REVIEW

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ARTIFICIAL INTELLIGENCE-BASED APPROACHES FOR IMPROVING REGULATORY MARKET ACCESS – A CASE STUDY WITH A SCOPING REVIEW FOR REPURPOSING OF MEDICINAL PRODUCTS IN THE PANDEMIC

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Abstract. *Artificial Intelligence (AI) has already proven its impact on medical practice and science. With the increasing generation of healthcare data, AI applications offer enormous potential in clinical and regulatory decision-making, public health and administration, as well as in research and development. We conducted a scoping literature review to identify publications that discuss potential AI-based technologies for identifying repurposing-eligible medicines and for improving access to innovative therapies. More than half of the articles (18/26, 69%) were published in 2020 and 2021, during the peak of the COVID-19 pandemic, and focused on developing AI-based algorithms to accelerate screening for medicines that could be potentially repurposed. These algorithms proved to be a powerful tool to save resources and time during the pandemic, fulfil unmet medical needs and facilitate faster access to innovations. Most articles aimed to provide the scientific community and researchers with a strong rationale and/or support for the application of AI-based tools in the process of drug repurposing. However, more studies need to be performed, as currently, AI-based tools for drug repurposing need further verification.*

Key words: *AI, drug development, market access, drug repurposing*

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INTRODUCTION

The increasing availability of public data on diseases and drugs has enabled the use of artificial intelligence (AI) methodologies to revolutionize drug discovery. In this respect, AI already has a big and important impact on medical practice and science as AI tools develop more and more digital health solutions [1, 2].

Given the growing amount of data generated in healthcare, the potential of AI applications has a huge impact on research and development, and on clinical and regulatory decision-making [2, 3, 4]. AI is re-

garded as a potent instrument that can transform the healthcare industry. The application of AI-based tools to analyze big healthcare datasets can significantly contribute to and improve clinical decision-making, such as diagnoses, screenings, and treatment from one side and also optimizing treatment adherence [5, 6]. Advances in biomedical data on molecular and chemical characteristics of diseases and compounds provide new opportunities for drug discovery through computational and AI-based predictions [7, 8]. The research and development process can be improved by analyzing already approved compounds to discover new indications. This method helps to reduce several steps in the traditional drug development framework and provides opportunities for better resource allocation, optimization of costs and improved access to novel treatments [9, 10]. Machine learning, in silico and biomedical artificial intelligence, are expected to improve the process of research and development from all perspectives, including drug discovery, drug design, chemical image interpretation, etc [11]. AI tools have already been successfully implemented in drug discovery and drug design. AI-powered computational chemistry, for example, uses advanced algorithms and high-performance computing models to simulate molecular interactions, discover new drug candidates, and identify potential drug candidates more efficiently through virtual screening [12].

AI is a dynamic branch of informatics focused on creating systems that effectively mimic human intelligence traits such as reasoning, learning, and adaptation. By utilizing powerful automated algorithms, AI processes information in ways that parallel the human brain's ability to learn and solve problems. The field encompasses several key areas: natural language processing, which ensures machines can understand human language; data mining, which transforms unstructured data into structured formats; machine learning, which enables systems to acquire knowledge from diverse inputs; and deep learning, an advanced subset of machine learning that leverages neural networks and substantial computing power to analyze complex datasets. AI is revolutionizing the way we interact with technology and offers immense potential for the future [13, 14].

The increased availability of public disease and drug-related data has enhanced the use of AI in drug discovery and repurposing. The goal of drug repurposing is to identify new uses for existing medications, especially when few treatments are authorized or when current options have high morbidity and mortality risks and cannot address medical needs in exceptional circumstances like pandemics, for example. This process helps to create additional treatment options, contributing to improved regulatory access and a more sustainable healthcare system. According to the European Medicines Agency (EMA), repurposed drugs can significantly benefit public health, especially for conditions with limited effective treatments or during health crises like pandemics [15, 16].

