Artificial Intelligence for Computer-Aided Drug Discovery

Authors
Aditya Kate[1], Ekkita Seth[1], Ananya Singh[1], Chandrashekhar Mahadeo Chakole[2, 3], Meenakshi Kanwar Chauhan[3], Ravi Kant Singh[4], Shrirang Maddalwar[1], Mohit Mishra[1]

Affiliations
1 Amity Institute of Biotechnology, Amity University, Chhattisgarh, India
2 Bajiraoji Karanjekar college of Pharmacy, Sakoli, Dist-Bhandara, India
3 NDDS Research Lab, Delhi Institute of Pharmaceutical Sciences and Research, DPSR-University, New Delhi
4 Amity Institute of Biotechnology, Amity University Uttar Pradesh, Noida, India

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Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

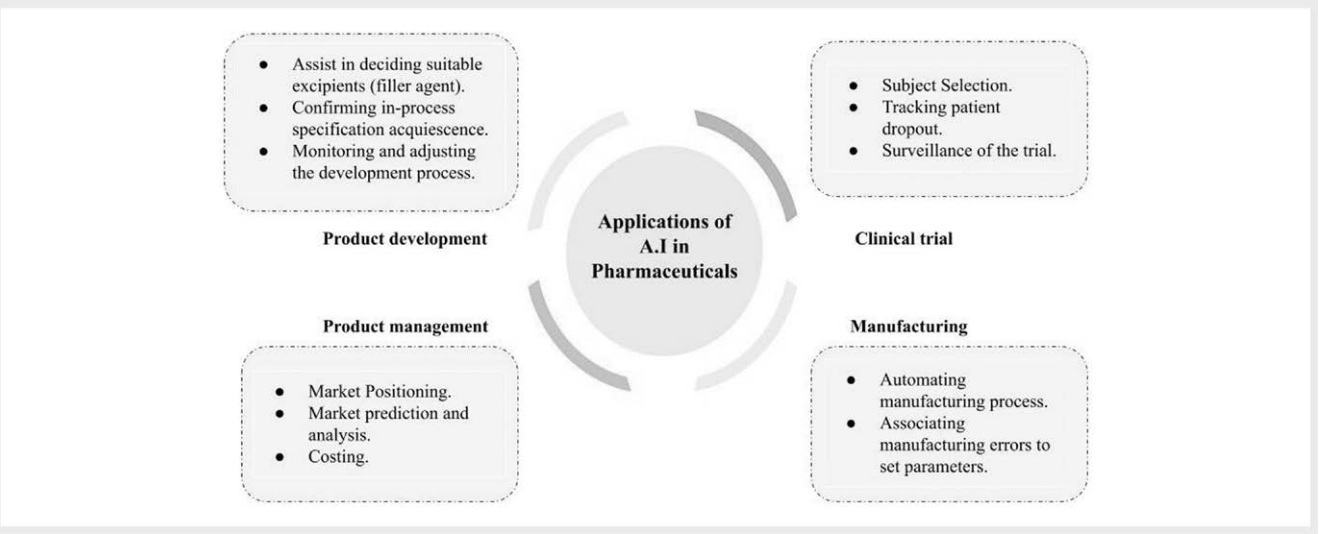
Correspondence
Dr. Mohit Mishra
Amity Institute of Biotechnology, Amity University, Chhattisgarh
493225 Raipur
India
Tel.: 917972238969,
msmishra002@gmail.com

