 111954, https://doi.org/10.1016/j.biopha.2021.111954.
51. Zhou, T.; Kuscsik, Z.; Liu, J.-G.; Medo, M.; Wakeling, J.R.; Zhang, Y.-C. Solving the apparent diversity-accuracy dilemma of recommender systems. *Proc. Natl. Acad. Sci. U. S. A.* **2010**, *107*, 4511–4515, https://doi.org/10.1073/pnas.1000488107.
52. Chen, H.; Zhang, H.; Zhang, Z.; Cao, Y.; Tang, W. Network-based inference methods for drug repositioning. *Comput. Math. Methods Med.* **2015**, *2015*, 130620, https://doi.org/10.1155/2015/130620.
53. Wang, M.; Tang, C.; Chen, J. Drug-target interaction prediction via dual Laplacian graph regularized matrix completion. *Biomed Res. Int.* **2018**, *2018*, 1425608, https://doi.org/10.1155/2018/1425608.
54. Pei, F.; Shi, Q.; Zhang, H.; Bahar, I. Predicting protein-protein interactions using symmetric logistic matrix factorization. *J. Chem. Inf. Model.* **2021**, *61*, 1670–1682, https://doi.org/10.1021/acs.jcim.1c00173.

55. Yan, Y.; Yang, M.; Zhao, H.; Duan, G.; Peng, X.; Wang, J. Drug repositioning based on multi-view learning with matrix completion. *Brief. Bioinform.* **2022**, *23*, bbac054, https://doi.org/10.1093/bib/bbac054.
56. Xia, L.-Y.; Yang, Z.-Y.; Zhang, H.; Liang, Y. Improved prediction of drug-target interactions using self-paced learning with collaborative matrix factorization. *J. Chem. Inf. Model.* **2019**, *59*, 3340–3351, https://doi.org/10.1021/acs.jcim.9b00408.
57. Ban, T.; Ohue, M.; Akiyama, Y. NRLMFβ: Beta-distribution-rescored neighborhood regularized logistic matrix factorization for improving the performance of drug-target interaction prediction. *Biochem. Biophys. Rep.* **2019**, *18*, 100615, https://doi.org/10.1016/j.bbrep.2019.01.008.
58. Gao, L.-G.; Yang, M.-Y.; Wang, J.-X. Collaborative matrix factorization with soft regularization for drug-target interaction prediction. *J. Comput. Sci. Technol.* **2021**, *36*, 310–322, https://doi.org/10.1007/s11390-021-0844-8.
59. Wang, X.; Yan, R. DDAPRED: A computational method for predicting drug repositioning using regularized logistic matrix factorization. *J. Mol. Model.* **2020**, *26*, 60, https://doi.org/10.1007/s00894-020-4315-x.
60. Cui, Z.; Gao, Y.-L.; Liu, J.-X.; Dai, L.-Y.; Yuan, S.-S. L2,1-GRMF: An improved graph regularized matrix factorization method to predict drug-target interactions. *BMC Bioinform.* **2019**, *20*, 287, https://doi.org/10.1186/s12859-019-2768-7.
61. Yang, M.; Luo, H.; Li, Y.; Wu, F.-X.; Wang, J. Overlap matrix completion for predicting drug-associated indications. *PLoS Comput. Biol.* **2019**, *15*, e1007541, https://doi.org/10.1371/journal.pcbi.1007541.
62. Wang, A.; Wang, M. Drug-target interaction prediction via dual Laplacian graph regularized logistic matrix factorization. *Biomed Res. Int.* **2021**, *2021*, 5599263, https://doi.org/10.1155/2021/5599263.
63. Yang, M.; Luo, H.; Li, Y.; Wang, J. Drug repositioning based on bounded nuclear norm regularization. *Bioinformatics* **2019**, *35*, i455–i463, https://doi.org/10.1093/bioinformatics/btz331.
64. Huang, L.; Li, X.; Guo, P.; Yao, Y.; Liao, B.; Zhang, W.; Wang, F.; Yang, J.; Zhao, Y.; Sun, H. Matrix completion with side information and its applications in predicting the antigenicity of influenza viruses. *Bioinformatics* **2017**, *33*, 3195-3201, https://doi.org/10.1093/bioinformatics/btx390.