In this respect, AI tools have the potential to impact regulatory access positively. Drug repurposing powered by AI and computational methodologies results in a shorter development phase and significantly speeds up the granting of marketing authorization (MA) [17].

During the COVID-19 pandemic, the urgent need for fast, accurate, and efficient drug discovery and regulatory access prompted us to identify artificial intelligence (AI)-based algorithms that could facilitate the rapid screening of authorized medicines. The current study aims to identify published articles that explore the potential role of AI-based technologies in identifying medicines eligible for further repurposing, thereby enhancing regulatory market access to innovative therapies that address unmet medical needs.

MATERIALS AND METHODS

Scoping review

Based on a scoping review of the literature, we searched the PubMed database using the following keywords: Artificial Intelligence (AI), computation, drug repurposing, pandemic, and articles published in the past 5 years in English. The Identified articles were first screened for title and abstract during the screening phase, and then those included in the scope were reviewed in full text. As inclusion criteria, we considered: (1) the presence of an abstract; (2) the English language; (3) publication in the past 5 years; and (4) focus on AI and repurposing, concerning treatment for unmet medical needs. Exclusion criteria were: (1) absence of abstract; (2) language other than English; (3) published beyond the last 5 years; and (4) not focusing on AI implementation for repurposing.

RESULTS

Out of 116 records, 26 (22%) met the eligibility criteria for the review. 18 of these articles (69%) were published in 2020 and 2021, during the peak of the COVID-19 pandemic. They discussed the latest AI-based algorithms for screening repurposable drugs, which can save time and resources, meet medical needs and facilitate innovation. The majority of the articles in question focus on providing scientific societies and researchers with strong evidence and

support for the utilization of AI-based tools for drug repurposing in the fight against COVID-19. About half of the articles provide a general overview of the current use of artificial intelligence for drug repurposing, with a focus on the main challenges and technical and methodological aspects of AI-based systems. The other half highlights the application of AI that can provide a better understanding of the structure of a virus, its enzymes, and the immune response, which is important for the development of effective treatments and vaccines. The medicines most frequently identified as potential candidates for repurposing are atazanavir, baricitinib, remdesivir, ritonavir, lopinavir, or a combination of these. They exert the highest inhibitory potential for all three above-mentioned proteins – Figure 1.

We summarized the results from the scoping review in Table 1.

With the scoping review, we aimed to analyze and systematize the potential role of AI-based tools for repurposing medicines to address unmet medical needs in the COVID-19 pandemic. The scoping review revealed that there is already a list of AI solutions available, particularly in the era of "Big data," and more are continuing to be developed. AI-based tools hold great promise for the development of healthcare solutions in the future. Additionally, they provide a more detailed overview of the current applications of AI-based tools in drug research and development, the lessons learned, and the challenges towards continual progress. The most analyzed AI-based methods include deep learning (DL), machine learning (ML), natural language processing (NLP), in silico methods, and neural network algorithms. Most of the reviewed articles concentrate on the promising applications of these AI algorithms in identifying existing or investigational medicines that may be suitable for repurposing in the treatment of SARS-CoV-2. This is particularly relevant in crises and for addressing unmet medical needs that require faster regulatory approval. The review also identifies existing medicines that were found through AI-based methods to be suitable for repurposing against the newly emerged SARS-CoV-2. The most frequently cited are summarized in Table 2.

