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REVIEW

Smart science: How artificial intelligence is revolutionizing pharmaceutical medicine

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Artificial intelligence (AI) is a discipline within the field of computer science that encompasses the development and utilization of machines capable of emulating human behavior, particularly regarding the astute examination and interpretation of data. AI operates through the utilization of specialized algorithms, and it includes techniques such as deep (DL), and machine learning (ML), and natural language processing (NLP). As a result, AI has found its application in the study of pharmaceutical chemistry and healthcare. The AI models employed encompass a spectrum of methodologies, including unsupervised clustering techniques applied to drugs or patients to discern potential drug compounds or appropriate patient cohorts. Additionally, supervised ML methodologies are utilized to enhance the efficacy of therapeutic drug monitoring. Further, AI-aided prediction of the clinical outcomes of clinical trials can improve efficiency by prioritizing therapeutic intervention that are likely to succeed, hence benefiting the patient. AI may also help create personalized treatments by locating potential intervention targets and assessing their efficacy. Hence, this review provides insights into recent advances in the application of AI and different tools used in the field of pharmaceutical medicine.

Keywords: artificial intelligence, machine learning, deep learning, drug discovery, clinical trials, precision medicine

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Introduction

Over the last several decades, there has been a notable increase in the application of artificial intelligence (AI), specifically machine learning (ML), within the realm of healthcare applications [1]. The domain of pharmacology encompasses the utilization of AI and ML methodologies to effectively scrutinize diverse data sources. These sources encompass a wide spectrum, spanning from the intricate chemical composition of a pharmaceutical substance to the comprehensive clinical attributes of patients [1]. Furthermore, genomic data and disease characteristics also fall within the purview of analysis [1]. Molecular fingerprints and other quantitative structure–activity relationship (QSAR) descriptors have been developed for the quantitative and categorical characterization of pharmaceutical compounds [2]. Computational algorithms, particularly those pertaining to AI and parallel processing, have witnessed noteworthy progress in recent decades, thereby endowing computer-based inference engines with the capacity to attain increasingly profound deductions [2]. AI functions with sophisticated mathematical calculations and investigations and analyzes the data sets, overpowering human capabilities [3]. ML is a type of AI that can use complex computer programmes to evaluate vast amounts of data without any human intervention [3]. ML makes predictions by using algorithms to learn from acquired data, identify patterns, and then make predictions. Hence, ML can provide valuable support throughout multiple phases of drug discovery, encompassing pharmacological investigations like the discernment of lead compounds [4]. Thus, this review provides an overview of the current developments and AI technologies used in drug discovery and design, clinical trials, precision medicine and pharmacovigilance. It is crucial for the researchers from various fields who collaborate with pharmaceutical specialists to have the knowledge on the current AI tools used in pharmaceutical medicine.

Discovery of Drug and designing

AI involvement in the development of a newer drug or any pharmaceutical product can be from the bench to the bedside due to its potential in planning rational drug design. As the pharmaceutical industry is expanding quickly, the absence of cutting-edge technology is impeding the development of drugs and making it a costly and time-consuming procedure [5]. The process of discovery is a multifaceted and labor-intensive endeavor encompassing the identification of prospective therapeutic targets, the synthesis and evaluation of novel chemical entities, and the subsequent introduction of a newly developed pharmaceutical product into the marketplace [6]. AI has the capability to manage the drug development process through its stages due to its potential to handle a vast quantity of data obtained from various sources. Further, it can be applied in identification of newer drug targets and to predict the potential toxicity and side effects of drugs in research [7]. The conventional drug discovery process depends on an array of computational and experimental data for the identification of the novel drug targets, their efficacy and

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toxicity [7]. AI algorithms can also have the potential to analyze genomic and proteomic data thereby helping in the identification of the potential drug targets for various disease categories such as cancer, cardiovascular disease, and neurodegenerative disorders, etc [5]. The medication for idiopathic pulmonary fibrosis was recently found by the in-silico Medicine company through the application of AI. Phase I trials of the therapy have shown promising results (https://clinicaltrials.gov/ct2/show/NCT05154240). The process of drug discovery and design involves various processes that utilizes AI quite effectively [8].