65. Tang, X.; Cai, L.; Meng, Y.; Xu, J.; Lu, C.; Yang, J. Indicator regularized non-negative matrix factorization method-based drug repurposing for COVID-19. *Front. Immunol.* **2020**, *11*, 603615, https://doi.org/10.3389/fimmu.2020.603615.
66. Liu, J.; Peng, D.; Li, J.; Dai, Z.; Zou, X.; Li, Z. Identification of potential Parkinson's disease drugs based on multi-source data fusion and convolutional neural network. *Molecules* **2022**, *27*, 4780, https://doi.org/10.3390/molecules27154780.
67. Liu, H.; Zhang, W.; Song, Y.; Deng, L.; Zhou, S. HNet-DNN: Inferring new drug-disease associations with deep neural network based on heterogeneous network features. *J. Chem. Inf. Model.* **2020**, *60*, 2367–2376, https://doi.org/10.1021/acs.jcim.9b01008.
68. Karimi, M.; Wu, D.; Wang, Z.; Shen, Y. DeepAffinity: Interpretable deep learning of compound-protein affinity through unified recurrent and convolutional neural networks. *Bioinformatics* **2019**, *35*, 3329–3338, https://doi.org/10.1093/bioinformatics/btz111.
69. Torng, W.; Altman, R.B. Graph convolutional neural networks for predicting drug-target interactions. *J. Chem. Inf. Model.* **2019**, *59*, 4131–4149, https://doi.org/10.1021/acs.jcim.9b00628.
70. Chen, C.; Shi, H.; Jiang, Z.; Salhi, A.; Chen, R.; Cui, X.; Yu, B. DNN-DTIs: Improved drug-target interactions prediction using XGBoost feature selection and deep neural network. *Comput. Biol. Med.* **2021**, *136*, 104676, https://doi.org/10.1016/j.compbiomed.2021.104676.
71. Cao, H.; Zhang, L.; Jin, B.; Cheng, S.; Wei, X.; Che, C. Enriching limited information on rare diseases from heterogeneous networks for drug repositioning. *BMC Med. Inform. Decis. Mak.* **2021**, *21*, 304, https://doi.org/10.1186/s12911-021-01664-x.
72. Yu, Z.; Huang, F.; Zhao, X.; Xiao, W.; Zhang, W. Predicting drug-disease associations through layer attention graph convolutional network. *Brief. Bioinform.* **2021**, *22*, bbaa243, https://doi.org/10.1093/bib/bbaa243.
73. Jiang, H.-J.; You, Z.-H.; Huang, Y.-A. Predicting drug-disease associations via sigmoid kernel-based convolutional neural networks. *J. Transl. Med.* **2019**, *17*, 382, https://doi.org/10.1186/s12967-019-2127-5.
74. Cai, L.; Lu, C.; Xu, J.; Meng, Y.; Wang, P.; Fu, X.; Zeng, X.; Su, Y. Drug repositioning based on the heterogeneous information fusion graph convolutional network. *Brief. Bioinform.* **2021**, *22*, bbab319, https://doi.org/10.1093/bib/bbab319.

75. Shim, J.; Hong, Z.-Y.; Sohn, I.; Hwang, C. Prediction of drug-target binding affinity using similarity-based convolutional neural network. *Sci. Rep.* **2021**, *11*, 4416, https://doi.org/10.1038/s41598-021-83679-y.
76. Eslami Manoochehri, H.; Nourani, M. Drug-target interaction prediction using semi-bipartite graph model and deep learning. *BMC Bioinform.* **2020**, *21*, 248, https://doi.org/10.1186/s12859-020-3518-6.
77. Xie, L.; He, S.; Song, X.; Bo, X.; Zhang, Z. Deep learning-based transcriptome data classification for drug-target interaction prediction. *BMC Genomics* **2018**, *19*, 667, https://doi.org/10.1186/s12864-018-5031-0.
