# AI-Driven Drug Repurposing: Developing Therapeutics Through Data and Discovery

**Adhithya Balasubramanian, Jaianand Jagadeesan, Meenaloshini Gopalakrishnan, Saranya Punniyakotti***

Department of Pharmacy Practice, SIMATS College of Pharmacy, Saveetha Institute of Medical and Technical Sciences, Thandalam, Chennai, 602105.

**Corresponding Author - Dr Saranya Punniyakotti**
**Email:** Saro08bpharm@gmail.com
**Doi:** 10.5281/zenodo.15569469
Received: 25 April 2025
Accepted: 13 May 2025

**Abstract**

This paper explores the transformative role of artificial intelligence (AI) in drug repurposing, a strategy for identifying new therapeutic uses for existing drugs. By leveraging pre-existing knowledge of drugs, AI enables rapid evaluation of drug efficacy, significantly shortening the drug development timeline compared to traditional methods. AI approaches, including machine learning and deep learning, enhance the identification of suitable biological targets, predict drug-disease associations, and facilitate the analysis of complex biological data and literature. Case studies demonstrate the effectiveness of AI in rapidly repurposing drugs, such as remdesivir during the COVID-19 pandemic. However, challenges remain, including data bias, model interpretability, and ethical considerations. The future of AI-driven drug repurposing holds promise for personalized medicine and collaborative innovations, potentially revolutionizing global healthcare outcomes.

**Keywords:** Drug Repurposing, Artificial Intelligence, Machine Learning, Deep Learning, Drug Discovery

## 1. Introduction

### 1.1. What is Drug Repurposing?

Drug repurposing is the process of finding new therapeutic applications for drugs that are already on the market, providing a quicker, less expensive alternative to conventional drug development. The approach takes advantage of existing knowledge about a drug's pharmacokinetics, pharmacodynamics, safety, and manufacturing processes, dramatically reducing development times. The most important advantages are a faster time to market, since the safety and dosing profiles are already established, and repurposed drugs tend to avoid early-phase clinical trials. This was illustrated in the COVID-19 pandemic with remdesivir, originally created to treat Ebola, being repurposed for SARS-CoV-2[1].

Repurposing techniques comprise experimental screening (in vitro/in vivo assays), computational approaches (AI and machine learning for target identification), and clinical observation (surprising therapeutic effects in patients). Successful examples are thalidomide (for multiple myeloma), metformin (anti-cancer studies), and sildenafil (Viagra for erectile dysfunction, Revatio for pulmonary hypertension). Drug repurposing hastens medical advances while minimizing the costs and risks of conventional drug discovery[2].

### 1.2. Limitations of Traditional Drug Discovery

Traditional drug delivery systems, such as oral tablets, injectables, and topical creams, are exposed to various disadvantages that limit their efficacy. These systems deliver drugs to the whole body, which results in side effects as the drugs lack specificity, as observed with anticancer drugs killing healthy cells. Oral medication is also plagued by pre-systemic metabolism in the gut, leading to decreased bioavailability and the need for increased dosages.

Conventional drugs tend to exhibit rapid drug clearance and metabolism, causing fluctuating drug levels and resistance to infection and cancer[3].

Barriers such as the blood-brain barrier prevent successful delivery for central nervous system disorders. Traditional methods also fail to provide high concentrations of drugs at disease locations while avoiding systemic toxicity, and repeated dosing can limit patient compliance. To overcome these problems, progress in drug delivery, including nanoparticle-based delivery systems, targeted delivery, and response to stimuli systems, is enhancing drug precision, efficacy, and safety, leading to more effective therapies with reduced side effects[4].