Drug interactions Predictions and target binding affinity

Drug-target interaction phenomena are the complex interactions that happen between chemicals and drug targets in the body that are physiologically active. To ascertain a drug's therapeutic efficacy, it is critical to predict the drug-target interaction [9]. The anticipation of the interaction between a pharmaceutical agent and a receptor or protein is of utmost importance in comprehending its therapeutic potency and efficiency [5,10]. The therapeutic action of the drug will be hampered by a lack of interaction between the drug molecules and targeted proteins [5]. Though *in vitro* and *in vivo* experiments can determine the bioactivity, these experiments are time-consuming and expensive [8]. Also, the interaction between an unintended protein or receptor and the drug molecule may result in toxicity. The bioactivity of the drug or the drug-target binding affinity (DTBA) is crucial for the intended drug response; hence, it is an important phase in drug discovery [5,8]. Since the development of high-throughput methods, sequencing technology, and computer-aided drug design, a wide range of proteins have been successfully sequenced and many compounds have been synthesized [11]. Through a comprehensive review of pertinent literature and the synthesis of accumulated expertise, pertinent information has been systematically collated and diverse databases have been established [11]. Thus, one of the innovative approaches documented for forecasting drug-protein interactions involves conducting an initial screening of established interaction data sourced from various databases such as DrugBank, UniProt database, PubChem database, KEGG database, etc [12]. The majority of the data contained within these databases is readily accessible to the public and can be obtained without charge [11]. This availability of data serves as a solid basis for addressing challenges in the prediction of drug-target interaction through the implementation of ML methodologies [13]. Researchers may get datasets from databases that include a variety of information based on their specific requirements [11]. However, the current understanding of drug-target interactions, derived from wet-lab experiments, is characterized by limited scope and depth. This disparity between the unknown and known drug-target pairs has sparked a significant curiosity in the pursuit of effective methodologies for predicting drug-target interactions (DTI) [13].

The newer computational methodologies involved in DTI predictions include the utilization of a docking simulation, a ligand-based approach, text mining methods, chemo-genomic approach, network-based methods, and ML/DL- based methods [13,14]. Drug target binding affinity (DTBA) prediction methodology and DTI prediction techniques are the two main computational methods used in drug target prediction [9]. AI- based methods can overcome the limitations posed by experimental methods. It can determine the drug's bioactivity either by recognising the features or similarities between the drug and the target. Feature-based interactions identify the target's and drug's chemical moieties to calculate the feature vectors. In contrast, the similarity between the drug and the target is considered in similarity-based interaction, where it is presumed that similar drugs would interact with the same targets [15]. DL and ML approaches have been used; DL performs better than ML as it applies network-based methods rather than 3D protein structure as in ML. A variety of ML and DL techniques, including KronRLS, SimBoost, DeepDTA, and PADME, have been used to ascertain DTBA. ML-based approaches such as Kronecker-regularized least squares (KronRLS), assess how similar drugs and protein molecules are to determine DTBA. Similarly, SimBoost takes into account both feature-based and similarity-based interactions and predicts DTBA using regression trees [15]. DL methods such as DeepDTA was the first DL model developed to predict binding affinity between drugs and their targets. It works with the principle of modelling compound 1D representations and protein sequences with convolutional neural networks (CNNs), which achieved better concordance index (CI) performance as compared to KronRLS77 and SimBoost [16]. Further, a newer DL-based prediction model wideDTA was utilized using chemical and biological word sequence information. It uses four different word- or text-based sources, namely the protein domains and motifs, ligand SMILES, protein sequence, and maximum common substructure words. It outperformed DeepDTA on the KIBA dataset with statistical significance [17]. This demonstrates that WideDTA, a word-based sequence representation method, is a viable substitute for DeepDTA, a character-based sequence representation technique used in DL models to predict the target binding affinity [17].

Prediction of Protein structure

The overexpression of various proteins has a significant association with the pathogenesis of diseases**.** Consequently, in order to design the drug molecule with the intention of selectively targeting the disease, it is essential to precisely predict the structural makeup of the target protein. [5,10]. By applying its predictive powers to ascertain the three-di-

mensional protein structure, AI has the capacity to make a significant contribution to structure-based drug discovery. This is especially useful because it allows us to design compounds that align with the target protein site's chemical environment. Thus, AI helps predict how a compound will affect the target protein and take safety precautions before the compound is synthesized or produced [10].