78. Korkmaz, S. Deep learning-based imbalanced data classification for drug discovery. *J. Chem. Inf. Model.* **2020**, *60*, 4180–4190, https://doi.org/10.1021/acs.jcim.9b01162.
79. Masoudi-Sobhanzadeh, Y.; Omidi, Y.; Amanlou, M.; Masoudi-Nejad, A. Trader as a new optimization algorithm predicts drug-target interactions efficiently. *Sci. Rep.* **2019**, *9*, 9348, https://doi.org/10.1038/s41598-019-45814-8.
80. Somolinos, F.J.; León, C.; Guerrero-Aspizua, S. Drug repurposing using biological networks. *Processes* **2021**, *9*, 1057, https://doi.org/10.3390/pr9061057.
81. Qiu, Y.; Cheng, F. Artificial intelligence for drug discovery and development in Alzheimer's disease. *Curr. Opin. Struct. Biol.* **2024**, *85*, 102776, https://doi.org/10.1016/j.sbi.2024.102776.
82. Xu, J.; Mao, C.; Hou, Y.; Luo, Y.; Binder, J.L.; Zhou, Y.; Bekris, L.M.; Shin, J.; Hu, M.; Wang, F. Interpretable deep learning translation of GWAS and multi-omics findings to identify pathobiology and drug repurposing in Alzheimer's disease. *Cell Rep.* **2022**, *41*, https://doi.org/10.1016/j.celrep.2022.111717.
83. Herráiz-Gil, S.; Nygren-Jiménez, E.; Acosta-Alonso, D.N.; León, C.; Guerrero-Aspizua, S. Artificial intelligence-based methods for drug repurposing and development in cancer. *Appl. Sci.* **2025**, *15*, 2798, https://doi.org/10.3390/app15052798.
84. Hua, Y.; Dai, X.; Xu, Y.; Xing, G.; Liu, H.; Lu, T.; Chen, Y.; Zhang, Y. Drug repositioning: Progress and challenges in drug discovery for various diseases. *Eur. J. Med. Chem.* **2022**, *234*, 114239, https://doi.org/10.1016/j.ejmech.2022.114239.
85. Naga, D.; Muster, W.; Musvasva, E.; Ecker, G.F. Off-targetP ML: An open source machine learning framework for off-target panel safety assessment of small molecules. *J. Cheminform.* **2022**, *14*, 27, https://doi.org/10.1186/s13321-022-00603-w.
86. Rao, M.; McDuffie, E.; Sachs, C. Artificial intelligence/machine learning-driven small molecule repurposing via off-target prediction and transcriptomics. *Toxics* **2023**, *11*, 875, https://doi.org/10.3390/toxics11100875.
87. Cortial, L.; Montero, V.; Tourlet, S.; Del Bano, J.; Blin, O. Artificial intelligence in drug repurposing for rare diseases: A mini-review. *Front. Med.* **2024**, *11*, 1404338, https://doi.org/10.3389/fmed.2024.1404338.
88. Jumper, J.; Evans, R.; Pritzel, A.; Green, T.; Figurnov, M.; Ronneberger, O.; Tunyasuvunakool, K.; Bates, R.; Žídek, A.; Potapenko, A. Highly accurate protein structure prediction with AlphaFold. *Nature* **2021**, *596*, 583-589, https://doi.org/10.1038/s41586-021-03819-2.
89. Yang, F.; Zhang, Q.; Ji, X.; Zhang, Y.; Li, W.; Peng, S.; Xue, F. Machine learning applications in drug repurposing. *Interdiscip. Sci.: Comput. Life Sci.* **2022**, *14*, 15-21, https://doi.org/10.1007/s12539-021-00487-8.
90. Gangwal, A.; Ansari, A.; Ahmad, I.; Azad, A.K.; Kumarasamy, V.; Subramaniyan, V.; Wong, L.S. Generative artificial intelligence in drug discovery: basic framework, recent advances, challenges, and opportunities. *Front. Pharmacol.* **2024**, *15*, 1331062, https://doi.org/10.3389/fphar.2024.1331062.