### 1.3. Emergence of Artificial Intelligence in Drug Research

Over the past 10 years, AI has transformed drug research and development, resolving the issues of lengthy timelines, high expenses, and uncertain outcomes. Conventional drug discovery takes 10-15 years and costs $2-3 billion, and it has high failure rates, particularly in clinical trials[5]. AI speeds up different phases of the process, enhancing efficiency and accuracy. AI accelerates the screening and testing of large chemical libraries for machine learning-based predictions of molecule and bio target interaction in hours rather than months, facilitating faster lead compound discovery[6]. AI applies biological information (genomics, proteomics, transcriptomics) to discover and validate disease-associated targets by deciphering subtle patterns in biology, accelerating target discovery and validation. AI determines new indications for available drugs by pairing disease mechanisms with biological pathways, saving much time and expense[7].

## 2. Foundations of AI in Drug Repurposing

### 2.1. Overview of Artificial Intelligence and Machine Learning

AI and its subfield, Machine Learning (ML), have revolutionized drug discovery and repurposing. AI encompasses techniques that simulate human intelligence, including learning, reasoning, and problem-solving, while ML applies statistical methods to enable systems to learn from data. In drug repurposing, supervised learning (e.g., support vector machines, random forests), unsupervised learning (e.g., k-means clustering), and deep learning (e.g., convolutional and recurrent neural networks) are widely used[8]. The success of ML models depends on the quality and diversity of biomedical data, helping algorithms identify patterns between chemical structures, gene expressions, protein targets, and phenotypic responses. Deep learning models like DeepDTnet and Graph Neural Networks have shown high accuracy in predicting drug-disease interactions, while reinforcement learning is emerging as a method to maximize drug combinations and discover new therapeutic regimens[9].

### 2.2. Data Types Used in Repurposing (Genomics, Clinical, Chemical, etc.)

Drug repurposing exploits varied datasets ranging from molecular to population-level data. The use of such heterogenous data is paramount in the discovery of hidden associations between drugs, targets, and diseases.

*Genomic and Transcriptomic Data*

High-throughput sequencing methods, including RNA-seq and whole-genome sequencing, produce massive genomic profiles that facilitate the detection of disease signatures. Data sources like The Cancer Genome Atlas (TCGA) and Gene Expression Omnibus (GEO) act as archives of disease-specific genomic data. These datasets are employed by AI models to cross-map drug-induced transcriptomic signatures to disease signatures, a strategy popularized by the Connectivity Map[10].

*Clinical Data*

Electronic Health Records (EHRs), real-world evidence (RWE), and adverse event reports yield rich clinical information for repurposing. Natural Language Processing (NLP) software derives useful phenotypic and therapeutic information from unstructured clinical notes. For instance, algorithms on EHRs have revealed hitherto unknown associations between metformin and cancer occurrence[11].

*Chemical and Structural Data*

Chemical structure information and physicochemical characteristics play a crucial role in the prediction of bioactivity. Chemical libraries are available from databases such as PubChem, ChEMBL, and DrugBank, which provide AI-based screening with vast chemical collections. Molecular docking, QSAR modeling, and cheminformatics tools are commonly coupled with AI to make predictions on drug-target binding probability[12].

*Pharmacological and Proteomic Data*

Proteomic profiles such as protein expression and interaction data (e.g., STRING and BioGRID) aid in the mapping of drug action mechanism. Coupling with pathway databases such as KEGG or Reactome improves the prediction of polypharmacological effects[13].

### 2.3. Big Data, Bioinformatics, and Databases' Role

The emergence of big data in biomedicine has revolutionized AI-based drug repurposing. It requires sophisticated bioinformatics infrastructures to process, curate, and analyze multi-dimensional data.

*Big Data Analytics:*

Big data in drug repurposing include huge, high-velocity, and high-variety datasets of omics technologies, clinical trials, social media platforms, and wearable devices. Cloud computing environments and parallel processing infrastructure such as Apache Spark and Hadoop allow such data to be handled effectively[14].

*Bioinformatics Tools:*

Bioinformatics and AI complement each other in providing computational pipelines for feature selection, normalization, and data preprocessing. Non-experts can leverage tools like AutoML platforms, GSEA for enrichment analysis, and Cytoscape for network analysis to integrate AI into drug discovery pipelines[15].