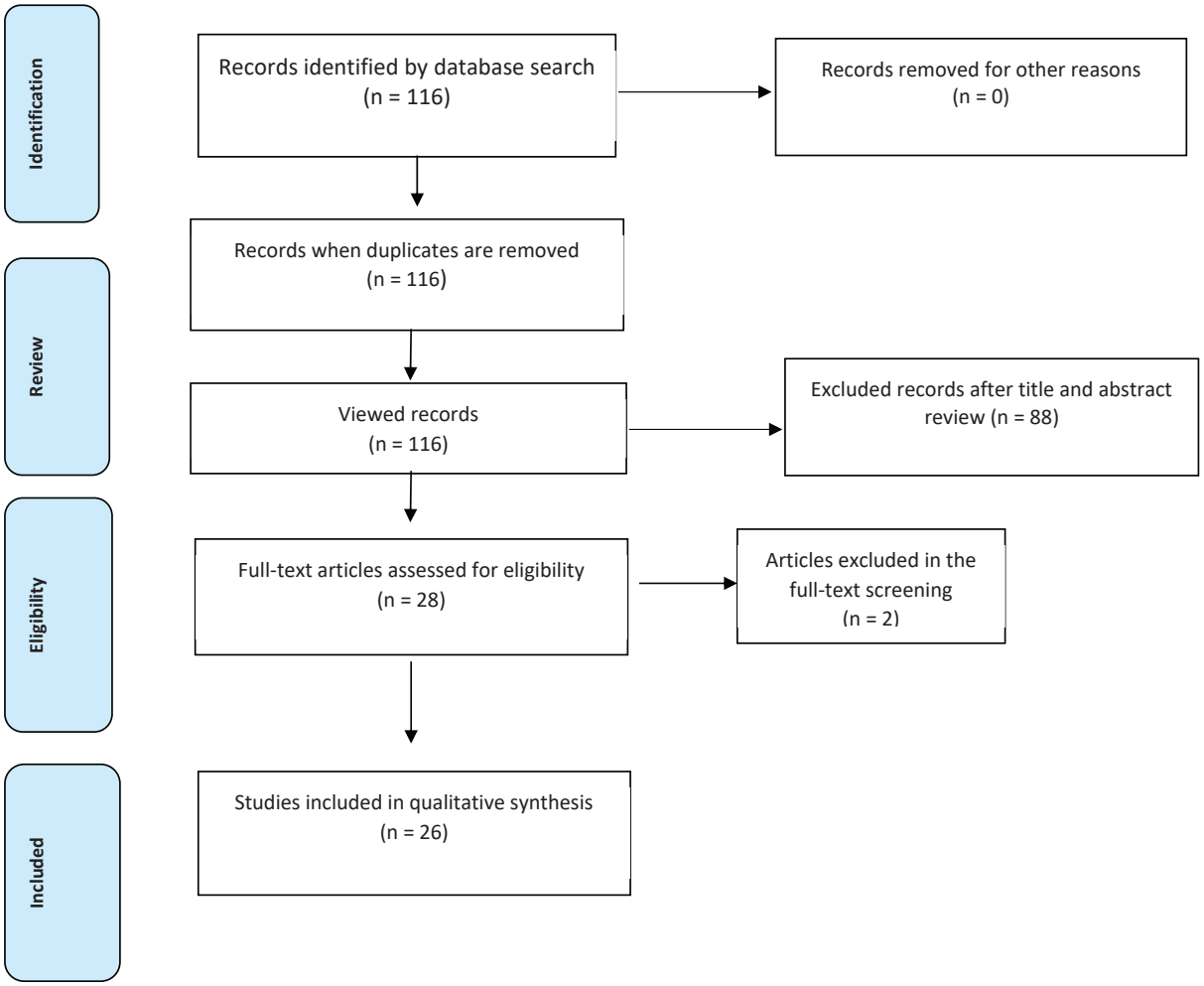

Fig. 1. PRISMA flow chart

Table 1. Scoping review summary

Research paper	Objective	AI method described	Result
Zhou Y, et al., 2020 [18].	To introduce guidance on the utilization of AI for drug repurposing, especially during a pandemic.	Deep learning, fully connected feedforward neural network (FNN), recurrent neural networks, machine learning	The review presents a compelling argument for utilizing AI-based assistive tools to repurpose drugs in human medicine. This strategy has proven to be a powerful solution in combating emerging diseases, including COVID-19. FNN was used to identify atazanavir, remdesivir, efavirenz, ritonavir, and dolutegravir for the potential treatment of SARS-CoV-2 infection;
Ke Yi-Ye et al., 2020 [19].	Application of computational drug-repurposing strategies regarding COVID-19.	Deep Neural Networks, AI-based self-learning platforms,	AI approach is an efficient way to help quickly identify potential drugs as antiviral therapeutics.
Mohanty S et al., 2020 [20].	To explore possible AI-based tools for identifying possible medicines eligible for repurposing in COVID-19	Deep learning	The potential benefit in combination with the pharmacology of AI-based tools facilitating drug repurposing
Gao K, et al., 2020 [21].	To develop validated machine learning models to screen 1553 FDA-approved drugs	Machine learning	The authors show that many existing drugs might be potentially potent for SARS-CoV-2 and provide a foundation for further experimental studies of COVID-19 drug repurposing through AI-based tools.
Beck B et al., 2020 [22].	To analyze the potential of deep learning models to identify potent drugs for SARS-CoV-2	MT-DTI Deep learning model	Deep learning models can potentially shorten the time needed to identify possible medicines for repurposing in the treatment of SARS-CoV-2.
