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Artificial intelligence for drug repurposing against infectious diseases

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ABSTRACT

Traditional drug discovery struggles to keep pace with the ever-evolving threat of infectious diseases. New viruses and antibiotic-resistant bacteria, all demand rapid solutions. Artificial Intelligence (AI) offers a promising path forward through accelerated drug repurposing. AI allows researchers to analyze massive datasets, revealing hidden connections between existing drugs, disease targets, and potential treatments. This approach boasts several advantages. First, repurposing existing drugs leverages established safety data and reduces development time and costs. Second, AI can broaden the search for effective therapies by identifying unexpected connections between drugs and potential new targets. Finally, AI can help mitigate limitations by predicting and minimizing side effects, optimizing drugs for repurposing, and navigating intellectual property hurdles. The article explores specific AI strategies like virtual screening, target identification, structure base drug design and natural language processing. Real-world examples highlight the potential of AI-driven drug repurposing in discovering new treatments for infectious diseases.

1. Introduction

From time immemorial, infectious diseases have tormented humanity and civilization. The 21st century presents a complex and concerning landscape for infectious diseases [1]. This includes the emergence of novel viruses like SARS-CoV-2 (COVID-19) [2], the re-emergence of antibiotic-resistant bacterial strains [3,4], and the ongoing burden of neglected tropical diseases (NTDs) [5]. The recent emergence of novel zoonotic coronaviruses, such as SARS-CoV-2 (COVID-19) and MERS-CoV, highlights the unpredictable nature of infectious diseases with cross-species transmission potential [6,7].

The irresponsible use of antibiotics, including unnecessary prescriptions and incomplete treatment courses, has fueled the emergence of antibiotic-resistant bacteria. These "superbugs" pose a significant threat as they can render existing antibiotics ineffective, making common infections difficult to treat [8]. Antimicrobial resistance (AMR) poses a significant challenge, ranking among the top global public health and development threats. A staggering 1.27 million deaths in 2019 were directly attributed to bacterial AMR, with an estimated additional 4.95 million deaths where AMR was a contributing factor. This highlights the urgency of developing new antibiotics and implementing stricter antibiotic stewardship programs [9].

Neglected Tropical Diseases (NTDs) are a significant global health issue, with over 1 billion people affected and 400,000 deaths annually (WHO)[10]. However, limited resources and research funding often lead to their neglect [11]. This is particularly concerning in the context of the COVID-19 pandemic, which has diverted attention and resources away from NTDs [12]. The burden of NTDs is further exacerbated by the emergence of neglected non-communicable diseases (NNCDs) [13].

These factors combine to create a complex global challenge. Emerging infectious diseases pose a constant threat of pandemics, while antibiotic resistance undermines our ability to treat common infections. Neglected tropical diseases continue to devastate communities, highlighting the need for increased investment in research and development. The emerging and re-emerging viral outbreaks, has urged the scientific community to develop effective and sophisticated remedies to address the escalating demands imposed by these deadly diseases which may be potential pandemics.

Traditional drug discovery, the longstanding approach for developing new medicines, faces significant hurdles in keeping pace with this evolving threat landscape. Another challenge lies in the very nature of microbial evolution. Pathogens are constantly adapting to survive in their environment, including the presence of drugs. This rapid evolution can render a newly developed drug ineffective within a short period, necessitating the constant development of newer generations of drugs to stay ahead of resistance [14]. Furthermore, the traditional model prioritizes diseases with a high potential return on investment, often neglecting those that disproportionately affect developing nations. Neglected tropical diseases (NTDs) like leishmaniasis and Chagas disease, despite causing significant morbidity and mortality, receive a

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fraction of the research funding compared to diseases like malaria [15].

In this direction, a drug repurposing method is a reliable tool for identifying new prospective drugs in a short window to address the challenges [16,17]. In the face of rising infectious diseases and the limitations of traditional drug discovery, Artificial Intelligence (AI) presents a beacon of hope for accelerating drug repurposing and discovery. This powerful technology has the potential to revolutionize the fight against pathogens by streamlining processes, uncovering hidden patterns, and guiding researchers towards promising new treatments [18–20].

In light of the growing threat posed by emerging and drug-resistant infectious diseases, this review article explores the transformative potential of Artificial Intelligence (AI) in accelerating drug repurposing. AI's ability to analyze massive datasets of drugs and disease targets offers a powerful tool for identifying new therapeutic applications for existing medications. We delve into the specific functionalities of AI in this domain, including target identification, virtual screening of candidate drugs, and prioritizing the most promising candidates for further investigation. Additionally, we showcase real-world examples of AI-predicted repurposed drugs currently undergoing clinical trials. By highlighting the effectiveness of AI-assisted drug repurposing methods, this review aims to emphasize their crucial role in combating the challenge of emerging infectious diseases.

2. The traditional drug discovery pipeline

The traditional drug discovery pipeline represents a multi-stage process for identifying and developing new therapeutic agents (Shown in Fig. 1) [21,22]. The initial stage focuses on identifying a specific molecule or pathway within a pathogen critical for its survival or virulence. This can involve biochemical assays, genetic manipulation, and computational modeling [23]. Once a potential target is identified, rigorous validation is essential to confirm its druggability and relevance to the disease process. The next stage involves identifying candidate drug molecules with the potential to interact with the validated target. Traditionally, this relied on high-throughput screening (HTS) of large chemical libraries or natural product extracts [24]. Additionally, medicinal chemistry plays a crucial role in optimizing lead compounds for potency, selectivity, and pharmacokinetic properties (absorption, distribution, metabolism, and excretion) [25]. Promising lead compounds undergo extensive *in vitro* and *in vivo* testing to assess their efficacy and safety. In vitro assays evaluate the compound's effect on isolated cells or tissues infected with the pathogen. In vivo studies, typically conducted in animal models, provide crucial data on efficacy, toxicity, and metabolism of the drug candidate. If preclinical studies are encouraging, the drug candidate progresses to human clinical trials. These trials are typically conducted in phases, with Phase I focusing on safety and tolerability in healthy volunteers, Phase II evaluating efficacy in a small group of patients with the target disease, and Phase III involving larger patient populations to confirm efficacy and safety compared to existing treatments. Following successful clinical trials, the drug candidate undergoes a rigorous review process by regulatory agencies. Approval for marketing is contingent on demonstrating the drug's safety, efficacy, and quality. Once approved, post-marketing surveillance is crucial to monitor the drug's long-term safety profile and identify any unforeseen adverse effect [26].