*Databases and Repositories:*

Large public and commercial databases are the foundation for model training and validation of AI. Some of the most crucial databases include[16]:

i. DrugBank: Integrates target, indication, and mechanism with drug information.

ii. LINCS (Library of Integrated Network-Based Cellular Signatures): Offers perturbation-response signatures useful in repurposing candidate identification.

iii. ClinicalTrials.gov: Offers trial-based evidence to assess drug efficacy and safety profiles.

iv. SIDER and FAERS: Offer side-effect data relevant for adverse event prediction in repurposing studies.

## 3. Computational Approaches for Drug Repurposing

### 3.1 Machine Learning Models (Random Forest, SVM, k-NN)

Machine learning techniques as illustrated in table 1 such as Random Forest (RF), Support Vector Machines (SVM), and k-Nearest Neighbors (k-NN) have proven to be of significant value in drug repurposing. Several research studies have shown them to be effective in the prediction of drug efficacy as well as the identification of potential drugs for repurposing[17]. For instance, RF was used for antiplasmodial activity prediction using data from the ChEMBL database. The model had employed molecules screened against *Plasmodium falciparum* and achieved impressive performance metrics, such as 91.7% accuracy and 97.3% AUROC, reflecting the potency of RF to classify antimalarial drugs[18]. Moreover, SVM and k-NN models have been applied to systems for predicting cancer driver mutations and drug repurposing. For example, a machine learning ensemble approach incorporating RF, logistic regression, and SVM was employed to order pathogenic and conservation scoring algorithms to separate pathogenic driver mutations from harmless mutations in cancer[19]. In addition, a precision drug repurposing platform based on machine learning was employed to prioritize Alzheimer's Disease drug candidates through the utilization of Polygenic Risk Scores (PRS) and biomedical knowledge graphs[20]. In COVID-19 drug repurposing, unsupervised machine learning systems like graph-based autoencoders have been utilized to identify drugs for repurposing by clustering pharmacological, chemical, and biological drug features[21].

### 3.2 Deep Learning Models (CNN, RNN, GNN)

Deep learning algorithms, particularly Convolutional Neural Networks (CNNs), Recurrent Neural Networks (RNNs), and Graph Neural Networks (GNNs), are increasingly being used in drug repurposing due to their ability to process complex, high-dimensional data[22]. ChemBERTa, a deep learning algorithm, has been employed to predict the biological activity of molecules against Leishmania and Coronaviruses with improved prediction accuracy compared to traditional machine learning algorithms[23]. Deep learning methods like CNNs, RNNs, and GNNs are best suited for handling image-based, sequential, and graph-structured data, respectively, to support rapid screening of vast chemical spaces. Moreover, IDentif.AI-x applies deep learning to identify multi-drug combination alternatives for COVID-19 and integrates experimental validation workflows to facilitate drug interactions[24]. Further, use of message-passing transformer networks (MPTN) on the basis of knowledge graphs has been revealed to be beneficial for drug repurposing by capturing semantic information from biomedical entities to predict novel therapeutic targets[25]. Another deep learning-based platform, DTA Atlas, predicts drug-target interactions across the human proteome and facilitates drug repurposing and toxicity studies by providing a vast database of drug-target binding affinities[26].

### 3.3 Natural Language Processing for Literature Mining

Natural Language Processing (NLP) plays a critical role in drug repurposing because it digs out enormous scientific literature to offer valuable information. CidalsDB is one such tool that uses literature mining to compile molecules with reported anti-pathogen activity, offering automated search that aggregates bioassay data for convenient retrieval. This approach is very useful in looking for known compounds for repurposing, for example, against Leishmania and Coronaviruses[27]. Similarly, the DrugRepo tool integrates chemical structures, drug-target interactions (DTIs), and disease-gene associations with the assistance of NLP, enabling drug candidate discovery for different diseases[28]. The same application is applied in PharmaRedefine, wherein sequence and structure alignment is integrated with protein pocket similarity analysis, enabling repurposed drug identification against pathogenic bacteria. They point to the growing importance of NLP in extracting actionable intelligence from unstructured information to accelerate drug discovery[29].