Acharya A, et al., 2020 [23].	To analyze the possibilities of in silico drug discovery that uses enhanced sampling molecular dynamics (MD) and ensemble docking, powered by a supercomputer	Supercomputer-driven pipeline for in silico drug discovery using enhanced sampling molecular dynamics (MD) and ensemble docking.	The authors show that the application of AI-based tools could be useful in discussing preliminary results and planned improvements for drug repurposing and discovery.
Unni S, et al., 2020 [24].	To identify the potential role of in silico screening, docking, and molecular dynamics simulation for drug repurposing	In silico screening of VEGFR-2 inhibitors for potential repurposing against COVID-19	The authors show that in silico screening and AI could be used in the identification of potential drugs that inhibit spike protein of human coronavirus SARS-CoV-2 in the process of drug repurposing
Zeng X, et al., 2020 [25].	To introduce a network-based deep-learning methodology for the identification of medicines that could be repurposed for COVID-19	Network-based deep learning methods	Deep-learning methodologies could be used to prioritize existing drugs that could be potentially repurposed for COVID-19
Kaushik A, et al., 2020 [26].	To analyze AI-driven platforms for the identification of medicines that could be repurposed to treat COVID-19	AI-based databases for drug repurposing	AI might prove impactful in the identification of suitable medicines for repurposing. It is a cost-effective method, but still validation of efficacy with clinical trials is required
Asselah T, et al., 2021 [27].	To focus on the discovery of SARS-CoV-2, the most appropriate tools for diagnostics and the ongoing drug discovery.	Not mentioned	Artificial intelligence has identified a group of approved drugs that may inhibit clathrin-mediated endocytosis, thus reducing viral infection in cells and making them suitable for repurposing.
Motataqui M et al 2021 [28].	To overview the recent applications of machine learning techniques contributing to the prevention, diagnosis, monitoring, and treatment of coronavirus disease (SARS-CoV-2)	Machine learning approaches	AI-based tools have the potential to reduce the time to identify eligible medicines that could be repurposed to treat COVID-19 and receive faster marketing authorization