The traditional drug discovery pipeline has played a vital role in developing numerous drugs. However, its limitations include high costs, lengthy development times (often exceeding 10 years), and a high attrition rate of potential drug candidates throughout the process. Additionally, the reliance on trial-and-error methods in early stages can lead to a high rate of attrition, with many promising candidates failing to reach the finish line [27]. This is particularly true for diseases like tuberculosis, where the pathogen's ability to persist in a latent state presents a significant barrier [28]. The use of animal models in drug discovery, while essential, has limitations in predicting human responses, leading to a low success rate in clinical trials [29]. For intracellular bacterial pathogens, the challenges include identifying effective drug targets and developing technologies for experimental investigation [30]. These studies collectively highlight the need for innovative approaches and technologies to improve the drug discovery process for infectious diseases.

3. Drug repurposing: a promising approach with caveats

Drug repurposing, a strategy that identifies new therapeutic uses for existing drugs, is a cost-effective and time-saving approach in drug discovery has gained significant attention in recent years [31]. It has been particularly effective in addressing the urgent need for interventions in various diseases, including the COVID-19 pandemic. This approach, which focuses on the polypharmacology of drugs, has the potential to design more efficient therapeutic agents for unmet medical disorders. As illustrated in Table 1, drug repurposing has yielded successful treatments for a broad spectrum of diseases, encompassing infectious agents, cancers, neurological disorders, and even rare conditions.

3.1. Drug repurposing approaches

When repurposing drugs, researchers typically use various approaches to identify potential drug candidates. It's important to note

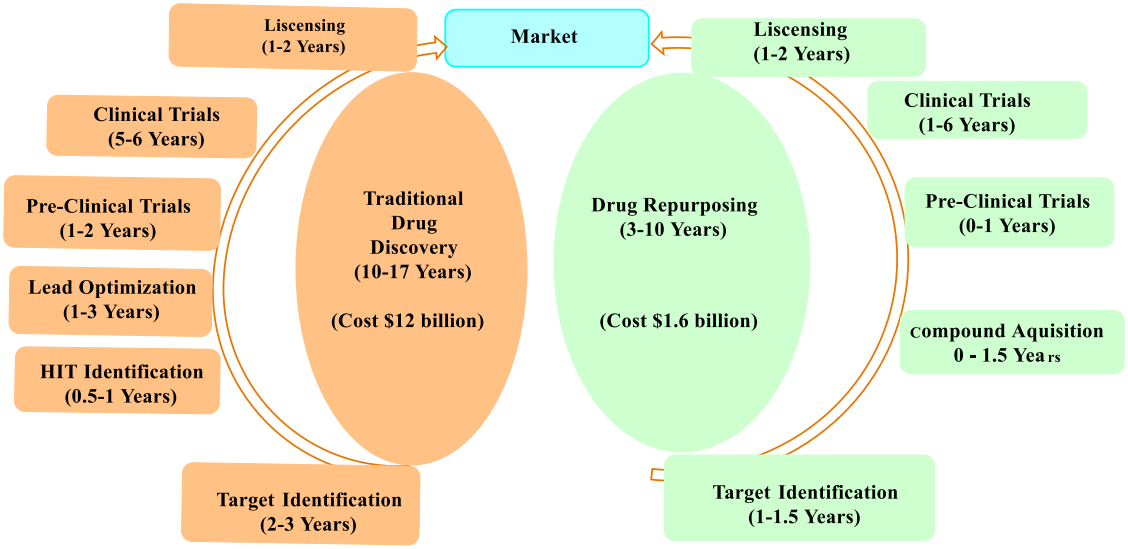


Fig. 1. The Drug Discovery and Development Pipeline.

Table 1
Examples of repurposed drugs for various infectious diseases.

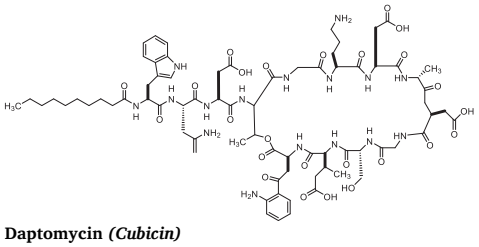
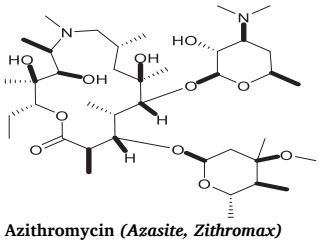
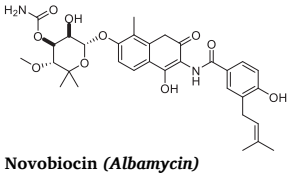
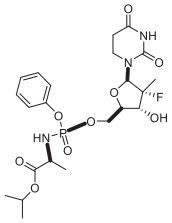
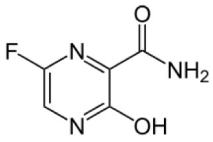
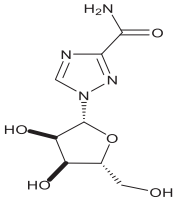
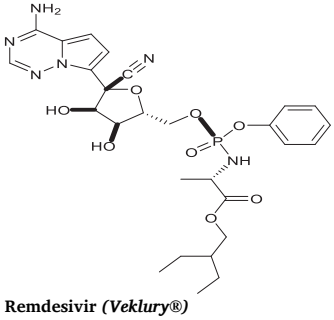
S. No.	Original drug (Brand name)	Original indication and mechanism of action	Current status of Repurposing
1.	 **Daptomycin *(Cubicin)***	• Cyclic lipopeptide antibiotics • Bacterial cell wall synthesis inhibitors [32]	• Tested in vitro against Zika virus but the target is not defined [33]
2.	 **Azithromycin *(Azasite, Zithromax)***	• Broad-spectrum Macrolide antibiotic for the treatment of respiratory, enteric and genitourinary infections. [34] • Bacterial protein synthesis inhibitors [35]	• While a small, early study showed promise for the combination of azithromycin and hydroxychloroquine in COVID-19 treatment, with all participants achieving viral clearance within 6 days, subsequent larger studies have not confirmed these findings. Further research is needed to determine the effectiveness of this combination therapy [36]. • Tested in vitro against Zika virus but the target is not defined [37]
3.	 **Novobiocin *(Albamycin)***	• Aminocoumarin antibiotics • competitive inhibitors of DNA gyrase ATP hydrolysis [38].	• Tested *in vitro* and *in vivo* (mouse model) against Zika virus; Target: NS2B/ NS3 protease [39].
4.	 **Sofosbuvir *(Sovaldi)***	• Nucleotide analogue inhibitor • hepatitis C virus; Target: NS5B polymerase	In the treatment of COVID-19 due to its ability to suppress positive-strand RNA viruses [39]. Tested *in vitro* and *in vivo* (mouse model) against Zika virus; Target: NS5 RNA polymerase [40,41]
5.	 **Favipiravir*(Avigan)***	• pyrazinecarboxamide derivative with activity against RNA viruses • Phase 2 clinical trial	selectively inhibited the RNA-dependent RNA polymerase of influenza virus, Ebola virus and SARS-CoV-2 [42–44].
6.	 **Ribavirin *(Rebetol, Copegus)***	• Nucleoside analogues approved to treat Respiratory Syncytial Virus (Respiratory Syncytial Virus) Infection, hepatitis C and some viral hemorrhagic fevers	• *In vitro, In vivo and* Clinical trials reported for viral haemorrhagic fevers; hepatitis C virus, Respiratory Syncytial Virus; SARS-CoVSARS-CoV-2 and MERS-CoV [45,46].
7.	 **Remdesivir *(Veklury®)***	• Broad-spectrum antiviral nucleoside analog active against HBV, Nipah virus, hepatitis C, and Marburg • Inhibition of RdRp activity	• Approved for HIV, Ebola, SARS-CoV-2, Bat CoVs, SARS-CoV, SARS-CoV-2 and MERS-CoV [47,48].

