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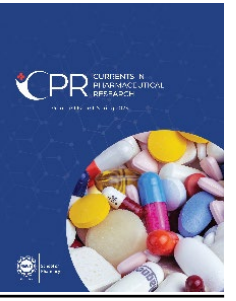

Title:	**Role of Artificial Intelligence in Drug Discovery and Design: From Foundational Principles to Emerging Applications in Antiviral Therapeutics**
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Role of Artificial Intelligence in Drug Discovery and Design: From Foundational Principles to Emerging Applications in Antiviral Therapeutics

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ABSTRACT

Artificial Intelligence (AI) has significantly transformed drug discovery by enhancing efficiency, reducing costs, and accelerating timelines, particularly in research related to antiviral drugs. Traditional drug discovery methods are not able to compete with rapidly occurring viral mutations, since these are often time-consuming and labor-intensive. Hence, they have been replaced with AI techniques, capable of handling massive datasets, predicting molecular interactions, and optimizing drug candidates rapidly. AI can be used to identify novel drug molecules, drug targets, and repurposed drugs. Furthermore, it can also be used to predict chemical properties, as well as pharmacokinetic, pharmacodynamic, and toxicology profiles by analyzing large datasets. In the early stages of drug discovery, AI aids in target identification and validation by analyzing the genomic, proteomic, and chemical data to predict disease-relevant proteins. In virtual screening and hit identification, AI replaces high-throughput screening with rapid *in silico* analysis. Generative chemistry approaches utilize reinforcement learning to design novel, drug-like molecules rapidly. Through off-target profiling using models such as DeepTox, AI reduces adverse effects by forecasting unintended protein interactions and drug-drug interactions, improving safety profiles. Its predictive capabilities at each development stage—from molecular screening to clinical trials—have not only accelerated the pace of antiviral drug discovery but have also reduced overall costs significantly, thus proving essential during global pandemics like COVID-19. AI can be implemented at each step of drug discovery and development, from identifying drug molecules and conducting virtual screening to lead optimization and designing clinical trials, as well as interpreting the data obtained from the trials. Antiviral drugs for viral diseases, such as COVID-19, dengue, influenza, hepatitis,

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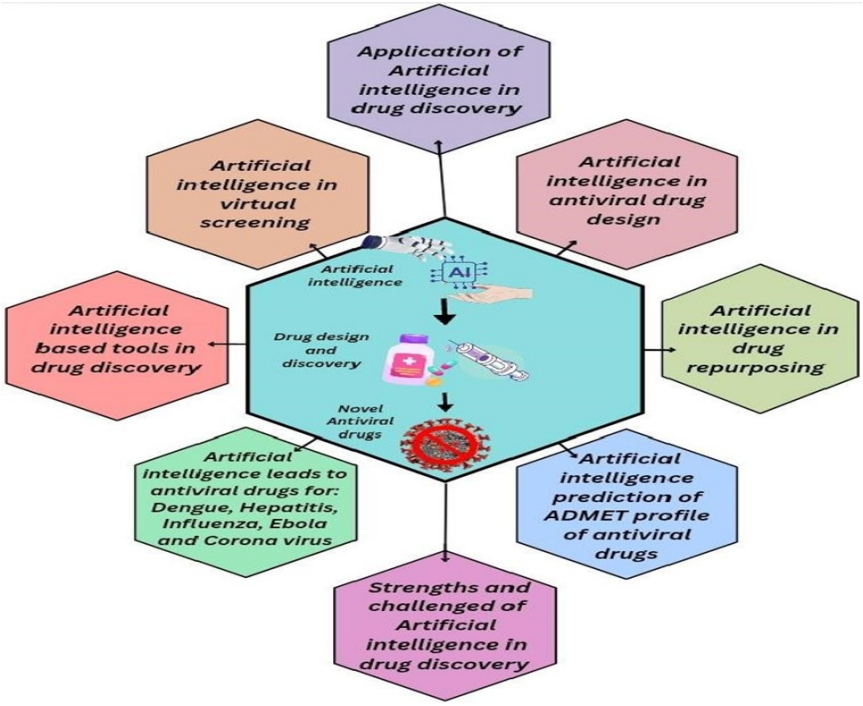
and Ebola, developed using AI are mentioned in this study. It also highlights the significance of AI in healthcare, particularly in novel drug development. There is also a dark side to AI, and concerns are rising about the accuracy and quality, as well as the legal and ethical aspects of fact-driven by datasets.

Keywords: Artificial Intelligence (AI), COVID-19, database, dengue, drug design and discovery, hepatitis, influenza, Machine Learning (ML), Natural Language Processing (NLP), virtual screening

GRAPHICAL ABSTRACT



Highlights

- A comprehensive review of drug design, discovery, and development of antiviral drugs.
- AI-assisted drug development, focused on antiviral drugs.
- AI is integrated into the drug discovery process involving drug design, target identification, virtual screening, drug repurposing, and predicting ADMET profiles.

- Antiviral drug development for specific viral diseases, including COVID-19, dengue, hepatitis, and Ebola.
- This review article uses a PRISMA flow chart as an explanation of the review methodology.

1.INTRODUCTION

The reemergence and spread of viral infections pose noteworthy challenges worldwide, as proven by the repeated flare-up of various viral illnesses, such as COVID-19, Ebola, Zika, and influenza [1]. The constant evolution of viral genomes and the limited availability of broad-spectrum antiviral experts necessitate the urgent development of new and useful techniques [2]. It usually takes over ten years and billions of dollars to bring a medicine to the market through the labor-intensive, time-consuming, and expensive process of traditional antiviral drug discovery. Additionally, the burden on pharmaceutical companies and public health systems has increased due to the high proportion of clinical trial failures brought on by safety or efficacy concerns [3].

Artificial intelligence (AI) is transforming drug discovery in this regard by providing creative, data-driven solutions that drastically save costs and time. From target identification and validation to lead compound screening, optimization, and even preclinical and clinical trial design, the use of AI, which includes a variety of techniques such as machine learning (ML), deep learning (DL), natural language processing (NLP), and reinforcement learning (RL), has shown impressive success [4]. By quickly identifying viable drug candidates against new viruses through the analysis of large biomedical datasets, forecasting drug-virus interactions, and repurposing current medications for novel viral targets, AI plays a significant role in antiviral research. Indeed, it is anticipated that a new era of AI-driven antiviral treatments will be ushered in soon by continuous improvements in AI algorithms, the emergence of better data-sharing platforms, and encouraging regulatory frameworks.

This study aims to demonstrate how AI is changing the strategy to fight viral infections and how its incorporation may result in more effective, accurate, and creative therapeutic options by methodically examining recent research and advancements [5]. In this regard, Table 1 provides an overview of AI techniques [3]. Further, this review aims to explore the current landscape of AI applications in antiviral drug discovery, including the

methodologies, key tools and platforms, success stories, and future perspectives. By systematically analyzing the recent literature and latest developments, it intends to highlight how AI is reshaping the approach to combating viral diseases and how its integration can lead to more efficient, precise, and innovative therapeutic solutions.

1.1.The Global Challenge of Viral Diseases

Global health systems have been continuously challenged by viral infections, resulting in substantial morbidity, mortality, and financial costs. Effective antiviral treatments are desperately needed, as seen by the resurgence of well-known infections and the appearance of new viruses including SARS-CoV-2. Conventional drug discovery procedures, which are expensive, time-consuming, and have poor success rates, are frequently unable to address such public health emergencies. The traditional drug development pipeline, for example, can take more than ten years and cost more than $2 billion, while the success rate from the preclinical stage to market approval is less than 10% [1, 3].

1.2. Emergence of Artificial Intelligence in Drug Discovery

In antiviral drug discovery, Al facilitates in the following ways.

- Target Identification: AI algorithms can analyze genomic and proteomic data to identify potential viral or host targets for therapeutic intervention.
- Lead Compound Discovery: Through virtual screening and generative models, AI can identify novel compounds with potential antiviral activity.
- Drug Repurposing: AI can uncover new therapeutic uses for existing drugs, expediting the availability of treatments during outbreaks.
- Optimization of Drug Properties: AI can predict pharmacokinetic and pharmacodynamic properties, aiding in the refinement of lead compounds.

1.3.AI Techniques in Antiviral Drug Discovery

1.3.1.Machine Learning and Deep Learning. Deep learning, particularly convolutional neural networks (CNNs) and recurrent neural networks (RNNs), has shown promise in modeling complex biological interactions and predicting molecular properties with high accuracy [6].

1.3.2.Natural Language Processing. NLP algorithms make it possible to extract pertinent information from clinical trial data, patents, and a large body of biological literature. NLP can evaluate unstructured text and find possible drug-target interactions, side effects, and therapeutic indications, all of which helps drug developers to make well-informed decisions [3].