Research paper	Objective	AI method described	Result
Prasad K, et al 2021 [29].	To focus on the utilization of artificial intelligence tools in drug repurposing and structural biology for SARS-CoV-2	AI, deep learning and machine learning algorithms	The authors show that currently, most of the AI applications are used either to analyze the virus structure or to find potential medicines for drug repurposing.
Smith DP, et al 2021 [30].	To identify potential COVID-19 drugs, by AI-empowered biomedical knowledge	Natural language processing	The authors show that the combination of artificial intelligence tools and human expertise is promising for the identification of potential treatments for COVID-19.
Djokovic N, et al 2021 [31].	The aim is to analyze the potential role of an in silico drug repurposing approach for the identification of potential inhibitors of SARS-CoV-19.	In silico study integrating structure-based molecular modelling	In silico studies could be an appropriate way for selecting FDA-approved drugs for COVID-19 drug development.
Behera SK, et al, 2021 [32].	The aim is to identify the existing medicines with better potential antiviral activity, which will be further analyzed by other computational tools for repurposing, such as COVID-19 therapeutics.	In silico approach based on information of drugs and experimentally derived crystal structure of RBD of SARS-CoV-2 S protein.	Chalcone, grazoprevir, enzaplatovir, dolutegravir, daclatasvir, tideglusib, presatovir, remdesivir, and simeprevir are predicted to be potentially effective antiviral drugs against RBD and may have good therapeutic efficacy for COVID-19.
Rajput A, et al., 2021 [33].	The aim is to show that AI and ML-based approaches could be useful for the prediction of repurposed drugs for Coronaviruses	AI and machine learning	The application of AI and ML-based tools that identify medicines with high protein binding affinity is useful for drug repurposing for SARS-CoV-2 and other Coronaviruses.
Sibilio P et al 2021 [34].	Applying in silico-based tools for identifying medicines that could be potentially repurposed for COVID-19	In silico methods	In silico methods could be beneficial for the identification of approved or currently investigated medicines that could be eligible for repurposing
Haneczok J, et al 2021 [35].	To identify ML models that could perform a series of drug discovery screenings to facilitate repurposing	Machine learning tools	ML models could have a predictive role in the process of repurposing medicines for the treatment of SARS-CoV-2
El-Hddad S et al 2022 [36].	The aim is to analyze the possibilities in silico docking to find potential SARS-CoV-2 main protease inhibitors.	In silico molecular docking	In silico docking could be useful for the identification of medicines eligible for repurposing in COVID-19
Cong Y et al 2022 [37].	To examine the role of AI-based tools in identifying existing medications for repurposing to treat COVID-19.	Machine learning	AI and ML are transforming drug repurposing for infectious diseases by utilizing data analysis and prediction models. These technologies enable faster identification of effective treatments, addressing urgent medical needs during outbreaks and enhancing drug discovery efforts.
Ozdemir E et al. 2022 [38].	Focus on how AI impacts COVID-19 drug repurposing strategies and compare it to more traditional computational techniques used in drug repurposing.	Deep learning, machine learning and neural network models	According to the authors, AI in repurposing is a promising strategy, especially when three-dimensional structural data is learned and exploited. Furthermore, successful repurposing is not only a question of science but also an economic issue, which also forms an integral part of the drug development model
Liu Z et al 2022 [39].	Analyzing artificial intelligence (AI) for enhancing drug repurposing, using COVID-19 as a case study from a data science perspective.	Machine learning, deep learning	Accumulated biological data profiles enhance AI-driven drug repurposing for COVID-19 therapies. Selecting appropriate AI strategies is crucial for revealing concealed relationships between drugs, targets, and diseases.

Research paper	Objective	AI method described	Result
Hu F et al 2022 [40].	To analyze the potential of a multi-task deep learning model for the purpose of screening commercially available and effective inhibitors against SARS-CoV-2	Deep learning model	Pretrained deep learning models have the potential to identify already approved medicines that could be eligible for drug repurposing in COVID-19
Pires C 2023 [41].	To systematically assess published literature on the use of AI in drug development of medicines for COVID-19 with focus on finding eligible for repurposing medicines	Deep Neural Network algorithms, machine learning, AI-integrated mechanistic modeling platform, artificial neural networks, etc.	AI showed to be an efficient tool to quickly analyze large amounts of data, to identify drugs eligible for repurposing against COVID-19
MacMahon M et al., 2023 [42].	To introduce a systematic network-based drug repurposing methodology based on data for virus-human, human protein-protein and drug-protein interactome data.	In silico methods	To facilitate drug repurposing in clinical trials, we utilized an artificial neural network that incorporates information about the mechanism of action and therapeutic value to identify potential medicines.
Singh A 2024 [43].	The aim is to explore specific AI strategies like virtual screening, target identification, structure-based drug design and natural language processing to find medicines eligible for repurposing.	Virtual screening, structure-based design, machine learning, deep learning, AI-based platforms, natural language processing.	AI can enhance repurposing efficiency by addressing data limitations and encouraging collaboration with traditional methods.