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Table 1 (*continued*)

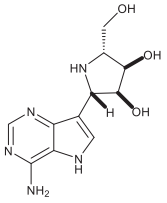
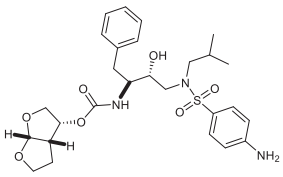
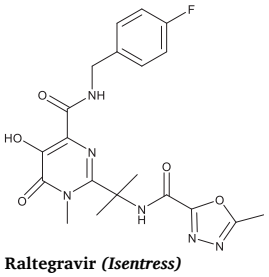
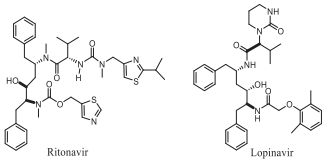
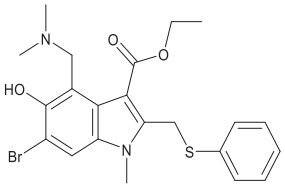
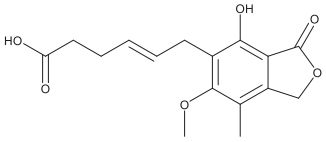
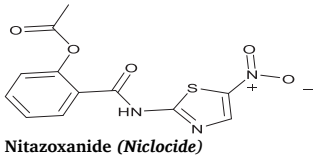
S. No.	Original drug (Brand name)	Original indication and mechanism of action	Current status of Repurposing
8.	 **Galidesivir**	• Inhibition of RdRp activity • Approved for hepatitis C virus	• *In vitro* & *In vivo* studies reported against Zika virus and different variations of CoV Clinical trial: Yellow fever and different variations of CoV[49]
9.	 **Darunavir *(Prezista)***	• Approved for HIV-1 • HIV-1 protease dimerization Inhibittiors	• Clinical trial: SARS-CoV-2 [50]
10.	 **Raltegravir *(Isentress)***	• Approved for HIV-1 • integrase inhibitors	• anti-myeloma effects • Clinical trial: Herpesvirus and SARS-CoV-2 [51, 52]
11.	 **Lopinavir- ritonavir**	• Approved HIV-1 • protease Inhibitor; blokes 3 chymotrypsin-like protease	• *In vitro, In vivo* & Clinical trial: different variations of CoV [53]
12.	 **Umifenovir*(Arbidol)***	• Approved anti Influenza • Impedes spike trimerization	• *In vitro, In vivo* and Clinical trial: hepatitis B virus, hepatitis C virus, Reovirus Hantaan virus, coxsackie virus B5 Zika virus, Chikungunya virus Influenza, SARS-CoV-2 [54].
13.	 **Mycophenolic acid*(Myfortic)***	• Approved immunosuppressive agent	***In vitro:*** Zika virus, Dengue virus, SARS-CoV-2 [55].
14.	 **Nitazoxanide *(Niclocide)***	• Approved antiparasitic and anthelmintic drug	***In vitro***: Zika virus, SARS-CoV-2 and yellow fever virus [56]

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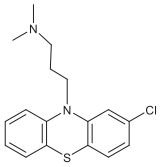
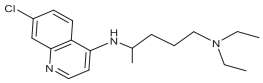
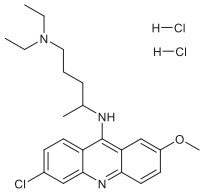
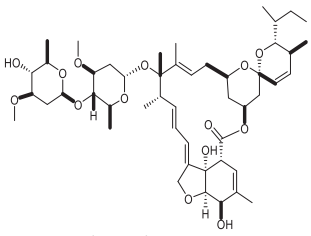
Table 1 (*continued*)

S. No.	Original drug (Brand name)	Original indication and mechanism of action	Current status of Repurposing
15.	 **Chlorpromazine (*Thorazine*)**	• Approved antipsychotic	• ***In vitro***: MERS and SARS-CoV [57,58].
16.	 Chloroquine *(Aralen)*	• Approved anti-malarial drug • Immuno-regulator	• ***In vitro***: HIV, SARS, Influenza, SARS-CoV-2 rheumatoid arthritis [59–61].
17.	 **Quinacrine Dihydrochloride**	• Approved anti-malarial drug • Inhibits NF-kB and prevents ACE2-Spike interaction. In addition to p53 signalling and lipid signalling activator.	• Anticancer • ***In vitro***: SARS-CoV-2 and yellow fever virus [62–64].
18.	 Ivermectin*(Zuvista)*	• Anti-parasitic agent	• ***In vitro***: Influenza, Dengue virus, Zika virus, SARS-CoV-2, Venezuelan equine encephalitis virus [65–68].

that the identification of new targets for repurposing existing drugs requires a multidisciplinary approach, involving computational analysis, experimental validation, and a deep understanding of the pathogen and host biology. Collaboration between researchers from different fields, such as microbiology, pharmacology, and computational biology, is often key to successfully identifying and repurposing drugs against infectious diseases [69].

The discovery of novel therapeutic applications for drug candidates can occur through serendipitous observation or through hypothesis-driven, rational approaches. Hypothesis-driven drug repurposing strategies encompass both experimental and computational methods. These methods hold significant promise for elucidating the underlying mechanisms and pathways involved in disease pathogenesis [70].