ABSTRACT

The continuous implementation of Artificial Intelligence (AI) in multiple scientific domains and the rapid advancement in computer software and hardware, along with other parameters, have rapidly fuelled this development. The technology can contribute effectively in solving many challenges and constraints in the traditional development of the drug. Traditionally, large-scale chemical libraries are screened to find one promising medicine. In recent years, more reasonable structure-based drug design approaches have avoided the first screening phases while still requiring chemists to design, synthesize, and test a wide range of compounds to produce possible novel medications. The process of turning a promising chemical into a medicinal candidate can be expensive and time-consuming. Additionally, a new medication candidate may still fail in clinical trials even after demonstrating promise in laboratory research. In fact, less than 10 % of medication candidates that undergo Phase I trials really reach the market. As a consequence, the unmatched data processing power of AI systems may expedite and enhance the drug development process in four different ways: by opening up links to novel biological systems, superior or distinctive chemistry, greater success rates, and faster and less expensive innovation trials. Since these technologies may be used to address a variety of discovery scenarios and biological targets, it is essential to comprehend and distinguish between use cases. As a result, we have emphasized how AI may be used in a variety of areas of the pharmaceutical sciences, including in-depth opportunities for drug research and development.

Introduction

Drug discovery and development is a crucial aspect of the medical field that contributes significantly to healthcare [1]. However, traditional drug development methods are challenging, costly, and time-consuming, taking around 12 years and costing approximately 3 billion US dollars [2]. The drug discovery process typically involves four steps: i) Target validation involves determining the specific illness and selecting a target associated with it, which requires genetic target evaluation, genomic and proteomic research, and bioinformatics predictions. ii) Molecules from molecular libraries are screened using virtual screening, high-throughput screening, and combinatorial chemistry to identify lead compounds. QSAR/QSPR investigations and in-silico work are performed in an iterative cycle to enhance drug candidate efficiency for cellular functional testing. iii) Pre-clinical studies include pharmacokinetic research and toxicity experiments in animal models to gather essential



▶ **Fig. 1** Application of AI in pharmaceuticals.

data on drug candidate viability, safety, and biological effectiveness. iv) Clinical trials involve administering the drug candidate to a target population in four stages with increasing numbers of patients. The focus is on observing side effects, drug dosage, and effectiveness [2–4]. Once the drug candidate's effectiveness and safety have been established, it is submitted for regulatory approval to bodies like the FDA for commercialization [5]. This entire process is lengthy, expensive, and requires a large team. To address these issues, researchers and scientists in the pharmaceutical industry are increasingly turning to AI to streamline the process, reduce overall costs, and improve efficiency. AI-based techniques are being used in various stages of the process, including real-time image-based cell sorting, quantum mechanism, complex property calculations, in-silico organic synthesis, creating assays, forecasting the three-dimensional structures of targeted proteins, etc. [6–8]. These procedures can be standardized and optimized with the application of Deep Learning, AI, and Machine Learning to considerably accelerate R&D drug development processes. The most commonly used methods in drug discovery can be classified into seven categories: supervised learning, unsupervised learning, semi-supervised learning, active learning, reinforcement learning, transfer learning, and multitask learning [6–10].

This review focuses on the implications of AI in the pharmaceutical industry, its applications, challenges, futuristic scope, along with the necessary tools and algorithms to reduce the efforts of humans in drug discovery by increasing success rates, lowering the cost of drug development, and reducing overall process time.