### 3.4 Knowledge Graphs and Network-Based Methods

Network-based and knowledge graph-based strategies have recently become the drug repurposing focus since they organize and visualize relationships between drugs-disease-target-biological pathway. Implicit drug-disease target relationships can be discerned by such strategies, which is invaluable for repurposing purposes. One such paradigmatic example includes Kinase drUgs mAchine Learning framework (KUALA), utilizing network-based methods to identify kinase-active ligands, suggesting repurposing possibilities in cancer and cardiovascular disease[30]. In addition, knowledge graphs have been applied in frameworks like PharmaRedefine, which makes predictions of FDA-approved drugs mapping to bacterial targets based on ligand-binding pocket similarities in order to improve drug repurposing for bacterial infections. The integration of patient-specific data with biomedical knowledge graphs has also led to the building of precision drug repurposing (PDR) frameworks that enable individualized repurposing predictions based on genetic profiles. MPTN models, built on top of knowledge graphs, learn entity and relation embeddings to predict new therapeutic routes for drug repurposing, and the significance of network-based methods in drug repurposing[31].

### 3.5 Structure-Based and Ligand-Based Virtual Screening

Structure-based and ligand-based virtual screening are key components in drug repurposing as they allow computationally predicting drug-target interactions. Structure-based techniques such as molecular docking and 3D structural examination have been applied to identify new inhibitors of viral replication enzymes such as SARS-CoV-2 Mpro and TMPRSS2[32]. The DrugSolver CavitomiX pipeline, for example, uses cavity point clouds to identify inhibitors against such enzymes and has, for example, flufenamic acid and fusidic acid as potent inhibitors[33]. These strategies are useful where traditional sequence- and structure-based strategies are plagued by low target protein sequence identity and repurposed drugs. Ligand-based virtual screening, that estimates chemical similarity between candidate drugs and target receptors, has found antimalarial inhibitors to be successful. Tools like the DTA Atlas utilize structure-based prediction to annotate drug-target interaction in the human proteome and provides valuable tools to drug repurpose and predict binding affinity. By screening large sets of chemicals and measuring the interactions between ligands and receptors, such screening procedures accelerate drug discovery, making it easier to find effective repurposed drugs[34].

**Table 1** Computational tools and methods used in drug repurposing across various techniques.

| **Computational Tool/Method** | **Type** | **Application in Drug Repurposing** |
|---|---|---|
| **Random Forest (RF)** | Machine Learning | Predicting drug efficacy, such as antiplasmodial activity for *Plasmodium falciparum*. |