Experimental approaches involve techniques like binding assays to identify direct interactions between drugs (ligands) and cellular components. Additionally, phenotypic screening methods can be used to identify promising drug candidates from large libraries based on their effects on whole cells or organisms. **Computational approaches** fall into several categories:

3.1.1. Drug-centric

Drug-centric repurposing focuses on identifying new therapeutic applications for existing drugs by leveraging their potential to interact with multiple molecular targets (polypharmacology) [71]. While polypharmacological agents can cause side effects, their ability to interact with diverse targets presents opportunities for novel indications. Identifying a drug's interactions with unintended targets (off-targets) through receptor binding studies can unveil novel therapeutic applications [72]. Sildenafil originally developed for angina (chest pain), is a prime example of how off-target effects can lead to new therapeutic applications. During clinical trials for angina, researchers observed an unexpected side effect – improved blood flow to the penis, leading to erections. This discovery led to the repurposing of Sildenafil as Viagra, a revolutionary treatment for erectile dysfunction. Sildenafil inhibits an enzyme called phosphodiesterase-5 (PDE5), which helps regulate blood flow. While the intended target was PDE5 in blood vessels supplying the heart, the drug also interacted with PDE5 in the penis, leading to the observed effect [73]. Furthermore, assessing drug-target binding facilitates the identification of structurally similar compounds with potential binding affinity for the same target. This approach, termed target hopping, expands the pool of candidate drugs for further investigation [74].

3.1.2. Target-centric

Target-centric drug repurposing, a strategy that identifies new therapeutic uses for existing drugs by focusing on specific molecular targets in disease pathways, has gained significant attention in recent years [75]. This approach has been particularly successful in cancer treatment, with the repurposing of metformin, originally used for type 2 diabetes, showing promise in inhibiting tumor growth [76]. The use of p53 as a therapeutic target in cancer treatment is another example of this strategy [77].

3.1.3. Disease-centric

Disease-centric drug repurposing flips the traditional approach on its head. Instead of focusing on a specific drug and finding new uses for it, this strategy starts with a particular disease and searches for existing drugs that might be effective in treating it [78,79]. In this approach researcher pinpoint the underlying biological mechanisms of a disease. They then search for approved drugs that target similar mechanisms, even if those drugs were originally developed for completely different conditions. Drugs with a good fit for the disease's biology are evaluated for their potential to be repurposed as treatments. For example

Disulfiram, used to treat alcoholism, is being investigated for its potential to slow the progression of amyotrophic lateral sclerosis (ALS) by targeting protein folding [80].

Despite their differences, all these strategies leverage similarity assessment to identify potential repurposing candidates. This assessment helps researchers predict which existing drugs might be effective against new targets or diseases [81–85].

Compared to traditional drug discovery, repurposing offers significant advantages in terms of reduced development time and cost as shown in Fig. 2 [86–89]. The availability of established safety and pharmacokinetics allows researchers to bypass these initial stages, leading to substantial resource savings. Additionally, understanding the known mechanism of action for a repurposed drug facilitates its application in novel therapeutic areas [90,91]. This knowledge guides researchers towards potential target diseases where the drug's mechanism might offer therapeutic benefit. Furthermore, the pre-existing safety information expedites clinical translation. Researchers can focus on evaluating the drug's efficacy in the new indication through clinical trials, potentially accelerating patient access to these novel treatment options [92–94].

4. Mitigating limitations of drug repurposing with AI

While drug repurposing offers a faster and more cost-effective approach compared to traditional drug discovery, it faces certain limitations. Repurposed drugs may have limited target specificity, leading to side effects and suboptimal efficacy. Additionally, the pool of potential drug candidates can be restricted, and repurposed drugs might require further optimization for the new use. Furthermore, intellectual property challenges and the need for additional clinical trials can hinder progress [95]. However, AI algorithms can be powerful tools to address these challenges. By analyzing vast amounts of biological and chemical data, AI can uncover hidden connections between existing drugs, disease targets, and potential therapeutic applications. This translates to several advantages for AI, such as:

4.1. *AI-powered prediction and minimization of off-target effects in drug repurposing*

Drug repurposing, leveraging existing drugs for new therapeutic applications, offers a promising approach to accelerate drug discovery.

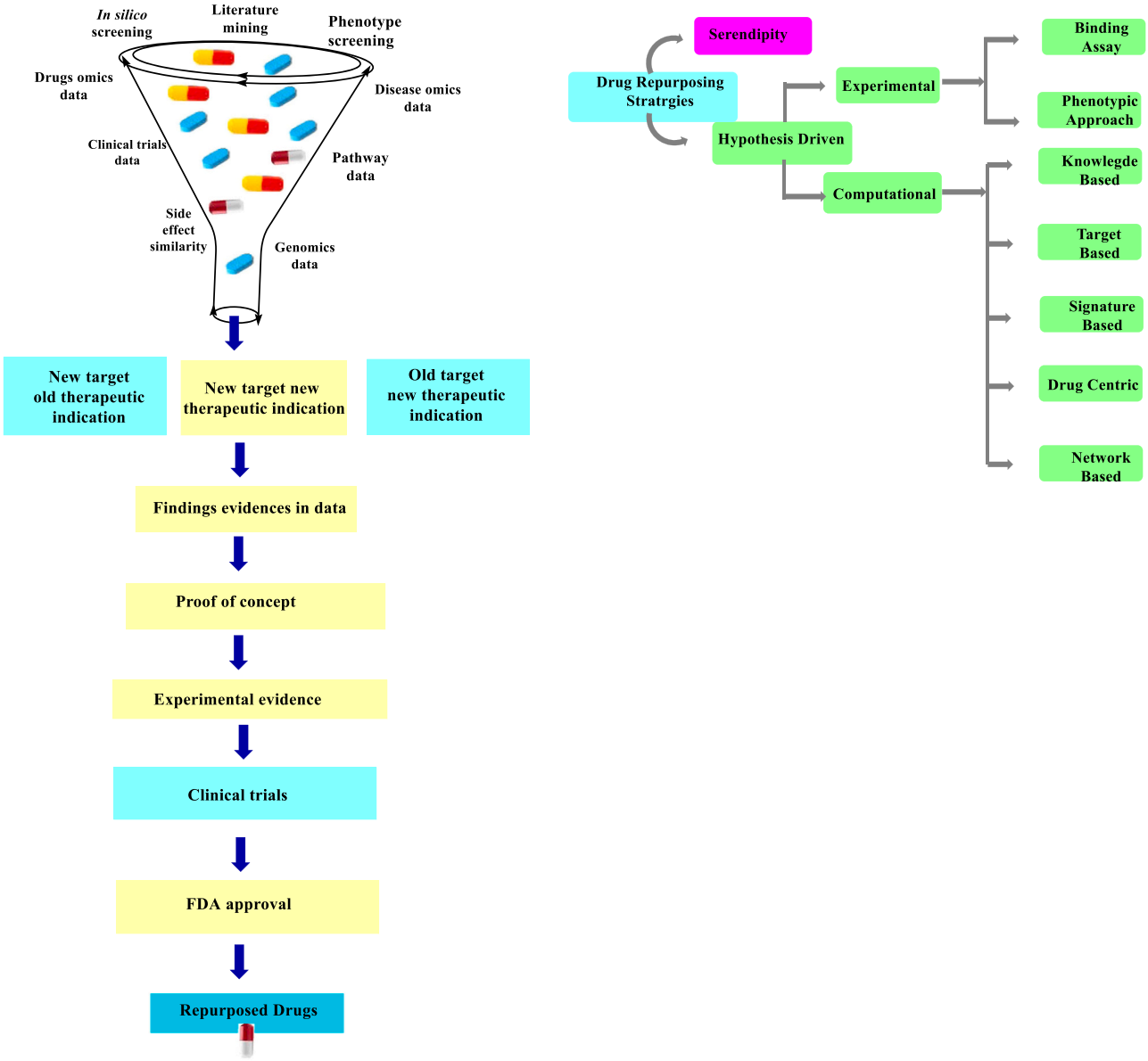


Fig. 2. A Roadmap for Drug Repurposing.