A group called CASP (Critical Assessment of Structure Prediction) tries to find ways to figure out how to use information from amino acid sequences to figure out the three-dimensional structure of proteins [18]. The main goal of the critical evaluation of protein structure prediction (CASP) is to push forward a technological approach that can figure out and put together a protein's three-dimensional structure using only its sequences. CASP has always been primarily concerned with computing the structures of individual proteins and domains [18]. The achievement can be primarily accomplished through two approaches based on the absence or presence of a pre-existing template structure. Template-free models and template-based models are the two approaches identified. Among these, template-based modelling is more reliable and can be easily employed. The existing protein structure is used as a foundation and, hence, is more advanced and can be used even by researchers with limited experience [19–21]. Alternatively, template-free modelling techniques can be used to construct the structure in the absence of a pre-existing template for the structure of the protein. Template-free modelling commonly involves the *de-novo* folding method. The de novo folding approach, in particular, endeavors to construct three-dimensional structures from the ground up, leveraging the principles of physics. Using a precise energy function is key to making it work because it lets you look specifically for conformations with the lowest energy state. This energy function also helps tell the difference between native-like structures and decoys, which adds to the overall success of the de novo folding method[19–21].

AlphaFold is a novel computational methodology developed for the prediction of protein structures by analyzing the covariation between physically adjacent homologous sequences [22]. AlphaFold was developed by DeepMind, a startup of Google, in 2018 and was the best performer in the 13th Edition of Critical Assessment of Protein Structure Prediction (CASP) [23]. The first version of AlphaFold can predict the protein structure by training a neural network with just the protein sequence using DL. It has a convolutional neural network that uses the Protein Data Bank (PDB) structures as training data to predict distance between pairs of residues and multiple sequence alignment (MSA) to predict the probability of distribution of backbone torsion angles, thus creating the distograms [22]. A simple gradient descent algorithm can be used to optimize the resulting potential and produce a protein's three-dimensional structure [22]. But the limitation lies with atomic accuracy when no homogenous protein structure is available. This was overcome with AlphaFold2, which can foresee the structure of protein with atomic accuracy. It adopts multilevel alignments using the DL algorithm, incorporating both physical and biological information about the protein of interest [24]. It outperformed experimental structures in the 14th edition of CASP [24].

New techniques have recently been released to address some of AlphaFold2's drawbacks, including its incapacity to forecast novel structures and its need for lengthy processing time. Natural language processing (NLP) is a new technique based on protein language models [23]. ESMfold uses a protein language-based model using DL trained with 12 billion biological parameters. Compared to AlphaFold2, it presented lower TM-scores but better accuracy and lower prediction time as compared to AlphaFold2 for structures with high confidence [25].

Prediction of drug toxicity

Toxicity refers to the degree to which a certain chemical or combination of chemicals might damage internal organs or systems. Prediction of drug toxicity is a crucial stage during drug development that helps researchers to recognize safety issues and develop and design drug that have fewer toxic effects [26]. The drug must meet the safety and effectiveness requirements established by regulatory bodies like the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) in the United States [17]. Support vector machines (SVM), k-nearest neighbor (k-NN), decision trees (DT), and random forests (RF) are ML techniques that are frequently employed in toxicity prediction [26]. Alternatively, deep neural networks (DNN), recurrent neural networks (RNN), convolutional neural networks (CNN), graph convolutional neural networks (GCNN), graph neural networks (GNN), and graph attention networks (GAT) are among the most sophisticated techniques used in DL. DeepTox is an AI tool based on three-layered DNN used to predict the toxicity of drugs, and is reported to outperform naive Bayes, support vector machines, and random forests [27]. Its pipeline involves cleaning data and quality control, 2D and 3D chemical descriptors with DNN-based model, evaluation of the model, and ensemble prediction [27].