1.3.3.Generative Models. Generative models, such as generative adversarial networks (GANs) and variational autoencoders (VAEs), can design novel molecular structures with desired properties. These models learn the underlying distribution of the chemical space and generate compounds that are structurally diverse and potentially bioactive [4, 7].

Table 1. AI Techniques for Drug Design [3, 8, 9]

AI Techniques	Description	Application
Machine learning (ML)	An algorithm that learns from data to make predictions and decisions.	Used to predict antiviral drug discovery, optimize lead compounds, and classify viral targets based on patterns.
Deep learning (DL)	A subset of ML involving neural networks with many layers that can capture complex data.	Enables the prediction of drug-virus interaction, identification of novel inhibitors, and drug repurposing for viral diseases.
Reinforcement learning (RL)	Learns optimal actions through trial and error by receiving feedback from the environment.	Assists in compound optimization by simulating the molecular environment to find the best drug structure.
Natural language processing (NLP)	Enables computers to understand and process human language data.	Extracts useful insight from scientific literature, patents, and clinical trials to identify potential antiviral agents.
Generative adversarial networks (GANS)	Comprises a generator and a discriminator to generate new, realistic data samples.	Used to design novel antiviral molecules by generating molecular structures similar to

AI Techniques	Description	Application
		known and effective antivirals.
Support vector machines (SVM)	Supervise learning algorithms effective for classification and regression tasks.	Classifies viral protein and drug candidates and predicts antiviral bioactivity.
Random forest (RF)	An ensemble learning method which uses multiple decision trees for predictions.	Predicts viral target binding and drug toxicity with a higher accuracy.
Decision trees (DTs)	A flowchart-like structure used for decision-making based on data features.	Identifies structural features of antiviral drugs that influence activity and safety.
Bayesian networks	Probabilistic graphical models representing conditional dependencies.	Estimate the likelihood of drug success and assist in target identification and prioritization.
Convolutional neural networks (CNNs)	Specialized deep networks that analyze visual imagery and molecular graphs.	Applied in analyzing molecular structures and predicting binding affinity with viral targets.
Recurrent neural networks (RNNs)	Neural networks are capable of learning from sequential data.	Model molecular sequences and predict drug response over time in viral infections.
Transfer learning	Using pre-trained models to solve similar problems with limited new data.	Accelerate model development for novel viruses.
Autoencoders	Unsupervised networks for data compression and reconstruction.	Help in denoising chemical data and extracting important features for drug candidates.

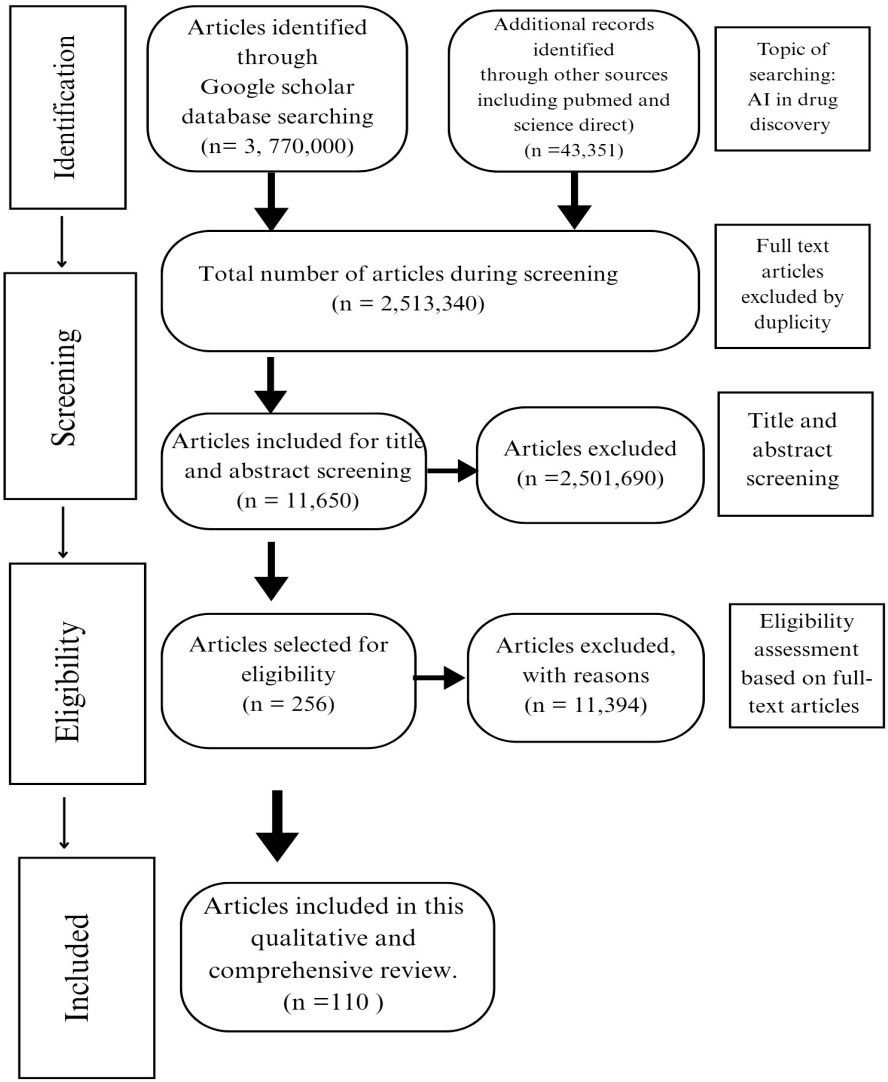


Figure 1. PRISMA Flow Diagram Representing the Article Search, Screening, Eligibility, and Inclusion Criteria

2.ROLE OF AI IN DRUG DESIGN

The use of AI in the field of medicinal chemistry is gaining popularity because of its potential to transform the discovery of drugs. Traditional methods are known to be slow and labor-intensive, such as trial-and-error

and high-throughput screening. AI techniques, such as machine learning (ML), deep learning (DL), and natural language processing (NLP), can speed up and enhance this process by analyzing vast datasets efficiently. This has shown promising results in predicting drug efficacy and toxicity. However, challenges remain, including ethical concerns and the need for further research [10].

2.1. Role of AI in Predicting Drug Efficacy and Safety

A very important use of AI in medicinal chemistry is to predict the efficacy and safety of a potential drug compound. Researchers can use AI to predict new potential drug compounds that are more effective and have fewer side effects in a shorter time, in comparison to the classical methods. It is done by training deep learning (a more advanced type of AI) on large data sets containing information about the biological activities and behaviors of the known compounds. After learning this data set completely, this tool can accurately and precisely predict how the new potential drug compounds would behave. AI also helps to identify the drug compounds that may cause toxicity in the body by training it on the dataset of both toxic and non-toxic compounds [11]. Another pivotal role of AI is to predict drug-drug interaction. The interaction occurs when the patient is on polypharmacy and can lead to harmful effects. AI learns and studies the known interactions and identifies the patterns to predict how the newly made combinations of drugs may interact with each other [12]. Hence, AI helps doctors to create personalized treatments based on a person's genetics and how their physiology responds to medicine. Such treatments are more effective and carry lower risks of adverse effects and side effects [10].

2.2. AI in Identifying Drug-Binding Sites

Currently, AI plays a key role in identifying drug-binding sites, especially in new drug compounds, where the location of these sites remains unknown. Some new AI models have been designed to recognize allosteric sites on proteins with the aim of predicting the ion-binding sites based on the amino acid sequence. For instance, one model that uses a position weight scoring matrix achieved over 80% accuracy in predicting metal ion binding sites (Zn^{2+}, Fe^{2+}, Mg^{2+}, etc).

Some of the tools that enable the 3D prediction of pharmacophore properties [13] are as follows:

- **HS-Pharm** – features in ML algorithms to identify cavity atoms important for ligand binding.
- **Pharm-IF –** uses ML to rank docking poses of small molecules.
- **DeepSite** – uses AI with images to predict how "druggable" protein binding sites are.

There are two more powerful ML-based models for the prediction of binding affinities.

- **TIES** (Thermodynamic Integration with Enhanced Sampling) [14, 15]: This tool uses multiple MD (Molecular Dynamics) simulations to achieve better accuracy and error control. Its advantage is its precision (mean error of 0.7 Kcal/mol), but the disadvantage is that it is computationally expensive.
- **ESMACS** (Enhanced Sampling of Molecular Dynamics with Approximation of Continuum Solvent) [14–16]: This is a faster method that uses ensemble short simulations, but it doesn't yield the results as accurately as TIES. Adaptive ensemble algorithms reduce the computing time of both TIES and ESMACS by 2.5 times, which is a significant improvement.