However, ensuring the safety of repurposed drugs in a new context remains a critical concern. Off-target effects, unintended interactions with molecules other than the intended target, can lead to unwanted side effects.

Here, Artificial Intelligence (AI) emerges as a powerful tool for predicting and minimizing these off-target effects. AI algorithms can analyze vast datasets encompassing drug-target interactions, protein structures, and known side effects. This allows for the identification of potential off-target interactions for a repurposed drug, paving the way for safer and more effective clinical trials. **For example, Baricitinib** originally developed for rheumatoid arthritis, shows promise as a COVID-19 treatment due to its anti-inflammatory and antiviral properties. AI analysis of Baricitinib's interactions helped researchers predict and mitigate potential side effects, enabling safer clinical trials [96–100]. Second example is **Lopinavir/Ritonavir,** HIV drug was explored for its potential to inhibit a vital SARS-CoV-2 enzyme (protease) [87]. AI analysis predicted potential off-target effects on liver function, highlighting limitations in its effectiveness. This paves the way for the development of novel, targeted inhibitors specifically against SARS-CoV-2, potentially overcoming limitations associated with repurposed drugs [101–105].

4.2. AI in drug repurposing: expanding the candidate pool

One of AI's most significant contributions lies in its ability to significantly expand the candidate pool for repurposing, accelerating the fight against various diseases. Previously, drug repurposing often relied on a limited scope. Researchers focused on drugs with known mechanisms of action (MOA) directly related to the target disease. This approach restricted the search space and potentially overlooked promising candidates with unexplored potential [106]. AI tackles this limitation by leveraging its prowess in analyzing vast datasets on existing drugs, including their structures, interactions with human proteins, and potential side effects. It then compares this information with data on the target disease, such as the proteins or pathways involved. This allows AI to identify unexpected connections between existing drugs and potential new targets, even if their original MOA wasn't directly related [107].

AI can delve beyond established medications for a particular disease category. By analyzing chemical structures and predicted interactions with disease targets, AI can identify candidates from diverse therapeutic areas that might be effective in new ways. Alendronate, a drug for osteoporosis, exemplifies the power of AI-driven drug repurposing. AI analysis identified its potential to inhibit a specific enzyme critical for the growth of certain cancer cells. This opens doors for repurposing Alendronate as a potential anticancer therapy, significantly expanding the pool of candidate drugs beyond traditionally explored options [108–110].

With a vast pool of potential candidates identified, AI acts as a powerful filtering tool. By analyzing predicted efficacy and potential off-target effects, AI can prioritize the most promising candidates for further investigation. This saves researchers valuable time and resources by focusing on drugs with the highest likelihood of success.

4.3. AI-powered drug optimization strategies for repurposing

Repurposing existing drugs for new therapeutic applications offers a promising approach to accelerate drug discovery. However, ensuring both efficacy (effectiveness) and safety in a new disease context remains a critical challenge. Here, Artificial Intelligence (AI) emerges as a powerful tool, leveraging vast datasets to predict and optimize various drug properties, leading to safer and more effective repurposed drugs. AI can be employed in several ways to optimize repurposed drugs. AI algorithms can analyze large datasets encompassing drug-target interactions, protein structures, and disease pathways to identify potential targets for repurposed drugs in the new disease context. This can increase the likelihood of the drug having a desired effect in the new disease. AI algorithms can analyze pharmacokinetic (drug absorption, distribution, metabolism, and excretion) data to predict optimal dosing regimens for repurposed drugs, maximizing efficacy while minimizing toxicity. For example, AI is being explored to optimize dosing regimens for existing antiretroviral drugs used to treat HIV, potentially leading to improved adherence and reduced side effects [111–113].

4.4. Navigate the intellectual property landscape

Patents provide crucial information about drugs, including their chemical structure, mechanism of action, and initial intended use. When a drug's patent expires, it becomes generic, meaning any manufacturer can produce it, often at a significantly lower cost. AI, coupled with patent data analysis, offers a powerful approach to identify and unlock the potential of existing drugs for other treatments. This strategy allows for faster, cheaper, and more accessible therapies, ultimately contributing to a more prepared and responsive healthcare system in the face of emerging pathogenic threats [114–116]. By analyzing expired patents, AI can identify drugs no longer under patent protection, making them readily available for repurposing. This is particularly beneficial for antiviral treatments targeting less common viruses where developing entirely new drugs might not be commercially viable. For example, Teicoplanin, an antibiotic whose patent has expired, was identified through AI analysis as having potential antiviral properties against Zika virus. This analysis considered both Teicoplanin's structure and its mechanism of action. The identification of this potential new use for Teicoplanin highlights the power of AI-driven repurposing in the fight against viruses, especially for less common viral threats [117,118].

4.5. Design efficient clinical trials

AI-powered design of targeted and efficient clinical trials can expedite the evaluation of repurposed drugs, reducing resource requirements and accelerating their time to market. AI algorithms can analyze vast datasets of patient demographics, medical history, and viral strain information. This allows researchers to select highly relevant patient populations most likely to benefit from the repurposed drug, leading to more conclusive trial results. AI can design efficient trials by identifying the most effective dosages, treatment durations, and outcome measures specific to the drug and targeted virus. This reduces unnecessary procedures and streamlines data collection. AI can leverage existing data to predict potential side effects and treatment outcomes. This allows researchers to prioritize the most promising candidates and identify potential safety concerns early on, leading to more focused and efficient trials [119–121].

5. AI driven drug repurposing methods

AI algorithms can analyze vast amounts of biological and chemical data, uncovering hidden connections between existing drugs, disease targets, and potential therapeutic applications. Here are some key AI-driven strategies revolutionizing drug discovery and repurposing for infectious diseases:

5.1. AI-driven virtual screening

Virtual screening uses computational methods to filter large libraries of molecules to identify those with the potential to interact with a specific biological target [122]. Machine learning (ML) and deep learning (DL) algorithms play a crucial role in AI-driven virtual screening, accelerating the identification of repurposing candidates [123].