91. Tripathi, S.; Augustin, A.I.; Dunlop, A.; Sukumaran, R.; Dheer, S.; Zavalny, A.; Haslam, O.; Austin, T.; Donchez, J.; Tripathi, P.K. Recent advances and application of generative adversarial networks in drug discovery, development, and targeting. *Artif. Intell. Life Sci.* **2022**, *2*, 100045, https://doi.org/10.1016/j.ailsci.2022.100045.
92. Howard, F.M.; Hieromnimon, H.M.; Ramesh, S.; Dolezal, J.; Kochanny, S.; Zhang, Q.; Feiger, B.; Peterson, J.; Fan, C.; Perou, C.M. Generative adversarial networks accurately reconstruct pan-cancer histology from pathologic, genomic, and radiographic latent features. *Sci. Adv.* **2024**, *10*, eadq0856, https://doi.org/10.1126/sciadv.adq0856.
93. Dhudum, R.; Ganeshpurkar, A.; Pawar, A. Revolutionizing drug discovery: A comprehensive review of AI applications. *Drugs Drug Candidates* **2024**, *3*, 148–171, https://doi.org/10.3390/ddc3010009.
94. Ekins, S.; Lane, T.R. Applications of artificial intelligence in drug discovery for neurological diseases. *Neurotherapeutics* **2025**, *22*, e00624, https://doi.org/10.1016/j.neurot.2025.e00624.
95. Stebbing, J.; Krishnan, V.; de Bono, S.; Ottaviani, S.; Casalini, G.; Richardson, P.J.; Monteil, V.; Lauschke, V.M.; Mirazimi, A.; Youhanna, S. Mechanism of baricitinib supports artificial intelligence-predicted

testing in COVID-19 patients. *EMBO Mol. Med.* **2020**, *12*, EMMM202012697, https://doi.org/10.15252/emmm.202012697.

96. Gao, Z.; Winhusen, T.J.; Gorenflo, M.; Ghitza, U.E.; Davis, P.B.; Kaelber, D.C.; Xu, R. Repurposing ketamine to treat cocaine use disorder: integration of artificial intelligence-based prediction, expert evaluation, clinical corroboration and mechanism of action analyses. *Addiction* **2023**, *118*, 1307-1319, https://doi.org/10.1111/add.16168.
97. Kim, J.-B.; Kim, S.-J.; So, M.; Kim, D.-K.; Noh, H.R.; Kim, B.J.; Choi, Y.R.; Kim, D.; Koo, H.; Kim, T. Artificial intelligence-driven drug repositioning uncovers efavirenz as a modulator of α-synuclein propagation: implications in Parkinson's disease. *Biomed. Pharmacother.* **2024**, *174*, 116442, https://doi.org/10.1016/j.biopha.2024.116442.
98. Gao, Z.; Gorenflo, M.; Kaelber, D.C.; Monnier, V.M.; Xu, R. Drug repurposing for reducing the risk of cataract extraction in patients with diabetes mellitus: Integration of artificial intelligence-based drug prediction and clinical corroboration. *Front. Pharmacol.* **2023**, *14*, 1181711, https://doi.org/10.3389/fphar.2023.1181711.
99. Carvalho, D.M.; Richardson, P.J.; Olaciregui, N.; Stankunaite, R.; Lavarino, C.; Molinari, V.; Corley, E.A.; Smith, D.P.; Ruddle, R.; Donovan, A. Repurposing vandetanib plus everolimus for the treatment of ACVR1-mutant diffuse intrinsic pontine glioma. *Cancer Discov.* **2022**, *12*, 416-431, https://doi.org/10.1158/2159-8290.CD-20-1201.
100. Agastheeswaramoorthy, K.; Sevilimedu, A. Drug REpurposing using AI/ML tools - for Rare Diseases (DREAM-RD): A case study with Fragile X Syndrome (FXS). *bioRxiv* **2020**. https://doi.org/10.1101/2020.09.25.311142.
101. Blanco-Gonzalez, A.; Cabezon, A.; Seco-Gonzalez, A.; Conde-Torres, D.; Antelo-Riveiro, P.; Pineiro, A.; Garcia-Fandino, R. The role of AI in drug discovery: challenges, opportunities, and strategies. *Pharmaceuticals* **2023**, *16*, 891, https://doi.org/10.3390/ph16060891.