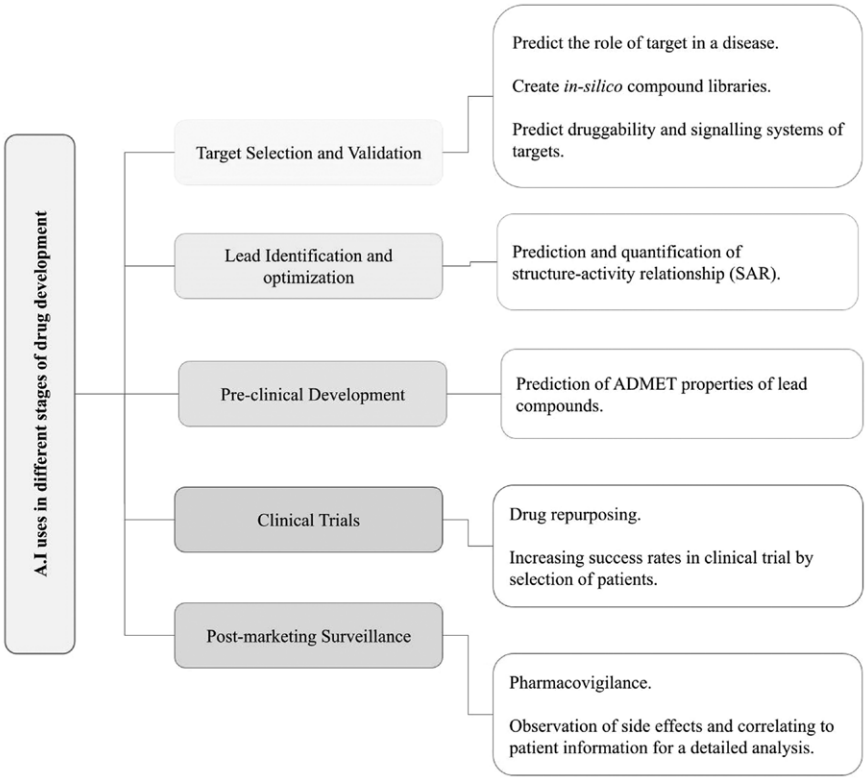
AI in Pharmaceutical Industry

AI has recently had its application in several sectors in society, particularly the pharmaceutical industry as a number one beneficiary. The pharmaceutical industry has seen a dramatic increase in the digitization of data in recent years. However, collecting, researching, and using such knowledge to address complex clinical problems becomes more difficult with digitization [11]. As a result, using AI is essential since it can process massive amounts of data quickly and without any problems. Outside of this, AI has also been used for pharmaceutical product management, pharmaceutical product development, clinical trial design and observation/tracking, and pharmaceutical manufacturing (▶ **Fig. 1**).

AI utilizes methods that can read and learn from feeding data and provide feedback in order to make autonomous judgments to reach towards specific set objectives. Its applications in the pharmaceutical business are continually being carried out. AI includes a variety of methodological areas, including knowledge representation, problem-solving, and a fundamental machine learning model (ML). In machine learning, algorithms are used to find patterns in sets of data that have been further classified. The Artificial Neural Network (ANN) depicts the cluster of interconnected and systematic components with computational capacity which imitate how electrical impulses are transmitted in the human brain by using “perceptons” that are symmetrical to actual human neurons. ANNs come in a variety of forms, including MLP networks, RNNs, and CNNs, which may be trained using supervised or unsupervised methods [12]. The IBM Watson supercomputer is one of the technologies created using AI (IBM, New York, USA). It evaluates a patient's medical data, compares it to a sizable database, and recommends cancer therapy. The IBM system may be used for quick illness diagnosis, as evidenced by its capacity to identify breast cancer in about 60 seconds [10].

AI in Drug Discovery

The estimation of protein secondary structure with the help of sequential information was one of the first applications of AI techniques in the fields of chemistry and molecular biology. Using AI in drug development is not new, particularly when modeling structure-activity connections. The idea of using a “descriptor set” and experimental values dates back to Hammett's [13] revolutionary method to connect reaction rates and equilibrium constants of benzene derivatives as well as Hansch's computer-assisted identification and measurement of physicochemical features of bioactive molecules, who is known as the “father of QSAR.” [14, 15]. Following that, numerous researchers and scientists globally have widely used a variety of AI techniques to tackle the main problem