3D-QSAR models, especially the Comparative Molecular Field Analysis and AutoMEP methods (combined with PLS or RSA), are helpful in predicting binding based on the molecular structure. For instance, when it was tested on the NMDA receptor antagonists, it yielded a prediction accuracy (r-value) of 0.81, along with autoMEP/RSA reaching 0.99. Other advanced methods to predict the binding affinity include free energy perturbation, QM/MM (Quantum Mechanics/Molecular Mechanics), and slow growth and thermodynamic integration.

2.3. Role of AI in Predicting Solubility

Solubility is an important drug property. A study by *Boobier et al.* tracked human predictions of solubility against ML models and found that tools/factors affecting solubility predictions for drug-like molecules are remarkably comparable in their accuracy to MLs [17]. This makes sense as long as developing ML remains time and cost-effective.

COSMO-RSol is a more theory-oriented approach developed by Klamt et al. [18]. It uses density functional theory (DFT) with conductor-like

screening model (COSMO). In contrast to earlier versions (e.g., COSMO-RS), COSMO-RSol can also account for solid-state solubility, integrating the energy of fusion into its calculations. It was trained on 150 neutral drug-like molecules with an RMSD of 0.66 log units, using only three fitting parameters. Subsequently, it was evaluated on 107 heterogeneous neutral pesticides, yielding an RMSD of 0.61 log-units. In most cases, such error can be attributed to the limitations present in the experimental data [11]. In terms of estimating solubility in any solvent or solvent mixture, COSMO-RSol differs in that it uses the same simulation data to calculate associated properties, such as partition coefficients, Henry's constants, and vapor pressures. However, because of its slow pace, the approach is not suited to high-throughput screening. The development of a fast version, namely COSMOfrag**,** addressed this shortcoming [11]. Molecular descriptors are employed to calculate solubility in models such as QSAR, but not their activity. The effect of temperature on solubility was the focus of another QSPR study.

2.4. Role of AI in Predicting the Toxicology of New Drugs

While *in vivo* toxicology testing is still required, *in silico* (computer-based) testing is a cost-efficient, ethical, and timely option. One of the most used measures of toxicity is LD_{50}, the dose that is lethal to half of the test population. Toxicity can be tested by single or repeated exposure at various doses and routes of intake. TOXNET, ToxCast, Tox21, PubChem, DrugBank, ToxBank**,** ECOTOX, and SuperToxic are among the major databases used for *in silico* toxicity studies [19]. One such prominent platform is OpenTox, which is based on transparency and interoperability and enables ML and QSAR models for toxicity prediction, according to the international regulatory standards. A variety of computational models have been created, such as structural alerts, rule-based systems, read-across, dose/time-response models, and pharmacokinetic/dynamic models [11].

The **TIMES** model is a hybrid computational tool that incorporates the theoretical knowledge of toxicity and considers 30 metabolic transformations, such as oxidation, hydroxylation, and glucuronidation. Other ML models (such as k-NN, SVM, and classification trees) are utilized to forecast the toxicity of 221 phenols towards Tetrahymena pyriformis, a protozoan model. For hepatotoxicity (liver toxicity) prediction, various ML models, including logistic regression, SVM, XGBoost, LightGBM, CatBoost, and ensemble classifiers, were tried out on the DILIrank dataset.

2.5. Role of AI in Blood-Brain Barrier Penetration Prediction

A drug's capacity to cross the blood-brain barrier (BBB) can be predicted with 75-97% accuracy using 67-199 molecular descriptors [20]. Yet, predictions of non-penetrating molecules are less accurate (60–80%). To overcome this bias, Zhao et al. applied recursive feature elimination to reduce the descriptors to only 19 significant features including polarizability, hydrogen bonding, surface area, and pKa [20]. Their model registered more than 90% training accuracy and more than 95% accuracy in the test set. Some other ML strategies have also delivered robust outcomes. A decision tree model labeled BBB permeability with 90% accuracy. Garg and Verma constructed a multilayer perceptron (MLP) ANN from seven descriptors—largely in view of their molecular weight and polar surface area—and obtained a correlation coefficient of 0.89 [21]. A Kohonen self-organizing map ANN based solely on five descriptors showed 97.2% accuracy for penetrants and 90.3% for non-penetrants. Another MLP ANN model was also found to be highly accurate with a correlation coefficient of 0.87 [11].

2.6. Role of AI in Predicting Chemical Properties

Machine learning (ML) has greatly improved the accuracy and efficiency of the prediction of chemical properties, including atomic charges, dipole moments, hydration energies, and hydrogen bonding strength. One such example is the Pfizer charge assignment method, which uses non-parametric random forest (RF) regression to predict atomic charges for atoms, such as H, C, N, O, F, S, and Cl, with an accuracy comparable to ab initio methods [22]. In addition, ML also predicts hydrogen bond strength for acceptors and donors using the free energy of interaction calculation with model molecules, such as acetone and 4-fluorophenol. One of the most popular methods of computational drug design is Quantitative Structure-Activity Relationship (QSAR) modeling. QSAR defines the relationship between the molecular structure and the biological activity of a molecule by examining its various properties, such as steric bulkiness, hydrophobicity, electron density, atomic charges, and topological properties. Such descriptors can be computed using quantum theories such as QTAIM (Quantum Theory of Atoms in Molecules), which evaluates the wave function. QSAR models typically employ ML techniques including random forests, linear regression, support vector machines (SVMs), deep neural networks (DNNs), and Bayesian neural

networks. Random forest is the best among them. QSAR approaches range from 1D to 6D, each providing greater dimensionality and data complexity.

- **1D-QSAR-** predicts global properties (e.g., pKa, logP).
- **2D-** and **3D-QSAR** are concerned with structural patterns and spatial contacts.
- **4D-** to **6D-QSAR-** encompass ligand conformations, induced fit, and solvation effects, respectively.

In another work, GB decision trees were applied to predict electrophilicity based on conceptual DFT descriptors and topological indices. The model reported a mean absolute error of 0.72 and an R^2 of 0.98. Likewise, three open-source QSAR models (SVM-kNN, XGBoost, and DNN) were applied to predict pKa values of 7,912 compounds, with RMSE ~1.5 and R^2 ~0.80, which compares favorably with commercial packages, such as ChemAxon and ACD/Labs. Lastly, meta-QSAR, a high-level modeling approach, was investigated by Olier et al. [23]. They examined 2,764 QSAR targets through multivariate random forest regression and identified that meta learning was superior to base-learning QSAR by as much as 13%, citing its potential within drug discovery workflows. Kausar and Falcao also advanced QSAR usability by developing an automated system that produces good models without the need for prior ML experience or parameter tuning, utilizing curated databases.

2.7. Role of AI in Predicting Bioavailability and ADMET Profile

Traditionally, ADMET (absorption, distribution, metabolism, elimination, and toxicity) evaluation of any new drug molecule relies on experimental and animal-based studies [24], which are both time- and resource-consuming and laborious. However, the rapid emergence of different AI tools and techniques, such as machine learning, deep learning, and neural-based models, has helped researchers to predict the ADMET properties in less time and more accurately (Fig. 2) [25, 26]. This has reduced the failure rates of new drugs and minimized the development costs significantly. The lack of efficacy and uncontrolled toxicity are the main causes of 90% of medication failure during clinical development. AI interprets complex biological data and provides information about molecular behavior. Table 2 represents some AI models used in the prediction of ADMET [24, 25].

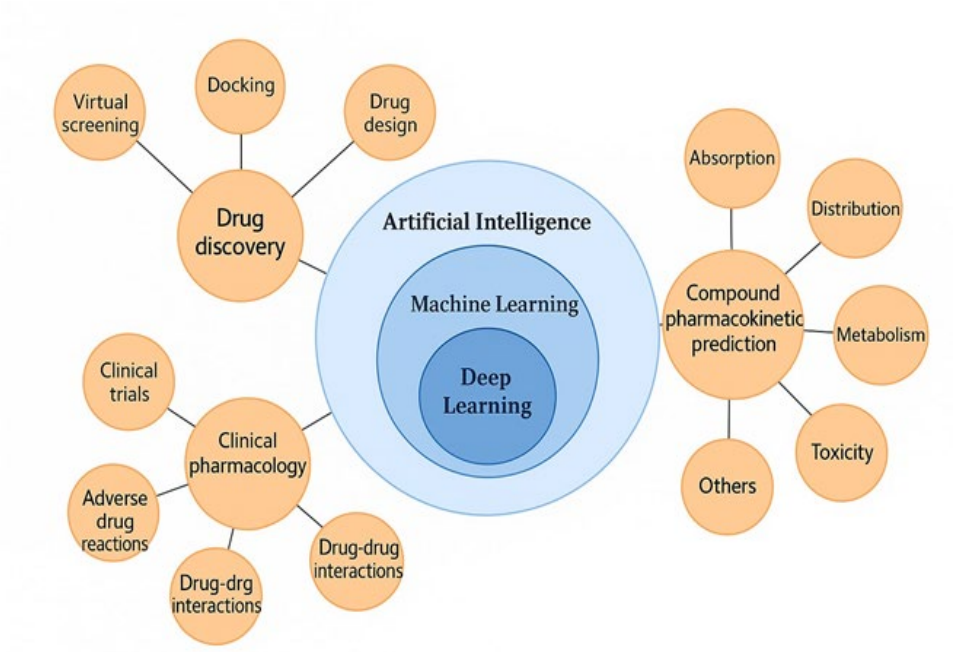


Figure 2. Machine Learning in Drug Discovery

Table 2. AI models used in the prediction of ADMET [24].