102. Baric-Parker, J.; Anderson, E.E. Patient data-sharing for AI: Ethical challenges, Catholic solutions. *Linacre Q.* **2020**, *87*, 471–481, https://doi.org/10.1177/0024363920922690.
103. Huang, D.Z.; Baber, J.C.; Bahmanyar, S.S. The challenges of generalizability in artificial intelligence for ADME/Tox endpoint and activity prediction. *Expert Opin. Drug Discov.* **2021**, *16*, 1045–1056, https://doi.org/10.1080/17460441.2021.1901685.
104. Saini, J.P.S.; Thakur, A.; Yadav, D. AI driven innovations in pharmaceuticals: Optimizing drug discovery and industry operations. *RSC Pharm.* **2025**, *2*, 437-454, https://doi.org/10.1039/d4pm00323c.
105. Seghier, M.L. ChatGPT: Not all languages are equal. *Nature* **2023**, *615*, 216, https://doi.org/10.1038/d41586-023-00680-3.
106. An, J.; Ding, W.; Lin, C. ChatGPT: Tackle the growing carbon footprint of generative AI. *Nature* **2023**, *615*, 586, https://doi.org/10.1038/d41586-023-00843-2.
107. Stokel-Walker, C.; Van Noorden, R. What ChatGPT and generative AI mean for science. *Nature* **2023**, *614*, 214–216, https://doi.org/10.1038/d41586-023-00340-6.
108. Ayers, J.W.; Poliak, A.; Dredze, M.; Leas, E.C.; Zhu, Z.; Kelley, J.B.; Faix, D.J.; Goodman, A.M.; Longhurst, C.A.; Hogarth, M. Comparing physician and artificial intelligence chatbot responses to patient questions posted to a public social media forum. *JAMA Intern. Med.* **2023**, *183*, 589-596, https://doi.org/10.1001/jamainternmed.2023.1838.
109. Sabry, Z.; Arora, H.S.; Chandrasekaran, S.; Wang, Z. AI-driven drug discovery and repurposing using multi-omics for myocardial infarction and heart failure. *Explor. Med.* **2025**, *6*. https://doi.org/10.37349/emed.2025.1001340.
110. Ravikumar, B.; Timonen, S.; Alam, Z.; Parri, E.; Wennerberg, K.; Aittokallio, T. Chemogenomic analysis of the druggable kinome and its application to repositioning and lead identification studies. *Cell Chem. Biol.* **2019**, *26*, 1608–1622.e6, https://doi.org/10.1016/j.chembiol.2019.08.007.
111. Yang, M.; Tao, B.; Chen, C.; Jia, W.; Sun, S.; Zhang, T.; Wang, X. Machine learning models based on molecular fingerprints and an extreme gradient boosting method lead to the discovery of JAK2 inhibitors. *J. Chem. Inf. Model.* **2019**, *59*, 5002-5012, https://doi.org/10.1021/acs.jcim.9b00798.
112. Li, B.; Dai, C.; Wang, L.; Deng, H.; Li, Y.; Guan, Z.; Ni, H. A novel drug repurposing approach for non-small cell lung cancer using deep learning. *Plos One* **2020**, *15*, e0233112, https://doi.org/10.1371/journal.pone.0233112.

113. Ramesh, P.; Karuppasamy, R.; Veerappapillai, S. Machine learning driven drug repurposing strategy for identification of potential RET inhibitors against non-small cell lung cancer. *Med. Oncol.* **2022**, *40*, 56, https://doi.org/10.1007/s12032-022-01924-4.
114. Rodriguez, S.; Hug, C.; Todorov, P.; Moret, N.; Boswell, S.A.; Evans, K.; Zhou, G.; Johnson, N.T.; Hyman, B.T.; Sorger, P.K. Machine learning identifies candidates for drug repurposing in Alzheimer's disease. *Nat. Commun.* **2021**, *12*, 1033, https://doi.org/10.1038/s41467-021-21330-0.