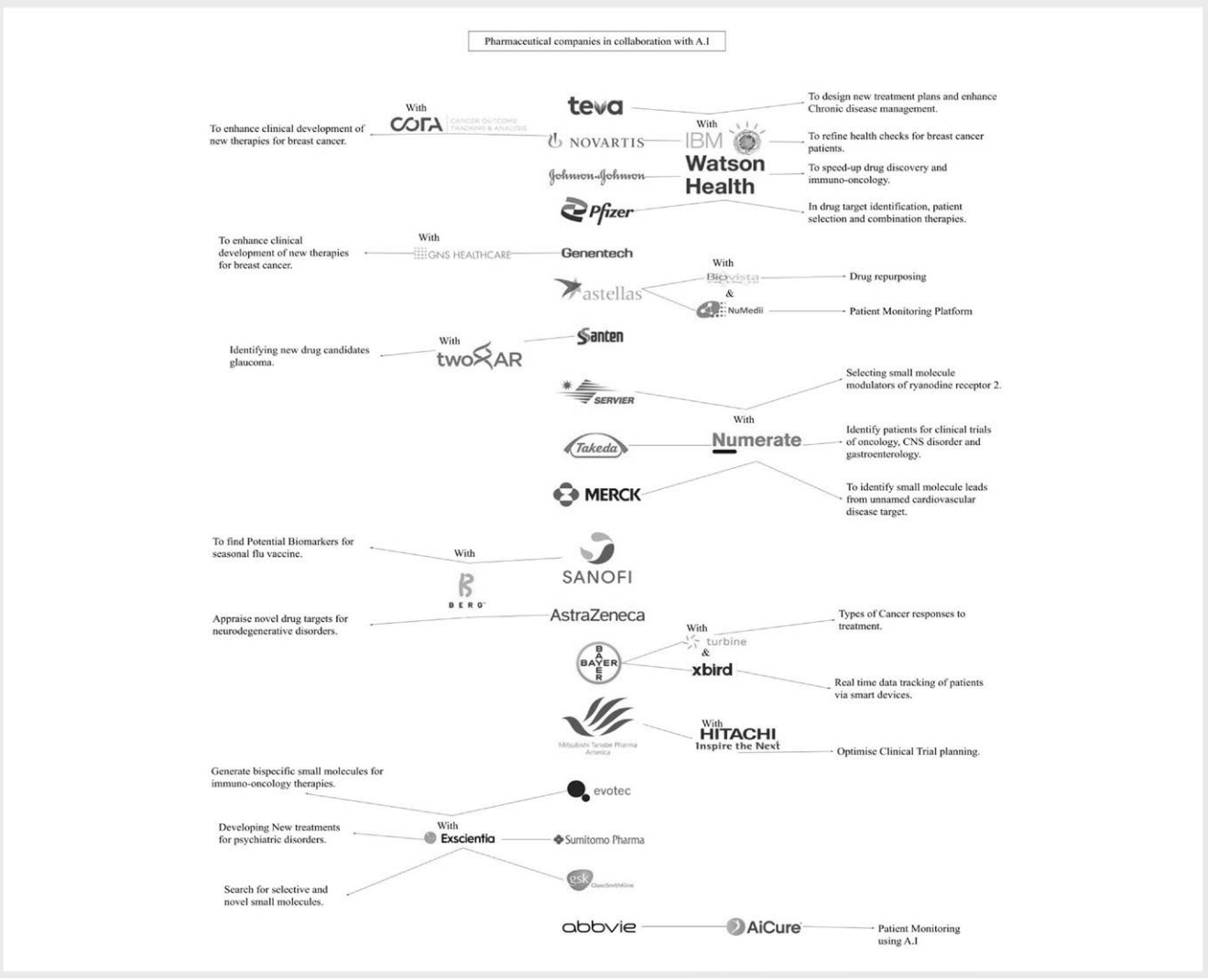
▶ **Fig. 2** Application of AI in several stages of drug development.

of assessing and forecasting chemical effects on the body. One well-known approach is pattern recognition, which primarily emphasizes the clarification and study of common arrangements across biochemical systems. Earlier versions of neural network implementation, such as the Perceptron, were released and showed promise as a way to address these issues. Around 1990, neural networks started having an impression on the pharmaceutical sector due to their usefulness as pattern recognition engines. A prominent instance from this period is a publication from 1992 in which Weinstein et al. described the mechanism of action of cancer medication by using neural networks [16]. These integrated learning and decision-making models, which include all aspects of AI, including the ability to 1) solve problems, 2) learn from experience, and 3) adapt to unforeseen circumstances, provide the earliest examples of the proactive learning algorithm. AI is used for different purposes throughout the drug discovery process. ▶ **Fig. 2** represents a quick outline of AI applications in several stages of drug development.