Model Type	Purpose
Deep Neural Network (DNNs)	Predict blood-brain barrier permeability, CYP450 inhibition, and toxicity.
Convolutional Neural Networks (CNNs)	Process molecular images to predict clearance and solubility.
Graph Convolutional Networks (GCNs)	Model drug structures as graphs to predict toxicity and metabolism.

2.8.AI-based Drug Distribution Property Predictions

The general structure of the drug distribution property prediction model using AI is shown in Figure 3 [25]. By detecting and eliminating compounds that are expected to have poor ADMET characteristics before clinical testing, these techniques can help to reduce the time and cost of the traditional testing methods. Distribution property prediction tools are shown in Table 3 [24, 25].

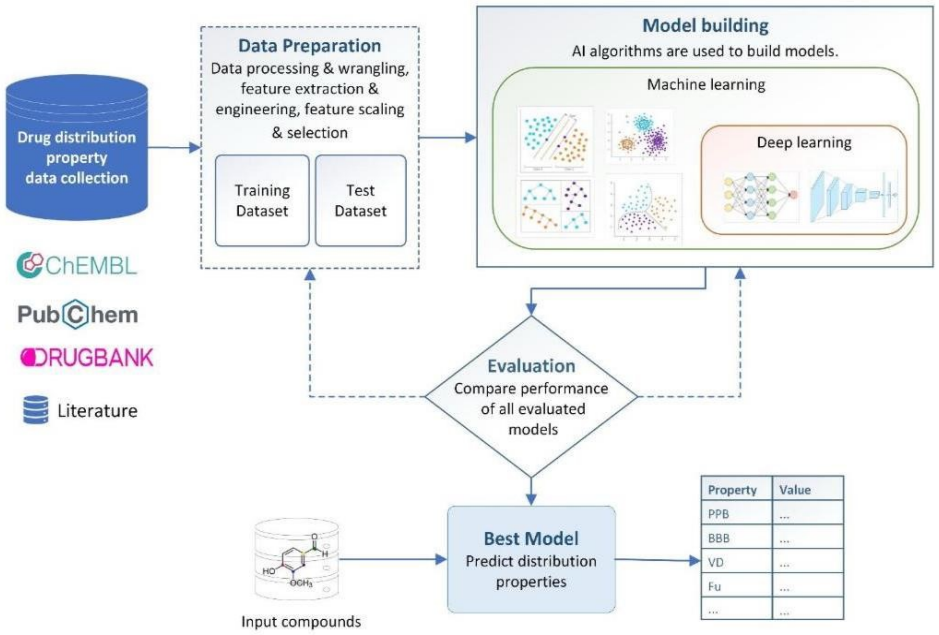


Figure 3. General Structure of A Drug Distribution Property Prediction Model using AI

Table 3. Tools Used for Distribution Property Predictions [24]

Property	Tool
BBB (blood-brain barrier) predictions	ADMETLab 2.0 FP -ADMET AdmetSAR 2.0.
PPB (plasma protein binding) predictions	ADMETLab 2.0 Interpretable -ADMET AdmetSAR 2.0.
Fu (fraction unbonded) predictions	ADMETLab 2.0 FP -ADMET HelixADMET AdmetSAR 2.0.
Vd (volume of distribution) predictions	ADMETLab 2.0 FP -ADMET Interpretable -ADMET AdmetSAR 2.0.

2.9.Drug Metabolism Prediction

In silico, metabolic prediction using AI falls into three major categories:

- The site of metabolism prediction
- Metabolite structures prediction
- Metabolic pharmacokinetics prediction

Table 4 presents the various tools used for metabolism prediction [24].

Table 4. Tools Used to Predict Metabolism [24]

Name	Metabolism Prediction	Method
GLORYx	Metabolite structure	ML (machine learning)
FAME 3	Site of metabolism predictions for CYP	ML
Bio Transformer 3.0	Metabolic transformation	ML
HelixADMET	CYP inhibitors and substrates	GNN (graph neural network)
FP -ADMET	CYP inhibitors and substrates	RF (random forest)

2.10. Drug Excretion Predictions

Different software have been developed to predict ADMET properties, such as FP-ADMET which integrates clearance prediction, including human renal clearance, intrinsic clearance, metabolic intrinsic clearance, and human liver microsomal clearance. AI methods used to predict clearance property from 2019 to 2022 are shown below in Table 5 [24].

Table 5. Tools Used to Predict Clearance [24]

Method	Data Sources	Dataset Size
RF (random forest)	Human renal clearance Intrinsic clearance Metabolic intrinsic clearance Human liver microsomal clearance	636 244 5278 5348
SVM (support vector machine)	AstraZeneca in-house data	73,620

Method	Data Sources	Dataset Size
ANN (artificial neural network)	Medivir in-house data	4794
MT-CNN (multi-task convolutional neural network)	AstraZeneca	139,907

3.AI REVOLUTIONIZES VIRTUAL SCREENING IN DRUG DESIGN

3.1.Accelerated Compound Screening

AI dramatically shortens the early-stage drug discovery timeline. Traditional high-throughput screening (HTS) techniques rely on physical assays of thousands of compounds against target proteins, which is time-consuming, expensive, and limited in scale [27]. A schematic illustration of AI in virtual screening is shown below in Figure 4.

3.1.1.With AI, Here's How It Changes.

- Compound Library Digitization: Billions of chemical structures can be represented using SMILES or molecular graphs [28].
- AI Pre-screening Models: Algorithms trained on known ligand-target pairs predict the likelihood of binding before docking even begins [29].
- Smart Prioritization: Instead of testing all compounds, AI ranks top candidates, reducing screening space by 90-95% [30].

3.1.2.Data Utilized

- Molecular fingerprints (e.g., ECFP4, MACCS keys)
- 3D structure-based features (electrostatic potential, hydrogen bonding)
- Public datasets: ChEMBL, PubChem BioAssay, BindingDB

Kwofie et al. [27] in a recent study, found that AI-driven screening pipelines reduced both cost and time by over 80%, when applied to antiviral compounds.

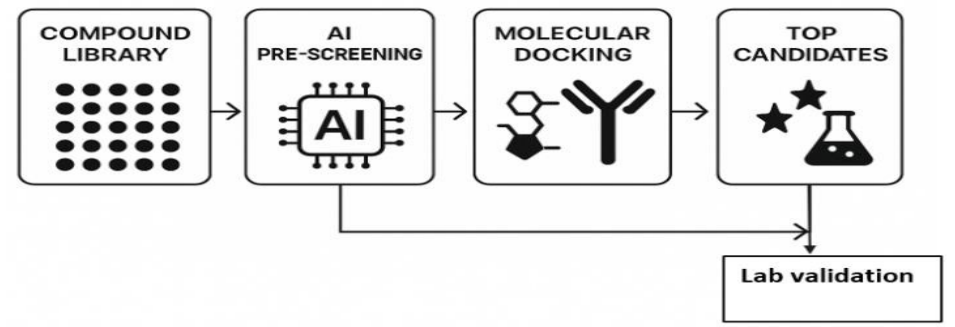


Figure 4. Roles of AI in Virtual Screening

3.2.Enhanced Accuracy with Deep Learning

Deep learning, especially the use of convolutional neural networks (CNNs) and transformer-based architectures, greatly enhances precision in molecular recognition tasks [31]. A comparison between traditional vs AI-assisted virtual screening for new drug development is shown below in Figure 5.

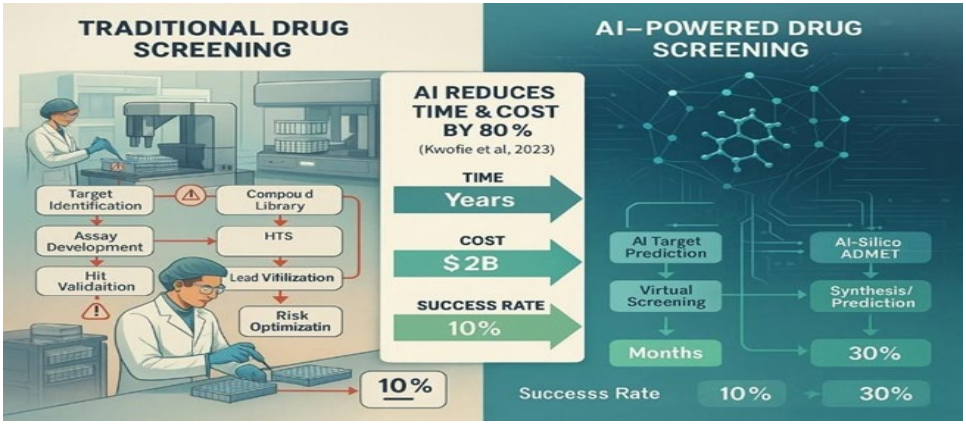


Figure 5. Comparison of Traditional v/s AI-assisted Virtual Screening

3.2.1.AI Tools and Approaches.