5.1.1. ML assisted virtual screening

Machine learning (ML) is a core subfield of artificial intelligence (AI) that focuses on developing algorithms that can learn from data without being explicitly programmed. In the context of drug repurposing, ML

plays a critical role in virtual screening by p**redictive modeling.** These algorithms analyze vast datasets of drug-target interactions, uncovering patterns and relationships. They then leverage this knowledge to predict how new compounds, including existing approved drugs, might interact with a specific antiviral target. This allows researchers to prioritize the most promising candidates for further evaluation [124]. Second, through d**ata-driven analysis,** AI can sift through a wealth of information, including existing drug databases, scientific publications, and patient data. This facilitates the identification of connections between existing drugs and novel antiviral targets, a process that would be incredibly time-consuming using traditional methods. The rapid response to the COVID-19 pandemic exemplifies this power. By analyzing existing drugs through AI-powered virtual screening, researchers were able to quickly identify antiviral candidates like remdesivir and favipiravir for potential treatment [125,126].

5.1.2. *Types of machine learning in repurposing*

There are two main categories of ML algorithms commonly used in drug repurposing:

5.1.2.1. Supervised learning. This type of learning involves training the algorithm on labeled data. In drug repurposing, this data might consist of known drug-target interactions. The algorithm analyzes these interactions and learns the patterns that differentiate effective drugs from ineffective ones. Once trained, the algorithm can then predict how new compounds, including existing approved drugs, might interact with a specific antiviral target. This allows researchers to prioritize candidates with a higher likelihood of success [127].

5.1.2.2. Unsupervised learning. This type of learning focuses on identifying patterns in unlabeled data. In drug repurposing, the data could be vast datasets of chemical structures or patient information. The algorithm analyzes these datasets to uncover hidden relationships between existing drugs and potential antiviral targets. This can be particularly useful for identifying unexpected connections that might not be readily apparent through traditional methods [128].

5.1.3. *DL assisted virtual screening*

A subfield of ML, deep learning utilizes artificial neural networks with multiple layers to learn complex patterns from data. Deep learning models are becoming increasingly powerful for virtual screening, particularly when dealing with large and intricate datasets [129]. Deep neural networks can automatically learn complex features from vast datasets of chemical structures, protein-drug interactions, and other relevant data sources. This allows them to identify subtle patterns that might be missed by traditional ML algorithms. In the case of viral targets, DL can be particularly effective when dealing with images, such as protein structures or electron microscopy data. Deep convolutional neural networks (CNNs) excel at image recognition and can be used to analyze these images to predict how existing drugs might bind to a specific viral target. Deep learning thrives on large amounts of data. As the amount of data available for drug discovery continues to grow, DL algorithms become increasingly adept at identifying promising repurposing candidates with high accuracy. However, addressing challenges like computational cost, data dependence, and interpretability will be crucial for maximizing the potential of deep learning in this exciting field [130–133].

Recent studies have demonstrated the potential of AI-assisted virtual screening for drug repurposing. Masuda (2022) and Raza (2022) both utilized deep learning frameworks to identify repositioned drugs for specific medical applications, such as pancreatic cancer and Parkinson's disease [134,135]. Gupta (2021) developed a machine learning-enabled pipeline for large-scale virtual drug screening, which addressed the challenges of handling large compound libraries and distinguishing true positives from false positives [136]. These studies collectively highlight the role of AI in enhancing the efficiency and accuracy of virtual screening for drug repurposing.

5.1.4. *Automated AI-driven VS platform for repurposing*

The development of *in silico* platforms for drug repurposing, particularly those integrating molecular docking, machine learning, and deep learning, has significantly advanced the field [137]. These platforms (as shown in Table 2) leverage big data and computational tools to predict new indications for existing drugs, accelerating the drug discovery process [138].

5.2. *Natural language processing (NLP) for extracting insights from biomedical literature and databases*

In the relentless pursuit of new treatments for infectious diseases, researchers navigate a sea of information. Countless research papers, clinical trial data, and biomedical databases hold valuable insights, but

Table 2
AI-driven drug repurposing platform.

Platform Name	Description	References
ZairaChem https://github.com/ersilia-os/zaira-chem	Cloud-based platform utilizing AI and ML based tool for automated **(quantitative structure-activity relationship) QSAR modeling**.	[139,140]
DrugRep http://cao.labshare.cn/drugrep/	Web-based platform leveraging AI and machine learning for drug repurposing, target identification, and personalized medicine. Focuses on repurposing, offers target prediction, personalized medicine functionalities.	[141,142]
Insilico Medicine https://insilico.com/	AI-powered Comprehensive platform, strong focus on AI and deep learning, offers lead optimization tools.	[143]
BenevolentAI https://www.benevolent.com/	AI-driven drug discovery platform utilizing ML and network analysis for target identification and drug repurposing. Focuses on leveraging large datasets and network analysis, strong ethical considerations.	[144]
AtomNet (NVIDIA) https://developer.nvidia.com/sdk-manager	Open-source, highly customizable, supports various deep learning architectures for VS.	[145]
OpenEye Scientific https://www.eyesopen.com/	Software suite with various tools for computational drug discovery, including a module for AI-powered VS. Open-source and commercial options available, versatile platform with various functionalities beyond VS.	[146]
XtalPi https://www.xtalpi.com/	Cloud-based platform offering AI-powered drug discovery solutions, including virtual screening and lead optimization. User-friendly interface, cloud-based for easy access, offers lead optimization tools.	[147]
LabFolder https://labfolder.com/	Electronic lab notebook platform with integrated AI tools for virtual screening and data analysis. Integrates with existing workflows, user-friendly interface, data management capabilities.	[148]
CloudPharma https://cloudpharm.eu/	Cloud-based platform for drug discovery and repurposing, offers AI-powered virtual screening and lead optimization. Cloud-based access, user-friendly interface, offers lead optimization tools.	[149]
BIOSOLVEIT http://www.biosolveit.com/	Software platform with AI-powered tools for virtual screening, molecular docking, and drug design. Offers comprehensive functionalities beyond VS, user-friendly interface.	[150]

manually sifting through this vast ocean can be a daunting task. Natural Language Processing (NLP) emerges as a powerful lifeboat, aiding researchers in extracting crucial knowledge from this sea of text and accelerating the pace of drug discovery. Conducting thorough literature reviews is crucial for drug discovery, but the sheer volume of research papers can make this process time-consuming. NLP tools can automate much of the legwork, summarizing key findings and identifying relevant articles. This allows researchers to stay abreast of the latest advancements in the field and identify potential areas for collaboration. [151, 152].