115. Miyazaki, Y.; Ono, N.; Huang, M.; Altaf-Ul-Amin, M.; Kanaya, S. Comprehensive exploration of target-specific ligands using a graph convolution neural network. *Mol. Inform.* **2020**, *39*, e1900095, https://doi.org/10.1002/minf.201900095.
116. Vignaux, P.A.; Minerali, E.; Foil, D.H.; Puhl, A.C.; Ekins, S. Machine learning for discovery of GSK3β inhibitors. *ACS Omega* **2020**, *5*, 26551–26561, https://doi.org/10.1021/acsomega.0c03302.
117. Stokes, J.M.; Yang, K.; Swanson, K.; Jin, W.; Cubillos-Ruiz, A.; Donghia, N.M.; MacNair, C.R.; French, S.; Carfrae, L.A.; Bloom-Ackermann, Z. A deep learning approach to antibiotic discovery. *Cell* **2020**, *180*, 688-702. e613, https://doi.org/10.1016/j.cell.2020.01.021.
118. Liu, G.; Catacutan, D.B.; Rathod, K.; Swanson, K.; Jin, W.; Mohammed, J.C.; Chiappino-Pepe, A.; Syed, S.A.; Fragis, M.; Rachwalski, K. Deep learning-guided discovery of an antibiotic targeting Acinetobacter baumannii. *Nat. Chemi. Biol.* **2023**, *19*, 1342-1350, https://doi.org/10.1038/s41589-023-01349-8.
119. Gao, S.; Xie, J.; Zhao, Y. A multi-source drug combination and omnidirectional feature fusion approach for predicting drug-drug interaction events. *J. Biomed. Inform.* **2025**, *162*, 104772, https://doi.org/10.1016/j.jbi.2025.104772.
120. Reuter, M.M.; Lev, K.L.; Albo, J.; Arora, H.S.; Liu, N.; Tan, S.; Shay, M.R.; Sarkar, D.; Robida, A.; Sherman, D.H. Ultra-high-throughput screening of antimicrobial combination therapies using a two-stage transparent machine learning model. *bioRxiv* **2024**, 2024.2011.2025.625231, https://doi.org/10.1101/2024.11.25.625231.
121. Gordon, D.E.; Jang, G.M.; Bouhaddou, M.; Xu, J.; Obernier, K.; White, K.M.; O'Meara, M.J.; Rezelj, V.V.; Guo, J.Z.; Swaney, D.L. A SARS-CoV-2 protein interaction map reveals targets for drug repurposing. *Nature* **2020**, *583*, 459-468, https://doi.org/10.1038/s41586-020-2286-9.
122. Aghdam, R.; Habibi, M.; Taheri, G. Using informative features in machine learning based method for COVID-19 drug repurposing. *J. Cheminform.* **2021**, *13*, 70, https://doi.org/10.1186/s13321-021-00553-9.
123. Bocci, G.; Bradfute, S.B.; Ye, C.; Garcia, M.J.; Parvathareddy, J.; Reichard, W.; Surendranathan, S.; Bansal, S.; Bologa, C.G.; Perkins, D.J. Virtual and in vitro antiviral screening revive therapeutic drugs for COVID-19. *ACS Pharmacol. Transl. Sci.* **2020**, *3*, 1278-1292, https://doi.org/10.1021/acsptsci.0c00131.
124. Zhu, S.; Bai, Q.; Li, L.; Xu, T. Drug repositioning in drug discovery of T2DM and repositioning potential of antidiabetic agents. *Comput. Struct. Biotechnol. J.* **2022**, *20*, 2839–2847, https://doi.org/10.1016/j.csbj.2022.05.057.
125. Nidorf, S.M.; Fiolet, A.T.; Mosterd, A.; Eikelboom, J.W.; Schut, A.; Opstal, T.S.; The, S.H.; Xu, X.-F.; Ireland, M.A.; Lenderink, T. Colchicine in patients with chronic coronary disease. *N. Engl. J. Med.* **2020**, *383*, 1838-1847, https://doi.org/10.1056/NEJMoa2021372.

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