Clinical trials (CT) of drugs

The utilization of AI is increasingly acknowledged as a viable approach for achieving sustainable and optimized drug development. Consequently, there is ongoing discourse and practical exploration regarding the various applications of AI in clinical trials [28]. There are software programs that can be utilized to predict the toxicity of drugs by leveraging target information. Effective toxicity predictions possess the potential to supplant conventional pre-clinical approaches, such as in vitro and animal models [29].

Forecasting patient outcomes in CT

Predicting clinical outcomes is the most important part of the rise of precision medicine. It also helps shape trial design by reducing the statistical changes seen in larger groups. Artificial intelligence (AI) could be used to simulate data in order to find better statistical outcome measures [30]. A new research suggests that shorter trial durations might arise from using an AI system to forecast participant outcomes and identify those who are more likely to advance quickly and reach end-points early [31]. AI can analyze the electronic medical records and predict the patient drop outs, hence additional education can be rendered to the patient for longer participation [32]. ML algorithms can also predict the clinical outcome in terms of mortality by analyzing the large databases and correlating the drug-related predictive biomarkers and survival data from interventional trials done in various tumors [33].

Predicting the clinical trial success

During the early phases of clinical trial AI can be used to predict the bioactivity, protein target interaction, and toxicity of drug, etc. Multi-instance learning (MI) algorithms can predict the prognosis of the disease and hence can analyze the full trail success [28]. The capacity to anticipate clinical trial results ahead of time may enhance the efficacy of pharmaceutical research and development (R&D), provide effective funding channels, and create novel financial instruments to support biotechnology research [34]. AI tools like PrOCTOR[35] can predict the likelihood of CT failure due to drug toxicity. The ensemble is trained mainly on a dataset with simple drug descriptors, drug target interaction and expression levels of launched drugs to predict the side effects due to toxicity[35]. Similarly, inClinico CTOP models predicted the outcome of Phase II trials by analyzing the target choice and efficacy of the drug [35]. The fact that inClinico was able to forecast the effectiveness of LNP023, a first-in-class factor B inhibitor, in treating the uncommon disease paroxysmal nocturnal hemoglobinuria suggests that the model may be helpful even in the absence of any prior knowledge regarding the clinical significance of the drug's mode of action [35]. Implementation of AI technology in randomized controlled trial (RCT) can also be in terms of creating an "AI arm" along with the study and control arm so that the potential of the CT can be validated irrespective of its primary outcome [36].

Recruitment of patients for CT

Among the many hurdles in conducting the CT, patient recruitment remains the critical challenge. The challenges in recruiting are brought on by complicated protocols, lack of awareness, psychological anxiety about taking part, or lack of desire to participate. The complex inclusion and exclusion criteria further makes the recruitment of right patient difficult [37]. By making information available to a wider range of possible trial participants via open CT platforms, AI might improve patient selection [37]. The database called clinicaltrials.gov has compiled the eligibility criteria for over 350,000 trials [28].

Several AI tools have been developed to manage the various phases of CT. AiCure is an innovative AI-driven platform that monitors the patient's adherence to instructions and prescriptions[38]. The efficacy of meticulously crafted protocols is contingent upon the adherence of participants to the prescribed instructions. An inadvertent oversight, such as an omission in pill consumption, may exert an adverse influence on the outcomes of the study. This tool facilitates the utilization of smartphones by clinical trial participants to capture video recordings of their medication administration. Utilizing computer vision algorithms, the AiCure software has the capability to anticipate the ingestion of substances by an individual. This tool additionally possesses the capability to assess the facial expression of an individual, thereby monitoring their reaction to therapeutic interventions and thereby facilitating the advancement of therapeutic modalities [38].

Trials.ai [38] is another innovative startup that leverages AI to facilitate the development of clinical trial protocols. Utilizing natural language processing and various AI methodologies, this system effectively employs advanced techniques for data analysis and interpretation. The software facilitates the collection and analysis of data from various sources, including journals, drug labels, and private hospital data, through established connections. The aforementioned data are utilized for the purpose of examining proposed trials, the stringency of eligibility criteria, and their impact on various aspects of clinical trial outcomes, such as cost, participant retention, and so forth [38].