- DeepDDS: Integrates drug features with target biology to predict synergy [30].
- Mol2Vec & ChemBERTa: Embed molecular structures in numerical space to find hidden relationships [28].
- Knowledge Graphs: Link diseases, genes, and drugs in a network to discover new uses

- [31].

3.2.2.Notable AI-led Discoveries

- Quinine: Repurposed for dengue through AI modeling of viral protease inhibition.
- Tilorone: Predicted by deep learning to act as a broad-spectrum antiviral, especially for Ebola.

4.ARTIFICIAL INTELLIGENCE IN DRUG REPURPOSING

AI has emerged as a transformative tool in accelerating drug repurposing efforts by analyzing vast biomedical datasets, predicting drug-target interactions, and identifying novel indications for approved drugs [32].

4.1.AI Approaches in Drug Repurposing

4.1.1.Machine Learning for Drug-Target Prediction. Supervised and unsupervised ML models have been used widely to predict drug-target interactions. For instance, deep neural networks (DNNs) and random forest (RF) algorithms successfully identify potential repurposing candidates by analyzing chemical structures and genomic data [33]. A comparison of traditional v/s AI-assisted drug repurposing is shown below in Fig. 6 [34].

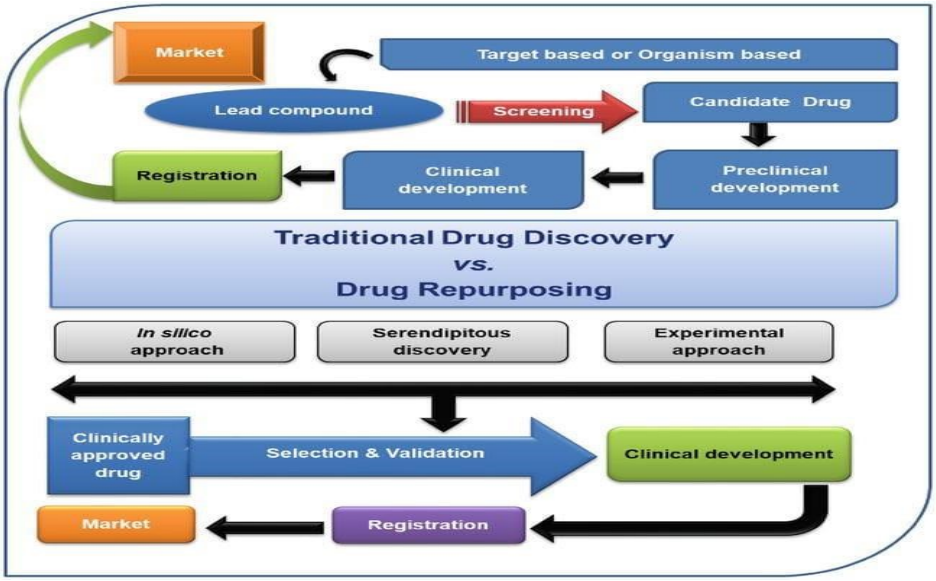


Figure 6. Comparison of Traditional v/s AI-assisted Drug Repurposing

4.2. Network-Based AI Approaches

Network medicine, combined with AI, enables the mapping of drug-disease relationships. The integration of network medicine with AI allows for the exploring of connections between drugs and diseases. Techniques like graph neural networks (GNNs) and knowledge graphs combine multi-omics data to reveal previously unknown relationships between them. Unlike traditional drug development, which involves lengthy preclinical and clinical phases, repurposing accelerates the process by leveraging the existing data. Repurposed drugs typically take 3-12 years to gain regulatory approval from various agencies, including the FDA or EMA, with costs reduced by 50-60%. Since these candidates have already undergone early-stage testing—including structural optimization, preclinical trials, and clinical evaluation—their safety and efficacy profiles are already partially established.

4.3. Natural Language Processing (NLP) for Literature Mining

NLP techniques, such as BERT and BioBERT, extract meaningful drug-disease relationships from scientific literature and clinical trial reports. A study by Wu et al. [35] employed NLP to uncover repurposing candidates for COVID-19 by analyzing over 24,000 research articles .

4.3.1.Case Studies of AI-Driven Drug Repurposing.

- Baricitinib (for COVID-19): An AI model by Richardson et al. [36] identified baricitinib, an arthritis drug, as a potential COVID-19 treatment by analyzing gene expression profiles.
- Thalidomide (for Crohn's disease): ML-based drug similarity networks suggested that thalidomide's anti-inflammatory effects could be repurposed for Crohn's disease [37].
- Metformin is used in diabetes but AI drug repurposing suggested it to be used to treat cancer by using the method of network pharmacology [38].

5.AI-BASED TOOLS IN DRUG DISCOVERY

AI-powered tools are essential to leverage the potential of artificial intelligence in drug discovery. The tools range from molecular modeling software and virtual screening to the tools used to assist with the generation of compounds, identification of targets, and optimization. DeepChem is one

of the leading tools that integrates cheminformatics and bioinformatics with deep learning techniques to assist the drug discovery processes, such as virtual screening and molecular property prediction. Its use of deep learning models has led to dramatic improvements in the identification of drug candidates, overtaking traditional methods for the most part. Another impactful AI technology is AlphaFold, a deep learning model developed by DeepMind to predict protein structures with high accuracy. The technology has revolutionized structural biology by providing insights into protein folding, a critical field of drug target discovery. By enabling a quicker and more accurate prediction of protein structures than the current methods, AlphaFold has greatly sped up the discovery of treatments against individual proteins, such as those in COVID-19.

In addition, computer programs such as Ligand Scout and AutoQSAR combine machine learning with traditional pharmacophore and QSAR modeling to refine drug candidates from predictive data based on their biological activity and interactions. In addition, AI software including COVID Moonshot has made it possible for researchers to collaborate and share data and computational models to rapidly generate candidate drugs for immediate global health crises like COVID-19. The collaborative platform uses reinforcement learning and other ML techniques to generate molecular candidates capable of inhibiting the SARS-CoV-2 virus.

5.1. Clinical Trial Optimization

- IBM Watson for Clinical Trials: Analyzes EMRs (electronic medical records) to match patients with trials. Reduce recruitment time for a melanoma study by 78%.
- Saama's AI CRO Platform: Uses NLP to extract data from unstructured clinical notes, cutting data cleaning time by 50%.

With innovations in the field of drug discovery for AI, novel platforms and tools are emerging to help drug researchers negotiate the intricacies of modern-day drug development. By performing most of the repetitive and time-consuming tasks associated with drug discovery, AI tools have the potential to reduce both the time and cost involved in bringing new drugs to the market and improving the success rate of drug candidates.

6.APPLICATIONS OF AI IN DRUG DESIGNING AND DEVELOPMENT FOR SPECIFIC VIRAL DISEASES

6.1. AI in COVID-19

COVID-19, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), reached epidemic proportions in China and across the world within weeks of its initial outbreak in December 2019 in Wuhan, China. The World Health Organization (WHO) first declared COVID-19 a Public Health Emergency of International Concern on January 30, 2020. On March 11, 2020, it was declared a pandemic. By August 6, 2021, there had been 200.8 million cases of COVID-19 worldwide and 4.26 million deaths [39].