| | | |
|---|---|---|
| **Support Vector Machine (SVM)** | Machine Learning | Ranking pathogenic mutations in cancer and identifying potential drug candidates for Alzheimer's Disease through Polygenic Risk Scores (PRS). |
| **k-Nearest Neighbors (k-NN)** | Machine Learning | Drug repurposing frameworks prioritizing Alzheimer's Disease candidates, leveraging multi-feature clustering. |
| **ChemBERTa** | Deep Learning | Predicting biological activity of molecules against *Leishmania* and Coronaviruses. |
| **Convolutional Neural Networks (CNN)** | Deep Learning | Identifying multi-drug combinations for COVID-19 repurposing. |
| **Recurrent Neural Networks (RNN)** | Deep Learning | Handling sequential data for drug-target interactions and drug repurposing. |
| **Graph Neural Networks (GNN)** | Deep Learning | Handling graph-structured data for predicting drug-target interactions and therapeutic pathways. |
| **Message-Passing Transformer Networks (MPTN)** | Deep Learning + Knowledge Graphs | Capturing semantic information from biomedical entities to predict new therapeutic pathways in drug repurposing. |
| **DTA Atlas** | Deep Learning | Predicting drug-target interactions and binding strengths across the human proteome, aiding drug repurposing and toxicity studies. |
| **CidalsDB** | Natural Language Processing (NLP) | Literature mining to identify molecules with known anti-pathogen effects, facilitating drug repurposing for infectious diseases. |
| **DrugRepo** | Natural Language Processing (NLP) | Integrating chemical structures, drug-target interactions (DTIs), and disease-gene associations to identify drug candidates for various diseases. |
| **PharmaRedefine** | Knowledge Graphs & Network-Based Methods | Mapping FDA-approved drugs to bacterial targets based on ligand-binding pocket similarities for repurposing bacterial infection drugs. |
| **KUALA** | Knowledge Graphs & Network-Based Methods | Identifying kinase-active ligands for cancer and cardiovascular disease repurposing by integrating molecular descriptors. |
| **DrugSolver CavitomiX** | Structure-Based Virtual Screening | Molecular docking to identify inhibitors for SARS-CoV-2 Mpro and TMPRSS2, facilitating structure-based drug repurposing. |
| **Ligand-Based Virtual Screening** | Ligand-Based Virtual Screening | Identifying potential inhibitors for diseases like malaria by analyzing chemical similarities between drug candidates and target receptors. |
| **PharmaRedefine** | Knowledge Graphs & Network-Based Methods | Uses ligand-binding pocket similarity analysis to identify repurposed drugs for bacterial infections. |

### 4. Case Studies and Success Stories

*Alzheimer's Disease*

In Alzheimer's studies, AI models that incorporate genome-wide association studies (GWAS), multi-omics, and protein-protein interaction networks have pinpointed 103 Alzheimer's risk genes (ARGs)[35]. Bayesian network and Gibbs sampling methodologies facilitated the repurposing of drugs such as pioglitazone, febuxostat, and atenolol through prioritization. Of interest, pioglitazone has been shown to display downregulation of neuroinflammatory markers such as GSK3β and CDK5, highlighting genotype-directed therapeutic repositioning[36].

*Parkinson's Disease*

A non-coding genome and brain-specific QTL-based network revealed 175 PD-related genes. Simvastatin was a repurposing candidate revealed by its gene interaction profile and was confirmed in patient data analysis[37]. Molecular docking and cellular assays-based drug screening disclosed Efavirenz, a drug for HIV, as an inhibitor of α-synuclein aggregation[38]. AI models also assisted in revealing therapies for l-DOPA-induced dyskinesia, pointing towards less typical drugs for the management of motor symptoms[39].

*Glioblastoma*

In glioblastoma (GBM), AI-supported analysis based on the iLINCS database and signature matching pinpointed Clofarabine and Ciclopirox as promising drugs that could reverse oncogenic expression patterns, thereby offering a precision-medicine strategy for malignant brain tumors[40].

*Cancer and Oncology*

Z29077885 was discovered through deep learning to be an STK33 inhibitor. It caused S-phase arrest and suppressed tumor growth in vivo, demonstrating the capability of AI in lead optimization[41]. Pitavastatin, a statin used to reduce cholesterol, was found to be a dual hIDO1 and hTDO2 inhibitor and had anticancer effects in liver cancer cell lines[42]. Fenbendazole, an anthelmintic for veterinary use, was repurposed for leukemia through a transcriptional repositioning approach and induced granulocytic differentiation[43]. The flavonoid eriocitrin was revealed by docking experiments to bind to CDK1 in colorectal cancer, inhibiting cell migration and invasion[44].