Pharmacovigilance

Pharmacovigilance (PV) is a practice that primarily attempts to limit the introduction of medications with unfavorable side effects in the general population. It deals with the systematic gathering, analysis, and reporting of data on the safety of medications, including prescription drugs, over-the-counter treatments, and herbal supplements. Following the thalidomide disaster, adverse drug reactions (ADRs) were systematically analyzed, coordinated, and regulated [39]. The major drawbacks of traditional pharmacovigilance are the large data volume, complexity, regulatory demands, and manual data processing. The AI tools can evaluate real-world data and effectively increase drug safety monitoring [39]. AI predicts and detects adverse drug events (ADEs) using ML and natural language processing (NLP). The increasing number of medication-related problems makes identification using varied data sources such as electronic health records and pharmacovigilance databases crucial [40]. The most significant obstacle that humans face when evaluating and analyzing massive amounts of data is time constraints [41]. The DL algorithms model and databases are publicly available that can detect and identify the unreported

adverse effects of drugs. One of the suggested models that achieved state-of-the-art performance in ADE detection and extraction was the DL-based technique with Bidirectional Encoder Representations from Transformers (BERT) models that reviewed 10,000 datasets from WebMD and Drugs.com. It demonstrated the potential of DL in healthcare tasks and information extraction, addressing the issues that doctors experience while prescribing of medications [42].

The WHO-collaborated centre for worldwide drug monitoring, the Uppsala Monitoring Centre (UMC), was founded in Uppsala, Sweden, in 1978. On behalf of the WHO, it runs various databases such as VigiFlow, VigiBase, and VigiLyze. VigiAccess is an open access database that is available and open to the public. PV also offers other techniques, such as VigiGrade, VigiMatch, and VigiRank, for the examination of case reports [43]. In India, MAHs (marketing authorization holder) is required to report the ICSR (Individual Case Safety Report) of any marketed drug to both the National Coordination Centre for Pharmacovigilance Programme of India (NCC-PvPI) and the Central Drugs Standards Control Organisation (CDSCO) (Pharmacovigilance Gsr 287 € dated 8-03-2016, REGD.D.L.-33004/99). Another, VigiFlow software, is used to transmit these reports to WHO-UMC, Sweden [44].

The pharmacovigilance Programme of India utilized AI firstly for inserting both structured and unstructured content regarding the case in the form of XML, DOCX, images and PDFs. The extraction of information from ICSR is carried out using NLP and ML in a way that complies with regulations. Secondly, AI is used for decision-making, as ICSR is often of low quality. AI may be crucial for performing correlations, medication classifiers, unlisted or individual random adverse events, etc [39]. MOdified NARanjo Causality Scale for ICSRs (MONARCSi), a causality decision support tool, was developed based on the Naranjo causality score. It exhibited high specificity (93%) and moderate sensitivity (65%) with high positive and negative predictive values (79 and 88%, respectively) and an *F*1 score of 71%, suggesting it to be potentially useful tool in assisting the PV safety professionals in assessing the drug-event causality in a more consistent manner [45].

Precision medicine

Personalised medicine, an evolving discipline within the realm of healthcare, endeavours to customise therapeutic regimens to the individualised requirements of patients, taking into consideration their genomic and medical information [46]. The goal of precision medicine is to identify the underlying cause of disease in an individual patient. Finding the underlying cause of a patient's illness can then be used to shed light on the biology and pathogenesis of the condition, ultimately assisting in the development of treatments that target the illness's root cause [47].

Precision medicine stresses how important it is to use both molecular profiling and well-known clinical indexes together to make personalised diagnostic, therapeutic, and prognostic methods for each patient group. The move towards a deeper understanding of disease based on molecular biology will inevitably lead to a new, more accurate taxonomy that incorporates new molecular knowledge [48].

Personalised medicine possesses the inherent capacity to revolutionise the therapeutic landscape, as it empowers healthcare providers to formulate customised treatment regimens that are meticulously tailored to the unique characteristics of each patient [46]. The remarkable progress in precision medicine is evident through the realisation of concrete advantages, including the timely identification of ailments and the increasing prevalence of tailored therapeutic interventions within the realm of healthcare [49]. Numerous data collection and analytics technologies contribute to the effectiveness of precision medicine in customizing care. Scientists have an unmatched opportunity to derive new phenotypes from real clinical and biomarker data because of the uncommon convergence of high-throughput genotyping and widely used electronic health records (EHRs) [50]. The influence of precision medicine on healthcare today, particularly in terms of genotype-guided treatment, is a subject that has been extensively researched and analysed [46].