To bridge the gap between serendipity-based and rational drug production, a range of machine learning algorithms, including the support vector machine (SVM) and random forest (RF), were created and applied in drug discovery. Garbage in, garbage out (GIGO) is a problem that affects all such models. The most persistent problem is figuring out which chemical properties should be merged to get the data that would produce the most accurate predictions. Deep learning has been established as a better-defined notion since roughly 2010, and more effective methods have been sought to support this progress. Since deep learning techniques can examine and forecast intricate connections between chemical representations and observations (such as toxicity and bioactivity), there is a good chance that these tools will result in more insightful and generalized findings. With numerous significant partnerships with AI businesses, pharmaceutical corporations that had previously watched from the sidelines are now participating. The advances achieved by this collaboration are a huge advancement in the field in terms of improvement in the efficiency of clinical trials, betterment of healthcare, enhancement in personalized medicine, and more [17]. ▶ **Fig. 3** signifies the various pharmaceutical companies collaborating with AI technologies for the drug development process.

AI-based Drug Discovery Algorithm

AI is an algorithm-based system that mimics human intellect using sophisticated tools and networks. Numerous articles highlight the potential benefits of AI for the whole drug research and development process. One such report focuses on big data and machine learning and claims that it will significantly influence the overall healthcare system [18]. AI has many benefits, one of which is that it can handle massive amounts of data with improved automation [19]. AI holds the potential to minimize the inaccuracies and risks associated with traditional drug development techniques, and to reduce time, R&D costs, and attrition rates while minimizing bias and human interference. The goal of machine learning, an applica-



▶ **Fig. 3** Collaboration between several pharmaceutical corporations and AI for medication development.

tion of AI, is to develop computer programs that further implement a self-learning approach on the basis of data collected and adapt accordingly without being specifically designed [20].

In machine learning (ML), algorithms are used to find an interlinking connection in a cluster of data that has been categorized. Mostly there are three types of machine learning techniques, supervised, unsupervised, and reinforcement learning, illustrated in ▶ **Fig. 4**.

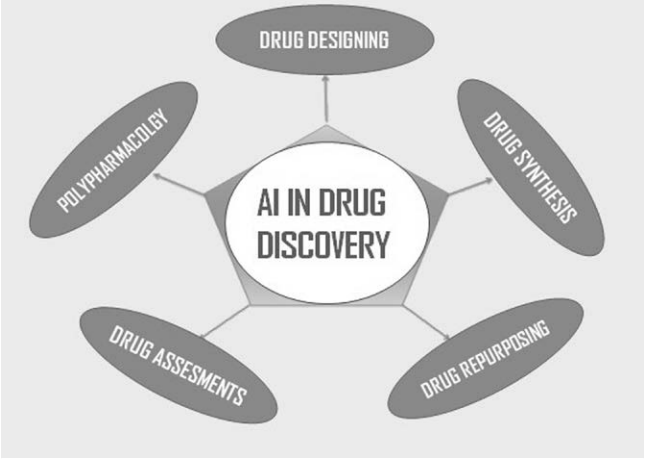
Using data from input and output sources, classification and regression techniques are employed to create prediction models during the supervision of learning. Under subgroup categorization, supervised ML's output includes disease diagnosis; under subgroup regression, it includes pharmacological efficacy and ADMET prediction [21]. Unsupervised learning utilizes feature-finding and clustering techniques by categorizing and analysing data based only on input data [22].

Deep learning (DL), a branch of machine learning, uses "perceptons," a group of highly interconnected computer components that resemble biological human neurons and simulate the transmission of electrical impulses in the brain, to adapt to and comprehend the enormous amounts of experimental data [9, 23]. Each node in an ANN accepts a unique response and collectively works for problem-solving by converting it into valuable output using algorithms [24]. Convolutional neural networks (CNNs), recurrent neural networks (RNNs), and multilayer perceptron (MLP) networks are three examples of ANN types that may be trained either supervised or unsupervised [25]. Through the use of feature-finding techniques and grouping, unsupervised machine learning can result in outcomes such as the identification of disease targets and illness subtypes [26].