NLP, a subfield of Artificial Intelligence (AI), empowers computers to understand and process human language. Imagine a computer program that can not only read scientific papers but also comprehend the complex concepts and relationships described within them. NLP algorithms achieve this by employing a range of techniques, including identifying and classifying relevant entities within text, such as genes, proteins, drugs, and diseases. Further to extract the **relationship** to uncover the connections between these entities, for instance, how a specific drug interacts with a particular protein within a pathogen. NLP algorithms helps in t**ext summarization,** condensing vast amounts of text into concise summaries, allowing researchers to quickly grasp the key findings of a research paper. These capabilities of NLP prove invaluable in the fight against infectious diseases. The sheer volume of published research in the field of infectious diseases is staggering. NLP algorithms can process vast libraries of scientific papers, identifying relevant articles that might hold clues to new drug targets or treatment strategies. By analyzing the text and identifying entities like genes and proteins associated with the disease of interest, NLP can highlight promising avenues of investigation that might have been overlooked by traditional search methods.

NLP can be used to analyze vast datasets of patient records and clinical trial data. By identifying patterns and relationships within this text data, NLP can assist researchers in formulating new hypotheses about potential drug targets or treatment approaches. This allows researchers to focus their efforts on the most promising avenues, streamlining the drug discovery process.

A significant portion of valuable biomedical information resides in unstructured formats, such as clinical notes, laboratory reports, and electronic health records. NLP algorithms can process this unstructured data, extracting key details like patient demographics, treatment history, and disease progression. This allows researchers to gain a more comprehensive understanding of the disease and identify potential links between patient characteristics and treatment outcomes [153,154].

6. AI Applications at different stages of drug repurposing

6.1. Identifying potential drug targets for infectious diseases

AI has emerged as a transformative force in drug repurposing, particularly in revolutionizing target identification and validation. This is achieved by leveraging its immense computational power to analyze vast and diverse datasets, such as genomics, proteomics, and clinical trial data. In the context of host-pathogen interactions, AI is being used to extract and learn from raw proteomics data, with unsupervised deep learning models showing promise in this area. Furthermore, AI is being applied to pathogen genomics, with emerging applications including genotyping whole genome sequences and identifying novel pathogens. These advancements are paving the way for a more holistic understanding of pathogens and the development of more effective drugs. Through the application of ML and DL algorithms, AI can unveil promising new targets with a higher degree of accuracy and efficiency compared to traditional methods. AI-powered target identification and validation utilize following approaches [155]:

I. Statistical Analysis: This method leverages omics data, such as genome-wide association studies (GWAS) and summary data-based Mendelian randomization (SMR), to identify potential disease-associated genes as candidate drug targets [156–158]. AI, in conjunction with human genetics, has the potential to revolutionize drug discovery by identifying pathogen-specific elements as ideal drug targets [159]. This is particularly significant in the design of drug delivery systems, where AI can accelerate drug discovery and improve treatment outcomes [160]. The integration of AI and big data from biological databases is also making a significant impact on the discovery of highly effective lead compounds [161]. Furthermore, AI is being increasingly applied in pathogen genomics, with emerging applications including genotyping whole genome sequences and identifying novel pathogens [162,163].

II. Network Analysis: Network-based approaches employ gene co-expression and miRNA-disease networks to reveal connections within pathways. These networks identify disease-associated gene sets and miRNA-disease associations, aiding in target identification. Knowledge graphs, representing entities, relationships, and semantic information, are also used for data analysis [164].

III. Machine Learning: Machine learning techniques, including classifiers (e.g., random forest, support vector machine, neural networks) and regression models, are employed to predict the likelihood of a gene being a viable drug target.Machine learning algorithms have shown promise in drug discovery and development, particularly in target identification and drug-target interaction prediction [165]. These algorithms leverage large datasets to predict bioactivities for targets and molecular properties, and to improve the accuracy of binding affinity prediction, thereby shortlisting potential drug targets for further investigation. They have also been applied to the prediction of drug-tissue relationships, which can accelerate the drug discovery process [166].

IV. Structural Analysis and Virtual Docking:

Recent advancements in AI, particularly in the field of protein structure analysis, have significantly enhanced drug discovery processes. Trisciuzzi (2022) and Stepniewska-Dziubinska (2020) both highlight the potential of machine learning models in identifying peptide-protein binding sites and druggable pockets on protein surfaces, respectively [167,168]. These models, when combined with virtual docking simulations, can effectively screen potential drug candidates and predict their binding to these sites, as demonstrated by Karelina (2023) [169]. However, the accuracy of these predictions is still a challenge, as discussed by Schauperl (2022), who emphasizes the need for further improvements in AI methods for protein structure prediction [170].

V. Leveraging Text Mining and Hidden Knowledge Extraction

The use of AI, particularly through Natural Language Processing (NLP), in mining biomedical literature and scientific databases has shown great potential in identifying hidden connections and suggesting novel drug targets. Raparthi (2023) and Perera (2020) both highlight the role of NLP in extracting information on known drug targets and disease mechanisms, with the latter specifically focusing on Named Entity Recognition and Relation Detection [171,172]. Mollaei (2022) further emphasizes the applicability of Machine Learning-based NLP in clinical notes databases, particularly in pathology reports [173]. Karaa (2021) presents a study on drug-disease relation extraction from biomedical literature using NLP and Machine Learning, achieving high accuracy and outperforming existing works [174]. These studies collectively underscore the significant impact of AI, particularly NLP, in revolutionizing drug discovery and biomedical research.

VI. Evolutionary Trajectory Prediction and Target Selection

AI and machine learning have been successfully applied to predict drug resistance in pathogens, such as Mycobacterium tuberculosis[175] and HIV-1 [176]. These methods have been shown to be effective in identifying resistant mutations and

predicting the emergence of resistance in bacterial infections [177]. Furthermore, AI has been utilized to accelerate antibiotic discovery, with a focus on open science best practices to enhance drug development [178]. These advancements in AI have the potential to revolutionize the field of drug development and treatment strategies, ensuring the long-term effectiveness of new treatments.

VII. Personalized Medicine and Target Tailoring

AI has shown great potential in analyzing individual patient data, including genetic makeup and specific pathogen strain, to identify potential drug targets for personalized treatment [179]. This approach has been particularly successful in predicting cancer patient responses to therapeutic drugs with high accuracy. The ability of AI to process large volumes of data quickly and accurately has also been highlighted, allowing for early detection of serious medical conditions and the development of more effective treatment plans [180]. However, the successful incorporation of AI into personalized treatment will require adjustments to healthcare infrastructure [181].

VIII. Dynamic Target Identification and Adaptive Strategies

AI has the potential to revolutionize the monitoring and management of infectious diseases and drug resistance. HealthMap, an AI-based system, can rapidly detect and disseminate information on emerging infectious diseases. Similarly, AI can aid in disease prediction and drug development, as demonstrated during the COVID-19 pandemic (Table 3). In the context of antimicrobial resistance, AI can improve diagnostic and treatment accuracy, reduce costs, and aid in the discovery of new antimicrobial drugs. Furthermore, AI can enhance the diagnosis, transmission understanding, treatment response, and resistance identification in infectious diseases, particularly in low-income countries [182–184].