Personalised medicine can be integrated with the translational workflow through various phases of drug trials. AI-based methods can be used to screen drug data and determine which of the many medications and compounds currently on the market are active against a particular therapeutic target and consistent with the molecular pathology that has been identified in a given patient [51]. It has also been shown that AI-based research may provide more accurate information on the potential effects of drugs and other chemicals on different structural and functional aspects of a cell [52]. Some of the chemistry-focused websites with extensive databases, such as DeepChem (https://deepchem.io/about.html), may be especially used to detect the properties of drugs and chemicals. If an existing medication or molecule is unable to effectively regulate a target, developing a new drug would be an option. AI has been utilised to develop new structures that might be useful for developing more effective treatments, such as medications or mechanical devices, and to help choose appropriate chemical syntheses [53]. In contrast to the conventional or "officinal" manufacture of medicines, "magistral" production is the recent advance in the production of therapies in real-time, depending on the specific needs of the patient [54]. One may envision using robotics technology driven by AI to facilitate the accurate and efficient manufacturing of precision medicines [55]. Given that the first 3D-printed medicine was approved by the US FDA in 2015, 3D printing of medicines may also make it easier to produce remedies in almost real-time [56].

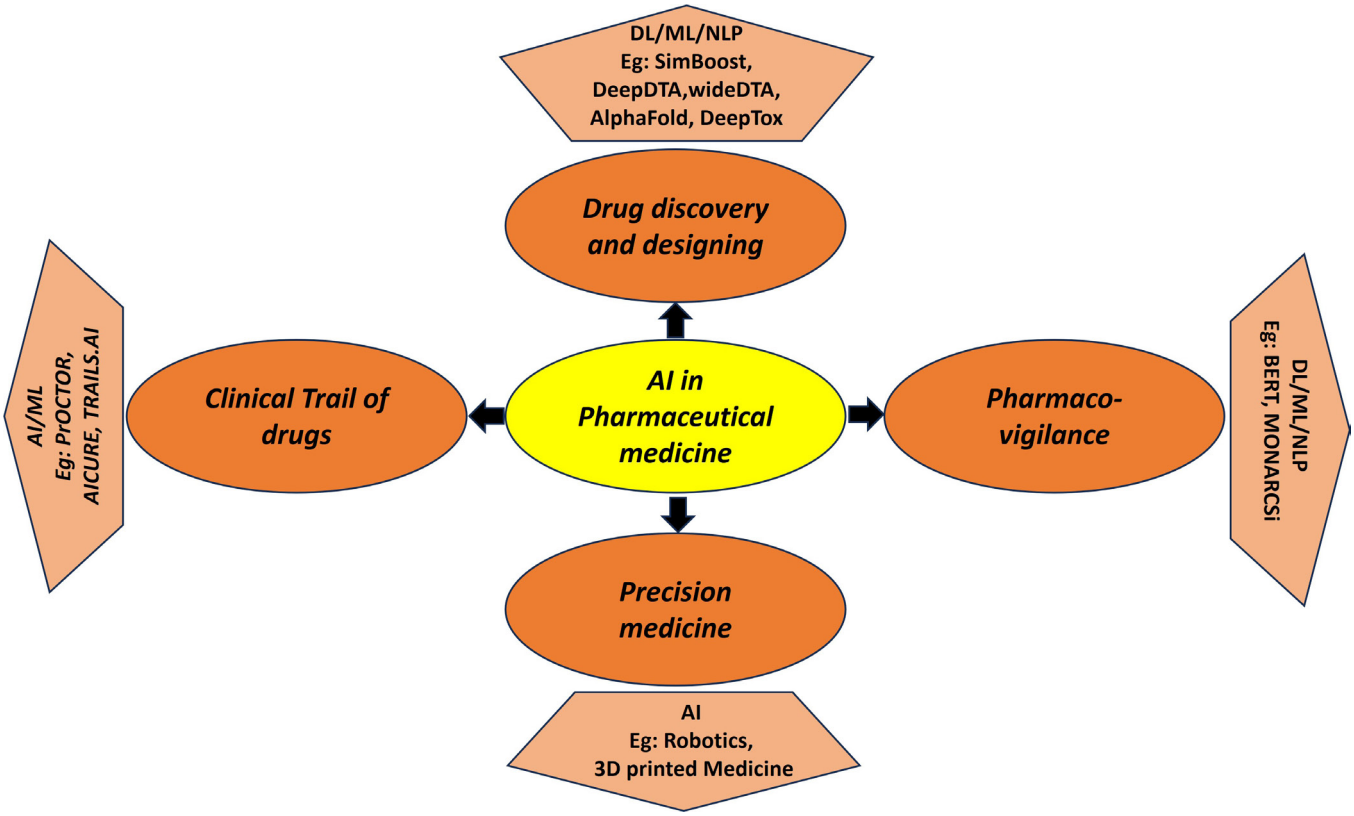

Fig 1. Application and tools of Artificial Intelligence (AI) used in Pharmaceutical Medicine.

Drawbacks of AI

There are various barriers to properly deploying any type of information technology in healthcare. The barriers include those related to data collection, technological advancement, therapeutic use, and ethical and societal issues. The first issue is that large datasets are needed in order for ML and DL models to accurately predict or identify a variety of jobs. The industries with easy access to large datasets have seen the biggest advancements in ML's capacity to generate more precise and accurate algorithms, according to Lubarsky *et al.* [57]. Information accessibility is a major issue for the healthcare sector. According to Baowaly *et al.,* AI-based systems lead to issues with data security and privacy. Health records are a common target for hackers during data breaches because they contain sensitive and important data. Therefore, protecting patient privacy in medical records is crucial [58]. S. Ji *et al.*, state the possibility of users mistaking the artificial systems for real people and granting permission for more covert data collection, posing serious privacy issues [57].