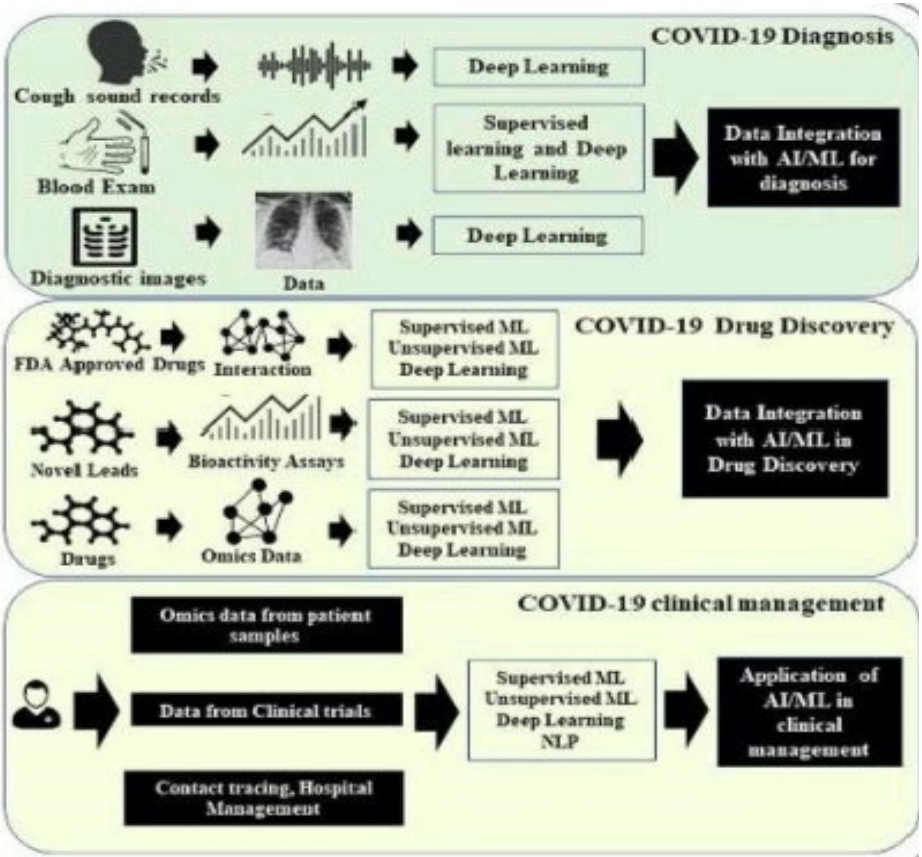


Figure 7. The Application of AI in Managing the COVID-19 Pandemic Highlights the Role of AI/ML in COVID-19 Diagnosis, Drug Discovery, and Clinical Management

6.1.1.Advancement of Computational Methods to Combat the COVID-19 Pandemic. Over the past 20 years, the way scientists study diseases have changed due to the digital revolution and artificial intelligence. This is due to the incorporation of AI in diagnosis and treatment. AI uses a range of methods, such as rule-based systems, machine learning, and deep learning. ML allows AI to learn from the past data to generate predictions, whereas DL uses specialized networks called artificial neural networks (ANNs) to handle huge and complicated data. These instruments are quite useful in the medical field. For example, IBM's Watson for Oncology aids in choosing cancer treatment, and Microsoft's Hanover Project offers specific therapy suggestions to cancer patients (Fig. 7) [39]. When COVID-19 initially came out, AI technologies were also used to read CT scans, X-rays, and cough sounds to detect infections.

6.1.2.Application of AI in Vaccine Development and Delivery. AI has played a pivotal role in the development of COVID-19 vaccines. By enhancing vaccine design and development, AI technologies have enabled researchers to predict which viral components—such as the whole virus, spike protein, nucleocapsid protein, or membrane protein—are most likely to elicit a strong immune response. AI tools are mentioned in Table 6 [39]. MARIA, MoDec, and Vaxign-ML programs are used to identify possible targets.

Table 6. AI Tools Used in COVID-19 [39]

AI Tool	Full Form	Role in COVID-19
CNN	Convolutional Neural Network	Used to analyze chest X-rays and CT scans for diagnosis.
A14COVID-19	AI-based Cough Sound Detection Tools	Diagnosed COVID-19 by analyzing patients' cough sounds.
IDVI	Infectious Disease Vulnerability	Predicted infection risk in different countries.
XGBOOST	Extreme Gradient Boosting	Predicted patient mortality risk using medical markers.
MARIA	Major Histocompatibility Complex Analysis with	Predicted antigen peptides for vaccine

AI Tool	Full Form	Role in COVID-19
	Recurrent Integrated Architecture	development.
DeepCE	Deep-learning-based Chemical Embedding	Helped find new drug candidates against COVID-19.
MoDec	Motif Deconvolution	Identified peptide sequences for vaccine design.
LSTM	Long Short-term memory Network	Predicted possible mutations in the virus genome.

6.1.3.Repurposing Candidate for COVID-19. A schematic illustration of the AI-based drug discovery screening for COVID-19 is shown below in Fig. 8 [40].

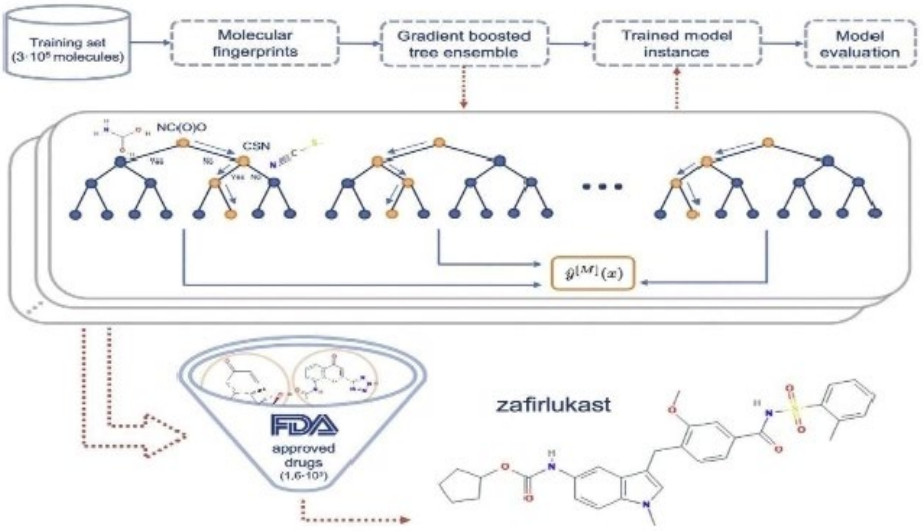


Figure 8. AI-based Drug Discovery Screening for COVID-19, Identifying the FDA-approved Drug "Zafirlukast" Using AI

An impressive study by Delijewski and Haneczok used supervised ML to predict repurposing candidates among FDA-approved drugs with

antiviral activity against SARS-CoV-2. The approach applied in this study, that is, molecular property prediction for drug discovery, is based on MACCS fingerprints computed using the RDKit library and the implementation of a GB tree learning method (XGBoost). Zafirlukast has emerged as a promising repurposing candidate against SARS-CoV-2 infection, complementing findings on the potential of other drugs in the same class, such as montelukast. It ranks among the top drug candidates due to its dual action—targeting the SARS-CoV-2 3CLpro to inhibit viral replication and blocking NF-κB to reduce hyperinflammation. Additionally, as an FDA-approved oral medication for asthma, it offers a favorable safety profile for drug repurposing in COVID-19 treatment [40].

6.2. AI in Drug Discovery and Development of Anti-dengue Drugs

Dengue fever is caused by the dengue virus (DENV), carried by mosquitoes named *Aedes albopictus* and *Aedes aegypti*. Dengue is now endemic to more than 100 tropical and subtropical countries in the Americas, Africa, Southeast Asia, and certain regions of Europe. Each year, an estimated 390 million dengue infections, in which clinical symptoms are exhibited in 96 million cases, are reported, along with 25,000 deaths [41]. DENV has four distinct antigenic serotypes: DENV-1, DENV-2, DENV-3, and DENV-4 [42]. Dengue shock syndrome (DSS) and dengue hemorrhagic fever (DHF) are serious diseases with complications caused by antibody-dependent enhancement (ADE) or original antigenic sin [41]. Dengue therapy is limited to curing symptoms. Currently, no FDA-approved medication is available to treat dengue. The first licensed dengue vaccine, named dengvaxia, is not considered to be safe and effective for certain age groups [43]. New antiviral drug development is essential to prevent and control dengue virus infection. AI provides benefits for the prevention, control, and management of dengue fever. Dengue outbreaks can be predicted and prevented by AI through analyzing factors such as climate, population density, and mosquito habitats. AI also takes part in vaccine development and new drug discovery.

6.2.1.Anti-dengue Inhibitors. Various studies have used AI to identify anti-dengue inhibitors. For example, a research used an ‘Anti-Dengue’ algorithm which employs ML to discover dengue virus inhibitors [44]. Moreover, a database named SWEETLEAD, which discovered medications with anti-dengue viral activity that were previously approved by the FDA, demonstrates the significance of computational screening in identifying

potential inhibitors [45]. Synthesis and evaluation of several compounds for their antiviral activity and efficacy against the dengue virus, such as heterocyclic molecules [46], baicalein-derived [47], and other compounds identified by virtual screening of molecular libraries [48]. Moreover, structure-activity relationship studies (SARs) and docking are used to synthesize and verify the inhibitory effectiveness of anti-dengue drugs, such as imidazole phenazine derivatives [49].