Table 2. Most frequently cited sources

Medicine	Initial indication	The AI-based methodology used for the identification for of repurposing eligibility
Atazanavir	HIV	Neural networks using deep learning and machine learning algorithms
Baricitinib	Rheumatoid arthritis	Deep and machine learning algorithms
Bedaquiline	Tuberculosis	DL, deep neural network
Dolutegravir	HIV	Neural networks using deep learning and machine learning algorithms
Efavirenz	HIV	Neural networks using deep learning and machine learning algorithms
Grazoprevir	HCV	Machine learning
Lapatinib	Breast cancer	Machine learning
Lopinavir	HIV	In silico
Remdesivir	Ebola	Neural networks using deep learning and machine learning algorithms
Ritonavir	HIV	Neural networks using deep learning and machine learning algorithms
Telmisartan	Hypertension	In silico

Remdesivir and baricitinib were among the top-ranked medicines found repurposing-eligible through AI-based methods. However, only remdesivir received marketing authorization for the treatment of coronavirus disease 2019 (COVID-19) (Figure 2). Based on applied AI-based methods remdesivir has been identified as one of the leading and highly effective candidates for further research. It was proven to inhibit the replication of coronaviruses even before the emergence of SARS-CoV-2. Subsequently, using traditional simulated molecular docking experiments, research succeeded in predicting that remdesivir would have a high affinity to bind to SARS-CoV-2 RdR, thus providing evidence-based ground for shorter clinical investigation and repurposing. Remdesivir, an active nucleotide analog, inhibits the SARS-CoV-2 RdRp. When incorporated in the growing RNA, it extends the RNA by three nucleotides before stalling []. It is already proven that this stalling mechanism is specific to coronaviruses because the RdRp of the ebola virus can add five RNA nucleotides [].

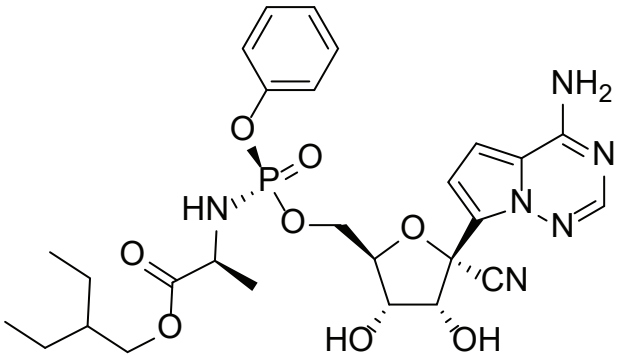

Fig. 2. Structure of Remdesivir

DISCUSSION

The COVID-19 pandemic has emphasized the urgency for rapid, precise, and efficient drug discovery pipelines. In times of crisis, the traditional way of drug discovery relying on in vitro high-throughput screening (HTS) appears to be time-consuming and costly. In this scenario, in silico drug repurposing (DR) has attracted the attention of the pharmaceutical industries and research communities worldwide because of its ability to predict 3D structures of targets, detect binding pockets/interaction hotspots of new drug targets, and screen the known drug candidates against new target structures [13]. Therefore, the utilization of advanced and efficient computational techniques and modern AI-powered algorithms for the prompt screening of repurposing-approved drugs, as well as natural products with established chemical and pharmacokinetic profiles, has proven to be a potent tool in the fight against COVID-19. This approach has helped save valuable resources and time [46].