The "black box" issue is a prevalent critique aimed at AI systems. Frequently, DL algorithms are unable to offer compelling justifications for the predictions they make. There is no legal means for the system to provide an explanation if the recommendations are incorrect. It also complicates the process by which scientists interpret the relationship between the data and their predictions. Moreover, people may completely lose faith in the medical system as a result of the "black box"[59].

Since the time of its inception, ethical questions regarding AI have been raised. Accountability, not the data security and privacy issues raised earlier, is the real problem. The current system demands that when poor decisions are made, especially in the medical field, someone be held accountable because of the severity of the consequences. Since the doctor was not involved in the creation or oversight of the algorithm, it may be difficult to hold them accountable. On the other hand, it can seem unconnected to the therapeutic context that the developer is at fault [60]. People have always worried that employment in healthcare could be eliminated by AI. Because they fear being replaced, some people are hostile towards and sceptical of AI-based projects [60].

Most of the research on AI's application has been conducted in a business context, so data on how it affects patient outcomes is lacking. Up until now, the majority of healthcare AI research has been carried out in non-clinical environments. It could be challenging to generalize study findings as a result. The gold standard in medicine, randomized controlled trials, cannot prove the advantages of AI in healthcare [61].

Conclusion

The advent of AI has resulted in a multitude of advantageous outcomes within the realm of pharmaceutical medicine. It has demonstrated significant promise across multiple domains, encompassing drug exploration, clinical experimentation, and patient management. Utilising AI-

powered tools facilitates the identification of novel drug targets and expedites the drug development trajectory, simultaneously mitigating financial and time constraints. These innovative applications have resulted in enhanced efficacy and diminished expenses in the realm of pharmaceutical development. Furthermore, the integration of AI holds the potential to contribute to patient stratification and the customization of pharmaceutical interventions. A patient-centric approach and the integration of AI with the RCTs can help in predicting and validating the clinical outcome, thereby conducting successful and cost-effective trials. This can result in enhanced therapeutic efficacy and improved overall health outcomes.

Author's contribution

SBV: Conceptualization, Writing review & editing, final draft.
SS: Writing review & editing, final draft
MS: Revision, editing, final draft
SSS: Conceptualization, Writing original draft, final draft.

Conflict of interest

None to declare.

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