6.2.2.Anti-dengue Inhibitor from Drug Repurposing Using AI. To combat DENV, drug repurposing can be achieved by using AI as a potential method. Many researchers found that metoclopramide, N-acetylcysteine, quinine, and indole derivatives are present in many anti-dengue drugs and DENV can be treated by them. A specific method of ML-assisted prediction of small molecule antivirals can be used to identify the repurposed pharmaceutical drugs to target and treat DENV. A computational scan named the SWEETLEAD database is used to find anti-dengue viral substances approved by the FDA. The identification and creation of effective anti-dengue treatments through medication repurposing can be easily done by using AI [44, 45, 50].

6.3. Role of AI in Anti-influenza Drugs Discovery and Development

Influenza, commonly known as 'the flu,' is one of the most persistent seasonal respiratory illnesses affecting millions worldwide each year. Despite being a familiar illness, its viruses constantly evolve, presenting ongoing challenges to public health systems, globally. The flu causes 290,000 to 650,000 respiratory deaths annually and results in 3-5 million cases of severe illness worldwide, according to the WHO [51].

6.3.1.Role of AI in Flu Management. Over the past decade, AI has dramatically transformed how we understand, track, and combat influenza. The integration of computational methods with traditional epidemiology has created powerful new tools that offer unprecedented advantages in the fight against this familiar yet ever-changing pathogen [52, 53]. AI tools used in influenza are shown below in Table 7.

Table 7. AI Tools for Influenza

AI Tool	Full Form	Role in Influenza
CNN	Convolutional Neural Network	Analyzes chest X-rays to differentiate influenza from other respiratory conditions with >92% accuracy [54].

AI Tool	Full Form	Role in Influenza
FIuAI	Flu Artificial Intelligence Detector	Processes patient symptoms and vital signs to distinguish influenza strains and predict severity.
AudioFlu	Audio-based Flu Diagnostic	Identifies specific acoustic signatures in cough patterns unique to influenza infection [55].
IFRRS	Influenza Rapid Recognition System	Combines clinical data with lab values to minimize false negatives in rapid testing [56].

6.3.2.Revolutionizing Vaccine Development. The traditional flu vaccine development process has been dramatically accelerated by AI systems. These systems

- Predict antigen drift in influenza viruses to better match vaccines to circulating strains.
- Identify conserved viral epitopes that might enable the development of universal flu vaccines.
- Optimize manufacturing processes to increase vaccine yield and purity.

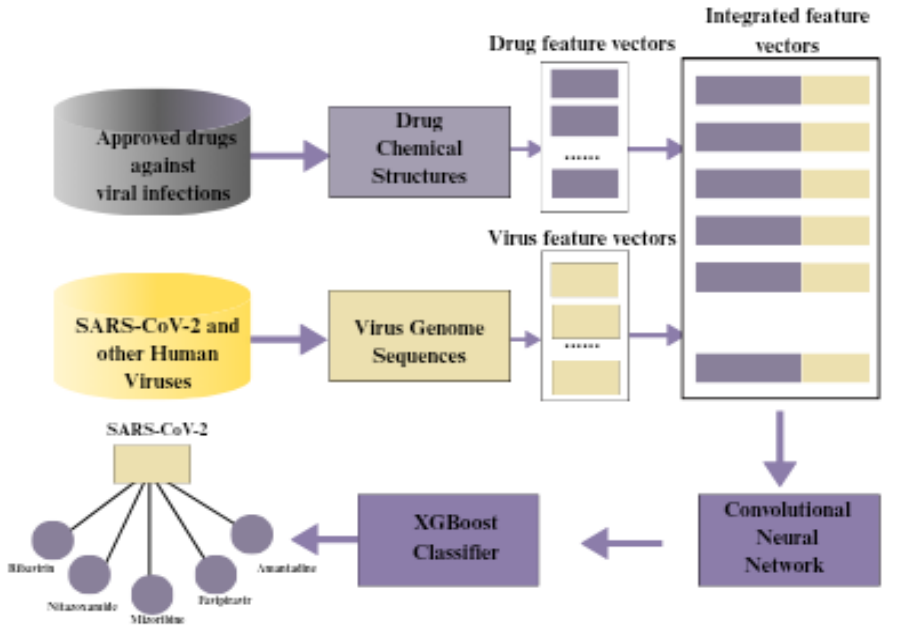


Figure 9. ML-assisted Drug Repurposing for COVID-19, Identifying Potential Existing Therapeutics

6.3.3.Drug Repurposing Through Machine Learning. Al-driven analysis has identified several existing medications with potential anti-influenza properties. Drug repurposing through ML is shown below in Figure 9. ML approaches similar to those used for COVID-19 have identified several promising candidates.

- Baloxavir was initially flagged by AI algorithms before becoming an FDA-approved influenza treatment [57].
- DL-based screening identified the combination of oseltamivir with specific antihistamines as particularly effective against resistant strains [58].
- Network pharmacology models discovered that certain cholesterol-lowering medications may disrupt influenza virus replication [59].

6.4. AI in Drug Discovery for Hepatitis

6.4.1.Role of AI in Targeting HAV IRES-Dependent Translation. HAV relies on its internal ribosomal entry site (IRES) for cap-independent translation, a critical step in viral replication. Researchers have identified host proteins, including La antigen and glucose-regulated protein 78 (GRP78), as key interaction partners of HAV IRES. ML and DL models have accelerated the identification of drugs targeting these host factors [60].

6.4.2.Drug Repositioning and Rescue. AI platforms have been used to screen FDA-approved drugs, such as amantadine and interferons (IFN-α, IFN-λ), which inhibit HAV IRES-mediated translation. These drugs have been validated using cheminformatics and bioinformatics tools, highlighting their potential for rapid therapeutic deployment. Zinc compounds and Japanese rice-koji miso extracts have been identified as well as GRP78 inhibitors, reducing HAV replication through AI-based structural analysis [61]. The crystallization of the HAV IRES domain V enabled a structure-based drug design. AI algorithms have been used to compare HAV IRES with other picornavirus structures in order to identify conserved motifs, facilitating the discovery of synthetic antibody fragments as potential inhibitors [62]. The role of AI in anti-HAV drug development is illustrated below in Figure 11 [63]. AI application in hepatitis and antiviral drug discovery is presented below in Table 8.

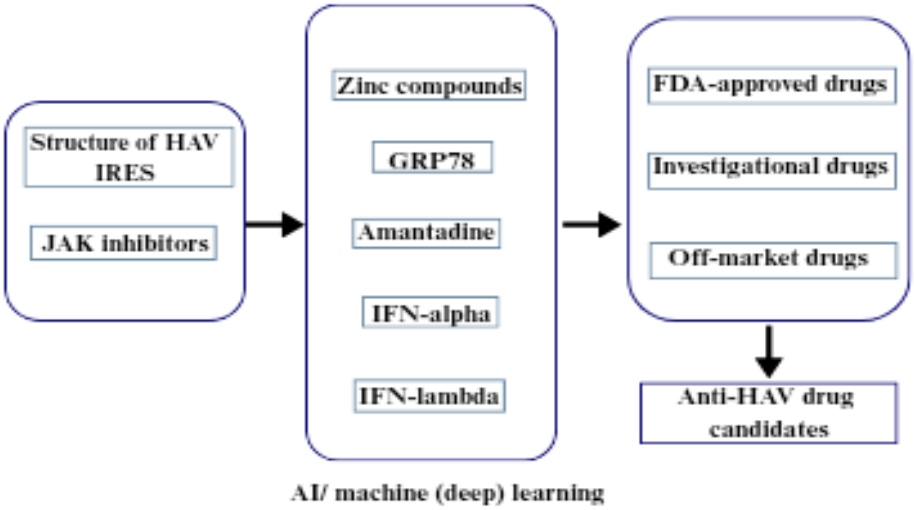


Figure 10. Flowchart Representation of AI Applications in Anti-HAV Drug Development, From Target Identification to Drug Discovery

Table 8. Role of AI in Anti-hepatitis Drug Discovery

Virus	Target Mechanism	AI/ML Method	Drug Candidates	Outcome
HAV	IRES-dependent translation	SVM, QSAR, deep learning	JAK inhibitors	Suppressed IRES activity and HAV replication
HAV	GRP78 interaction	Structure-based ML	Zinc Sulphate	Reduced HAV replication and GRP78 inhibition
HBV	Polymerase/protease	QSAR model	Bis (amino acid) ester prodrugs	Identified anti-HBV compounds
HBV	Liver fibrosis diagnosis	Deep learning radiomics	N/A	No invasive fibrosis staging
HBV	Quasispecies analysis	Machine learning (NGS data)	Host targeted therapies	Predicted HCC risk

6.5.AI in the Ebola

6.5.1.Overview of Ebola Virus and Disease Transmission. The Ebola virus (EBOV) is a highly virulent pathogen from the Filoviridae family, causing severe hemorrhagic fever with mortality rates reaching 90% in some outbreaks [64]. While fruit bats serve as natural reservoirs, transmission to humans occurs through contact with infected animals (primates, bushmeat), followed by human-to-human spread via bodily fluids [65]. The disease progresses rapidly from initial symptoms (fever, fatigue) to severe manifestations, including vomiting, hemorrhage, and multi-organ failure.