The fundamental drivers of reinforcement learning are making judgments in a particular context and acting on those decisions to enhance efficiency. One of the outcomes of this type of machine learning is de novo drug design for decision-making, which may be achieved by utilizing modelling and quantum chemistry, together with theoretical methodologies for implementation.

convolutional neural networks (CNNs) are clusters of complex schemes having links that are identified by their topology and are utilized for a variety of tasks, including the processing of images and videos, the modelling of biological systems, the analysis of

▶ **Fig. 4** Illustrations of AI techniques may be used to produce new drugs in various fields.



▶ **Fig. 5** The importance of AI in the Drug Discovery cycle.

brain reasoning, pattern recognition, and signal processing [27]. RNNs, like Boltzmann constants and Hopfield networks, are confined networks with the ability to learn and store data [28]. As a general-purpose pattern classifier, the MLP network may be created using supervised training procedures that only function in one direction [29]. Due to the versatility in the construction of neural networks, such as CNNs, recurrent neural networks (RNNs), and fully connected feed-forward networks, deep learning (DL) varies markedly from other fields of AI [30]. Machine Learning is applied at each level of the drug production cycle, with a few examples including identifying prognostic biomarkers, validating targets, and analyzing digital pathology data in clinical trials [9].

Current scenario of AI in Drug Discovery & Development

Machine learning currently has numerous applications, specifically in the healthcare industry. Among these categories are the detection and diagnosis of illnesses. One such instance of AI in disease diagnosis is in the field of depression, where Oxford's P1vital Predicting Response to Depression Treatment (PReDicT) project wherein the predictive analysis is taken into consideration to assist in diagnosis and cure with an ultimate objective to develop it and make it commercially available as emotion meter [17].

There are several other sectors where AI is being widely incorporated for ease, automation and better results, more than 800 cancer treatments and vaccines are now being tested, according to a 2015 study by Pharmaceutical Research and Manufacturers of America, which could advance the science of genetically based personalized medicine by producing new compounds that could develop into new treatments, uncovering or repurposing current drugs that might be more effective when used alone or in combination [17].

AI is also being used to provide customized treatments for more accurate disease assessments in clinical trial research, radiology and radiotherapy; In order to enhance radiation treatments, University College London Hospital (UCLH) and Google's DeepMind Health are working together to develop machine learning algorithms that can discriminate between malignant and healthy tissues [31].

Additionally, AI is being used to create smart electronic health records and one such example of it is a MATLAB-based Artificial Neural Network for the identification of handwritten characters. The endeavor to integrate ML/AI into the next generation of intelligent electronic health records is being led by the MIT Clinical Machine Learning Group to assist with tasks including diagnostics, clinical judgments, and individualized therapy recommendations. In addition, ML and AI technologies are being used to track and predict disease outbreaks using data from satellites, web-based data, real-time data acquired from social media, and various other sources. Support vector machines and artificial neural networks have predicted malaria outbreaks with the help of collecting various data such as temperature, monthly rainfall, the total number of impacted cases, and other relevant data [31, 32].

At different levels of developing the drug, a variety of AI tools and techniques have been employed, including drug targeting, designing, identification, validation, poly-pharmacology, chemical synthesis, drug repurposing, and drug screening of which importance of AI in drug discovery cycle is represented in the ▶ **Fig. 5** [10, 17] as well as to improve the selection of patients for clinical trials and increase the effectiveness of R&D [33, 34].