By wielding these diverse AI techniques, researchers can embark on a more targeted approach to drug discovery. AI's ability to analyze vast datasets, predict interactions, and identify hidden connections empowers us to identify and exploit the vulnerabilities of infectious diseases, paving the way for the development of more effective and targeted therapies.

7. Challenges and considerations for AI-driven drug discovery

While AI has emerged as a powerful weapon in the fight against infectious diseases, its potential is not without limitations. The role of big data and AI in drug discovery is crucial, with AI models being used for virtual drug screening, de novo molecule design, and other processes. However, the quality and quantity of available data pose significant challenges, with incomplete or inaccurate data potentially leading to biased results [194]. Strategies to address this data gap include data curation efforts, collaboration for data sharing, and the development of AI models that can learn from smaller datasets [195].

The inner workings of some AI models, particularly complex deep learning algorithms, can be opaque. These models arrive at their conclusions through intricate calculations that are difficult for humans to understand. This lack of interpretability presents a challenge in drug discovery. Researchers need to understand how an AI model arrives at a specific drug target or repurposing suggestion to ensure its scientific validity and assess potential risks associated with the identified candidate. The development of more interpretable AI models and the use of explainable AI techniques are crucial steps towards overcoming this challenge. Explainable AI (XAI) techniques, such as SHAP and LIME, have been proposed to address this issue [196]. These methods aim to provide transparency and accountability in AI systems, which is crucial in sensitive areas like healthcare [197]. In the context of drug discovery, a taxonomy of XAI methods has been proposed, taking into account the specific issues related to the design of molecules [198]. Furthermore, the development of an interpretability-based model for AI algorithms in healthcare has been suggested, which could potentially be applied to drug discovery [199].

AI is not a replacement for traditional drug discovery methods; rather, it is a powerful tool that can augment and accelerate these existing processes. However, integrating AI seamlessly into the drug discovery pipeline can be challenging. Traditional methods rely heavily on human expertise and intuition, while AI operates on data and algorithms. Researchers need to establish effective communication channels between AI and human experts to ensure optimal utilization of both approaches. This collaboration can involve human scientists guiding AI model development with their knowledge of disease biology, and then using AI outputs to prioritize and refine further investigation into promising candidates. Kim (2020) provides a comprehensive review of AI-guided drug discovery, discussing its applications and data sources, while also addressing the remaining challenges and proposing future directions [200].

8. Conclusion & future directions

The revolutionary potential of AI, especially in its capacity to expedite drug repurposing, is propelling the fight against infectious diseases into an entirely novel phase. AI has advanced traditional drug research considerably, but it has a greater effect on discovering novel applications for already approved drugs. In order to combat infectious diseases

Table 3
Some examples of AI assisted drug repurposing against antiviral infectious diseases.

S. No.	Existing Antiviral	Original Target Virus	Potential Repurposed Target	Reasoning for Repurposing	AI Method Used	Reff
1.	Acyclovir	Herpes simplex virus (HSV)	Cytomegalovirus (CMV)	Proven efficacy against a related DNA virus	Similarity analysis & Network analysis	[185]
2.	Valacyclovir	Varicella-zoster virus (VZV)	Epstein-Barr virus (EBV)	Similar mechanisms of replication in herpesviruses	Structural analysis & Virtual docking	[186]
3.	Ribavirin	Hepatitis C virus (HCV)	Respiratory syncytial virus (RSV)	Broad-spectrum antiviral activity against RNA viruses	Machine learning for target prediction & Text mining of antiviral properties	[187]
4.	Oseltamivir (Tamiflu)	Influenza A and B viruses	Emerging coronaviruses (e.g., MERS-CoV)	Similar viral replication machinery	3D molecular modeling & Docking simulations	[188]
5.	Zanamivir (Relenza)	Influenza A and B viruses	Parainfluenza viruses	Targets a conserved viral protein for entry	Machine learning for pattern recognition in viral protein structures	[189]
6.	Tenofovir (DFG)	Hepatitis B virus (HBV)	Dengue virus	Inhibits viral reverse transcriptase enzyme	Sequence homology analysis & Machine learning for target prediction	[190]
7.	Emtricitabine (FTC)	HIV-1	Chikungunya virus	Targets viral RNA polymerase enzyme	Network analysis & Pathway enrichment analysis to identify shared mechanisms	[191]
8.	Sofosbuvir (Sovaldi)	Hepatitis C virus (HCV)	Flaviviruses (e.g., West Nile virus)	Inhibits a crucial viral enzyme for replication	Machine learning for target prediction based on antiviral properties	[192]
9.	Favipiravir (Avigan)	Influenza virus	Hand, foot, and mouth disease (HFMD)	Broad-spectrum antiviral activity against RNA viruses	Similarity analysis of viral replication mechanisms	[193]

more quickly and possibly more affordably, this repurposing strategy makes use of existing resources and knowledge.

The next generation of AI models in pathogen biology will move beyond genomic datasets, incorporating a multimodal approach. This will involve the integration of protein structures, metabolic pathways, and host-pathogen interaction networks, as well as high-resolution electron microscopy imagery. These models will be crucial in identifying vulnerabilities in pathogen biology for the development of novel therapeutics. AI algorithms will play a key role in analyzing the extensive data produced by Next Generation Sequencing (NGS) technologies [201]. The integration of NGS data with electronic medical records will enable the creation of predictive models for infectious diseases [202].

Advanced models, such as genome-scale metabolic modeling and deep generative models for graphs, are revolutionizing the analysis of biological networks within pathogens and their human hosts [203]. These models can identify crucial network nodes, which can be targeted with drugs to effectively cripple the pathogen, offering a more holistic and potentially more durable approach than targeting single proteins. The use of network modeling, including bipartite, multi-scale, and multiplex networks, is also proving effective in addressing the complexity of drug-disease systems [204]. The integration of AI in biological research, particularly in epidemiology, the study of host-pathogen interactions, and drug design, is further enhancing the potential of these advanced models.

This cutting-edge technology empowers AI not only to identify potential repurposing opportunities for existing drugs but also to virtually generate novel drug candidates with desirable properties. Through iterative simulations, AI can refine these candidates, potentially leading to the identification of existing drugs with optimized efficacy against the pathogen and minimal side effects. This approach has the potential to significantly accelerate drug repurposing efforts, leading to the development of more targeted and effective treatments for infectious diseases.

Human-AI collaboration and open data sharing are crucial for unlocking AI's potential in repurposing existing drugs for infectious diseases. AI excels at analyzing vast datasets to identify promising candidates, accelerating drug discovery and addressing emerging threats. Despite challenges, AI can significantly improve repurposing efficiency by overcoming data limitations and fostering collaboration with traditional methods. This approach empowers human ingenuity and paves the way for new treatments, ultimately safeguarding global health.

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Further reading

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