*Infectious Diseases*

A deep learning method traced host-virus interactions and predicted compounds such as NADH, Fostamatinib, Cannabidiol, Copper, and Zinc. Docking and dynamics validated antiviral efficacy[45]. An independent research with binding pose prediction highlighted FDA-approved drugs targeting MPXV proteins, exhibiting rapid-track of antiviral leads[46]. A lactoferrin-nitazoxanide nanodrug had excellent in vitro activity against SARS-CoV-2 with an IC50 of 1.34 µM, confirming the synergy of repurposed drugs in new delivery systems. More extensive AI research identified a number of antiviral medications, such as HIV and flu drugs, that speeded up the therapeutic response to the pandemic[47].

*Rare and Chronic Diseases*

Lubiprostone, employed as a treatment of constipation, was repurposed as an antifibrotic for chronic kidney disease. It protected renal architecture and decreased fibrosis markers in preclinical models[48]. AI-driven mapping of imaging biomarkers in intestinal fibrosis created personalized therapeutic and predictive diagnostic cartography.

## 5. Current Limitations and Ethical Considerations

AI models in drug repurposing are limited by biased training datasets, which may lead to skewed predictions, especially for underrepresented groups. Furthermore, many deep learning models operate as "black boxes," offering limited transparency. This lack of explainability can hinder clinical acceptance and regulatory approval, as stakeholders may lack trust in opaque models. XAI aims to enhance model interpretability by providing insights into the predictions, such as identifying key genes or interactions that influence outcomes. While promising, XAI in drug repurposing remains in its early stages, and ensuring scientifically accurate, clinically meaningful explanations is still challenging[49]. Drug repurposing often involves sensitive data, requiring strict privacy adherence (e.g., HIPAA, GDPR). AI models must be fair, avoiding disproportionate benefits or harms to specific groups. Reproducibility remains an issue, as many AI studies lack open-source datasets or clear methodological details, hindering independent validation and clinical trust[50].

## 6. Future Perspectives and Opportunities

AI can make drug repurposing strategies individualized to specific patients by incorporating multi-omics data and clinical histories. Treatment becomes more effective and less likely to cause side effects, particularly in multifaceted diseases such as cancer and neurological disorders, opening the way for personalized, individualized medicine. Quantum computing has the potential to speed molecular simulations and protein-ligand predictions, whereas digital twins virtual models of biological systems can model drug interactions and toxicity in silico. Integrating these technologies with AI will make drug repurposing quicker, more precise, and safer. Federated learning models and cloud-based platforms will make data sharing possible globally, particularly for low-resource neglected diseases. Open-source AI platforms and global health consortia can make drug repurposing innovations accessible to all, making healthcare equitable. Interdisciplinary collaboration will ensure responsible, inclusive technological advancement.

## 8. Conclusion

AI is transforming drug repurposing by speeding up therapeutic discovery using data-driven models, network-based methods, and deep learning architectures. It improves drug-target interaction predictions, reveals biological connections, and facilitates hypothesis generation, with real-world success being experienced during the COVID-19 pandemic. Challenges such as ethical issues, data bias, model interpretability, and reproducibility persist. The future of AI in drug repurposing demands a balance between innovation and clinical validation, with close cooperation between AI experts, clinicians, and regulatory agencies to provide safe, effective treatments. Led by transparency and equity, AI has the potential to democratize drug discovery and revolutionize global healthcare.

## CRediT authorship contribution statement

All authors contributed to the review. **Saranya Punniyakotti:** Conceptualization, supervision, writing – review & editing. **Adhithya Balasubramanian:** Writing – original draft and editing. **Jaianand Jagadeesan:** Data curation. **Meenaloshini Gopalakrishnan:** Literature search, data analysis. All authors read and approved the final manuscript.

## Acknowledgement

We thank our esteemed institution, Saveetha Institute of Medical and Technical Sciences for their support and encouragement.

## Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

## Disclosure

This manuscript has not been published or presented elsewhere in part or in entirety

**Data availability:** Not applicable.

**Code availability:**Not applicable.

## Declarations

**Ethics approval: Not** applicable.

**Consent to participate:** Not applicable.

**Consent for publication:** Not applicable.

**Competing Interests:** The authors have no relevant financial or non-financial interests to disclose.

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