Identification of compounds

Finding novel, efficient therapies is typically the most challenging aspect of medication development. This is due to the enormous

▶ **Table 1** Various AI tools with applications in drug development cycle

S. No.	AI Tools	Description	Reference
1	AlphaFold	Predict the 3D structure of a protein given its amino acid sequence.	[48]
2	DeepTox	Predict the toxicity of chemical compounds	[49]
3	PrOCTOR	Predict the stability of protein mutations via expert-curated training sets	[50]
4	SPIDER	Predict the RNA secondary structure, which is crucial for understanding RNA function and designing RNA-based therapeutics	[51]
5	Read-across structure activity relationships (RASAR)	Accurate prediction of toxicity using read-across structural activity relationships and graph convolutional neural networks	[52]
6	AiCure	It utilizes computer vision and machine learning algorithms to improve medication adherence in clinical trials and patient care	[53]
7	KronRLS, SimBoost, DeepDTA	Determining Drug Target Binding Affinity (DTBA)	[54–56]
8	TargeTox	Predicts the toxicity of chemical compounds using a combination of machine learning algorithms and expert-curated toxicological data	[57]
9	ChemMapper & similarity ensemble approach	Predicts the potential targets of small molecule compounds based on their chemical structure	[58–59]
10	WideDTA and DeepAffinity	Predict the binding affinity of small molecule compounds and protein targets	[54, 60]
11	PADME	Predict the metabolic fate of drugs and other small molecules	[61]
12	MANTRA and PREDICT	AI-based tool that predicts the toxicity of compounds by analyzing their chemical structures and known toxicological data	[62–63]
13	PubChem	The database contains a vast amount of data on chemical structures, properties, and bioactivities, including information on drugs and their targets, chemical safety, and toxicity.	[64]
14	DeepVS	It uses deep learning algorithms to predict the binding affinity of small molecules to target proteins	[65]
15	XenoSite, FAME and SMARTCyp	Computational tools used in drug development to predict the metabolism of xenobiotics (foreign compounds) by cytochrome P450 (CYP) enzymes	[66–68]

chemical space, which is projected to contain 1060 molecules [35]. Predictive model software and machine learning techniques allow to identify the drug-specific targets and their linkage with the correspondence while providing the required safety and effectiveness [17]. A range of *in-silico* profile selection strategies can be employed using small-molecule modulator probes or knowledge of their structural biology, including virtual ligands or structure-based design approaches. Drug design techniques such as Coulomb matrices and molecular fingerprinting also consider physical, chemical and toxicological properties when selecting compounds [36].

Additionally, chemical descriptors such as SMILES strings, potential energy scales, electron densities around molecules, and 3D atomic coordinates are included in the drug design logarithm [37]. A quantitative structure-property relationship (QSPR) approach, called the Estimation Program Interface (EPI) Suite, was developed to determine the six physicochemical properties of environmental chemicals provided by the Environmental Protection Agency (EPA) [38]. AI-based systems can calculate a binding affinity on the basis of the characteristics between the medication and the target molecule. The target's and the drug's chemical moieties are identified through feature-based interactions to produce the feature vectors [39]. Since the traditional approach to de novo drug design suffers from a number of drawbacks, such as difficult bioactivity prediction and complicated synthesis pathways, the latter approach is being replaced by new DL methodologies [40]. The reinforced adversarial neural computer (RANC), a Deep Neural Networks (DNN) architecture, was examined in a recent work for the de novo creation of small chemical molecules [41].

Predicting physiochemical characteristics

Predicting physiochemical characteristics has also been made easier by AI, a vast number of chemicals, and prospective drug candidates can be possibly shown with future possibilities by using algorithms specifically based on the Quantitative Structure-Activity Relationship (QSAR) [5]. Several other AI-based techniques also incorporate features such as Machine Learning to predict the outcome of the physicochemical features by training the algorithms with the considerable amount of data sets generated during compound optimization[38]. Lipophilicity and solubility of various compounds were predicted using neural networks based on ALGOPS software and ADMET predictors [42], and DL methods were applied to predict the solubility of compounds such as neural networks (CVNN) [43]. ANN-based models, graph kernels, and kernel ridge-based models have been used many times to evaluate the acid dissociation constants of substances [38]. The computational platform DeepDDI was created for a deeper knowledge of drug-drug interactions and associated mechanisms, as well as for the prediction of alternative pharmaceuticals with desired therapeutic utilization and no negative effects on health [44].