The recovery trial was one of the first analyzing potential medicines for COVID-19 based on an AI-enabled drug discovery algorithm, with baricitinib being the first medicine repurposed for COVID-19 [22, 47]. Following the efforts in this area, AI-based approaches for drug repurposing proved as a successful solution. All this, combined with the established safety profile, has led to increased interest in remdesivir for treating SARS-CoV-2. Consequently, remdesivir has been the first medicine approved by the FDA and later by EMA for the treatment of COVID-19 [48]. Saving time and resources while addressing the high demand for an effective COVID-19 treatment worldwide would be beneficial for policy, regulatory and clinical decision-making [48].

In 2023, the World Health Organization (WHO) declared that COVID-19 is no longer a public health emergency [50].The COVID-19 pandemic, however, gave a boost to the implementation of AI-based technologies in the pharmaceutical industry for a variety of therapeutic indications [51].

Recent research shows that drug repurposing could also be applied to reverse molecular mechanisms of lung injury and severe respiratory failure in post-COVID-19 patients. These mechanisms are mainly based on inhibition of angiotensin-converting enzyme 2 (ACE2). He B et al proposed an AI-based drug repurposing analysis to find medicines and chemical compounds that could impact SARS-Cov-2-induced injury of the lungs [52].

In the most recent research Singh A explores the possibilities of AI-based drug repurposing in the treatment of infectious diseases, especially in emerging ones. By reviewing different medicines (i.e. daptomycin, azithromycin, sofosbuvir, darunavir, raltegravir, etc.) the author focuses on the benefits of AI-based tools for repurposing, such as optimization of time and better allocation of resources and prediction of possible side effects [53].

The main advantage of AI-based drug repurposing discussed in the reviewed articles is the significant reduction of cost and time – discovery and pre-clinical steps, which usually take around 5 years, can be shortened to several months. It is anticipated that clinical studies will follow a similar trend. This has already resulted in changes in the business strategies of the innovative pharmaceutical industry [54].

This scoping review of literature aimed to summarize all published data focusing on the role of artificial intelligence-based approaches in speeding up market access in times of crisis and unmet medical needs.

The example with remdesivir repurposing for COVID-19 shows that AI is an effective tool for improved market access that could find potential medicines and accelerate their clinical and economic impact through the mechanisms of adaptive pathways and horizon scanning.

There are certain restrictions on our survey. Using the COVID-19 pandemic as a case study, we sought to examine the most popular AI-based methods for locating medications that would be viable candidates for drug repurposing in the event of a pandemic. Only remdesivir, a medication used to treat SARS-CoV-2, has made it to the market thus far and has been granted marketing authorization under the EMA marketing authorization processes for early access. The emphasis in the remdesivir instance is on AI-based repurposing techniques that shorten clinical research duration and expedite marketing authorization. The cost-effectiveness and cost-saving features of using AI in drug discovery and repurposing, however, are the subject of numerous studies. Already, a lot of studies analyze the possible role of AI-based drug repurposing in other therapeutic areas like oncology, rare diseases and neurological diseases. Numerous studies have already examined the potential application of AI-based drug repurposing in different therapeutic domains, such as neurological disorders, uncommon diseases, and oncology [56, 57].

Another drawback of the current study is that it ignores the relative benefits of the conventional computational approaches for drug discovery that are now routinely employed in repurposing. Even though AI-based techniques have been shown to save money, time, and speed up discovery, they still need subsequent validation of the results and additional investi-

gation of the potent medicine. Traditional techniques still offer structured validation, mechanistic insights, and safety [58].

Further analysis is needed to analyze how AI-based repurposing will affect access to therapy for unmet medical needs, but undoubtedly the COVID-19 pandemic revealed its crucial role in medical research and the development of medicines in a more cost-effective and time-saving manner [59].

CONCLUSION

The scoping literature research assisted us in identifying a large number of AI solutions that are currently in development, particularly in the big data era. Remdesivir is the prime example of how AI-driven medication repurposing may expedite regulatory approvals and drastically reduce clinical trial durations.

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Author Contributions: *RT conducted the scoping review. MD and GP drafted the manuscript. MP, GP, and GS reviewed the paper. All authors have provided valuable contributions to the manuscript, read, and approved the final manuscript.*

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