6.5.2.Role of Big Data in Drug Discovery. The integration of multi-omics data (genomic, proteomic, chemical) enables computational drug discovery at unprecedented scales. Key applications include

- Drug repurposing: Identifying existing drugs (e.g., chloroquine derivatives) with potential anti-EBOV activity.
- Virtual screening: Rapid evaluation of millions of compounds against EBOV targets.
- Network pharmacology: Mapping virus-host protein interactions to identify vulnerable pathways.

6.5.3.Data Resources for Databases Powering AI-driven Discovery. The success of AI-driven Ebola drug discovery relies heavily on robust, well-curated databases that provide essential molecular and pharmacological data. The most valuable resources include

- PubChem BioAssay: This offers over 500 EBOV-related screening datasets containing vital information on compound activity and cytotoxicity profiles.
- ChEMBL: Serves as another indispensable repository, providing meticulously curated drug-target interaction data that helps researchers to identify promising lead compounds.
- DrugRepV: Stands out as a specialized database compiling hundreds of experimentally validated compounds with potential anti-EBOV activity. Used for drug repurposing efforts.
- EbolaBase: Offers unique insights by mapping the complex network of

virus-host protein interactions, enabling researchers to pinpoint critical pathways for therapeutic intervention [66]. These databases collectively form the foundation to train accurate ML models and accelerate the discovery of effective Ebola treatments. A detailed summary of AI and ML applications in Ebola (EBOV) research is provided below in Table 9.

Table 9. AI and ML in Anti-Ebola Virus Drug Discovery

Tool/Algorithm	Application	Example/Tool Used	Remarks
Bayesian ML Models	Predication anti EBOV compounds from screening data set	Tilorone, Quinacrine, Pyronaridine Tetraphosphate	High ROC value (0.86), EC50 values confirmed *in vitro*
Support Vector Machines (SVM)	Predict drug target interactions, bioactivity prediction	Anti-Ebola Initiative, EBOLApred	Robust, widely used; good performance with accuracy up to 0.86
Random Forest (RF)	Small molecules screening. Classification models	EBOLApred	High accuracy (up to 0.89); used with PubChem datasets
Artificial Neural Networks (ANN)	Drug screening and virtual screening	Anti-Ebola Initiative	Accuracy up to 0.95; useful for nonlinear relationships
Naïve Bayes (NB)	Compound classification	EBOLApred	Moderate accuracy (~0.65); simple and interpretable
k-Nearest Neighbor (kNN)	Similarity-based classification	EBOLApred	Accuracy ~0.80; useful for small datasets
Recursive Partitioning	Ensemble model for the	Used with Bayesian &	ROC 0.75–0.85 in anti-EBOV

Tool/Algorithm	Application	Example/Tool Used	Remarks
Forest	prediction of activities	SVM in early studies	applications
Deep Neural Networks (DNN)	Advanced prediction of small molecule inhibitors	AtomNet, DEEPScreen	Outperforms traditional models; high AUC (>0.83)
Convolutional Neural Networks (CNN)	Predict drug–target interaction from the 2D structure	DEEPScreen	High performance; applied in multiple virus-related studies
Deep Docking (DD)	Structure-based virtual screening on massive libraries	Used for SARS-CoV-2 (1.3 billion compounds)	Suggested for future EBOV research
Generative Reinforcement Learning	De novo compounds design and optimization	DDR1 Inhibitor Design (Zhavoronkov et al., 2019)	Can generate entirely new potential drugs

7. STRENGTHS OF AI IN DRUG DESIGN

Artificial Intelligence (AI) is emerging as a potent tool in drug designing, with numerous strengths that are transforming the way we identify and develop new drugs. One of the biggest strengths of AI is its capacity to process enormous amounts of data at very high speed. It aids to identify potential drug candidates much quickly than previously possible. Another significant strength of AI lies in it being able to identify patterns that are not immediately apparent to human researchers.

AI analyzes the information from previous experiments and clinical trials. AI algorithms can identify and predict which kinds of molecules are most likely to be effective against specific diseases. This helps to make better predictions about new drugs, saving time and resources. It can also predict how a drug will behave after entering the body. AI models help to develop personalized and targeted treatments. It also has the capacity to assist in repurposing drugs. AI systems help to estimate the possibility of a

compound binding to disease targets even before conducting any physical testing. Further, they can process data-intensive tasks, while humans can offer ethical judgment, emotional intelligence, and profound scientific knowledge. For instance, reinforcement learning algorithms that are trained to collaborate with humans can make more informed decisions by integrating machine efficiency with human empathy and ethics. Overall, AI contributes numerous strengths to drug designing: it accelerates research, decreases costs, enhances precision, enables personalized medicine, aids in drug repurposing, and streamlines clinical trials. Although there are still obstacles to overcome, its advantages are already making a significant impact in the medical field and holding out hope for speedier, wiser, and more effective treatments down the line [11].

8.CHALLENGES AND LIMITATIONS

Al has shown promise in antiviral medication discovery; however, there are still several obstacles to overcome. Some of these are given below.

- AI implementation for drug discovery introduces numerous ethical, legal, and pragmatic issues. Intellectual property is also a massive concern.
- Data Quality and Availability: To train, Al models need substantial, superior datasets. However, model performance may be constrained by the lack of data, particularly for newly discovered viruses. Creating bias-free AI and ethics-free AI systems is a key challenge.
- Interpretability of the Model: A lot of Al models, especially DL architectures, operate as “black boxes,” making it challenging to decipher their predictions and understand their mechanisms [67].
- Integration with Experimental Validation: To verify efficacy and safety, experimental investigations must be conducted in addition to Al forecasts, requiring interdisciplinary cooperation.

9.FUTURE PERSPECTIVES

The following are some potential future directions.

- Explainable AI Model Development: Improving the predictability of AI forecasts to encourage adoption and trust in the biomedical community.
- Multi-Omics Data Integration: Bringing together transcriptomic,

proteomic, metabolomic, and genomic data to offer a thorough understanding of viral pathogenesis and host reactions.

- Personalized Medicine Approaches: Using AI to customize antiviral treatments according to the patient profile, increasing treatment effectiveness and lowering side effects.
- Active Learning Approaches: These approaches enable AI systems to guide iterative experimentation cycles, strategically selecting the most informative compounds for testing to maximize discovery efficiency.
- Quantum Computing Technology: It offers the potential for dramatically accelerated molecular simulations, allowing researchers to explore vast chemical spaces and protein-ligand interactions that are currently computationally prohibitive [68].
- Development of Digital Twin Technology: It creates patient-specific treatment models that simulate individual responses to potential therapies before clinical administration. These emerging technologies, combined with increased collaboration between computational and experimental researchers, are paving the way for more effective and rapid development of treatments in future outbreaks.

10. CONCLUSION

Artificial intelligence (AI) has emerged as a transformative force in modern drug discovery and development, offering innovative solutions to overcome the limitations of traditional approaches. By integrating AI into each and every stage of the drug pipeline—ranging from target identification, virtual screening, lead optimization, and ADMET prediction, as well as drug repurposing—the process has become more rapid, efficient, and cost-effective.

This review underscores AI's pivotal role in antiviral drug discovery, particularly for diseases such as COVID-19, dengue, influenza, hepatitis, and Ebola. AI tools and models enable the precise prediction of drug properties, identification of viable candidates, and accelerated development timelines. The application of DL, ML algorithms, and specialized platforms enhances the accuracy of target validation and pharmacokinetic profiling, while supporting the discovery of novel inhibitors and repurposed therapeutics.

Despite these advancements, challenges remain, including data quality, model transparency, ethical concerns, and the need for regulatory alignment. Moving forward, the development of robust, interpretable, and ethically responsible AI models trained on high-quality, diverse datasets is essential to fully realize the potential of AI-driven drug discovery, particularly in addressing global health threats posed by viral diseases.

Author Contribution

Nimra Ameer: writing – original draft. **Saba Razzak:** supervisor, writing – review and editing, **Isha Fatima:** writing – original draft. **Sehrish Haider:** writing – original draft. **Erum Hassan:** data curation. **Amna Baig:** data curation. **Osama Ilyas:** visualization. **Sohail Abbas:** visualization

Conflict of Interest

The authors of the manuscript have no financial or non-financial conflict of interest in the subject matter or materials discussed in this manuscript.

Data Availability Statement

Data supporting the findings of this study will be made available by the corresponding author upon request.

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Generative AI Disclosure Statement

The authors did not used any type of generative artificial intelligence software for this research.

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