AI and synthesis of drug

The most crucial and challenging task following the identification of molecules is synthesizing the selected molecules, which is traditionally accomplished through the process of retrosynthesis [28]. The Synthia program, formerly known as Chematica, can suggest potential synthesising pathways for eight medicinally important targets by encoding a series of rules into the computer. This pro-

gram has demonstrated efficiency concerning raising produce and cutting expenditures. Additionally, it's reported to be useful in the synthesis of substances that have not previously been produced and be able to offer alternative synthetic methods for trademarked items [45]. De novo drug synthesis was examined using the Reinforcement Learning for Structural Evolution method, which employs generative and predictive DNNs to create novel molecules [46]. ▶ **Table 1** represents multiple AI tools that describe various approaches in the process of the drug development cycle [47].

Conclusion & Future Perspective

AI has a promising approach in many domains, and it is efficiently integrated into the initial stages of drug discovery techniques like target acquisition, lead identification, lead optimization, pharmacokinetic characteristics, and toxicity evaluation, coupled with clinical testing structures, are used to find new drugs and enhance overall performance at a lower cost. However, the challenges faced despite the initial high success rate of AI applications are yet to be overcome. In particular, gathering adequate, high-quality, and highly exact data continues to be a significant obstacle when using AI-assisted technology to solve problems. During the machine learning approach, the problem statement is highly reliable in other fields, but in drug discovery, the data is distributed along with minimal information, unlike in other fields where there is a sufficient amount of data to build models and predict the valuable output. As a result, the process of AI-assisted drug development needs data evolution apart from the reliable approach, which will significantly improve the quality and availability of the data accessible for subsequent implementation. To overcome complications with the well-known "garbage-in, garbage-out" concept, improving the efficacy and dependability of molecular representations is another significant problem. The complex molecular representations may be adjusted to meet any requirement, including task specificity, and the AI system can automatically learn specific properties from raw data interpretation. The aforementioned issues are possibly attainable due to increasing time and cost considerations along with technological advancement. In a time when traditional development experiments are expensive and have a high probability of failure for the development of potential chemically synthesized drugs, the AI-assisted drug discovery and development approach will significantly improve the cost efficiency and risk-reward profile while offering the treatments wherein the traditional approach neglected to provide in the process. In conclusion, the application of AI approaches possesses the capability to efficiently improve some pipelines, allowing researchers to concentrate on other problem sets and handing off the easy tasks to AI to get cost-efficient results in a timely manner to reduce the likelihood of failure. AI will transform the drug discovery processes and similarly will promote the innovative approach for the study and development of future prospective drugs.

Author contributions

All authors contributed to planning of the manuscript, conducting it, reviewing the results, and preparing the original and further revised draft.

Authors' contributions

Aditya Kate·Ekkita Seth and Ananya Singh: Writing of main body and initial draft of the manuscript. **Chandrashekhar Chakole, Ravi Kant Singh** Abstract, conclusion writing, plagiarism check, validation and editing of the manuscript. **Shrirang Maddalwar and Mohit Mishra and Meenakshi Kanwar Chauhan:** Validation, editing and supervision of the manuscript. Formal analysis, visualization, conceptualization, and supervision. All authors read and approved the final manuscript.

Conflict of Interst

All authors declare that they have no competing interest.

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Notice

This article was changed according to the following Erratum on June 12th 2023.

Erratum

In the above mentioned article the affiliations were not correct..
Correct is:
Aditya Kate[1], Ekkita Seth[1], Ananya Singh[1], Chandrashekhar Mahadeo Chakole[2,3], Meenakshi Kanwar Chauhan[3], Ravi Kant Singh[4], Shrirang Maddalwar[1], Mohit Mishra[1]