Intelligent Pharmacy 3 (2025) 167–180

Contents lists available at ScienceDirect

Intelligent Pharmacy

journal homepage: www.keaipublishing.com/en/journals/intelligent-pharmacy

Review article

Machine learning & deep learning tools in pharmaceutical sciences: A comprehensive review

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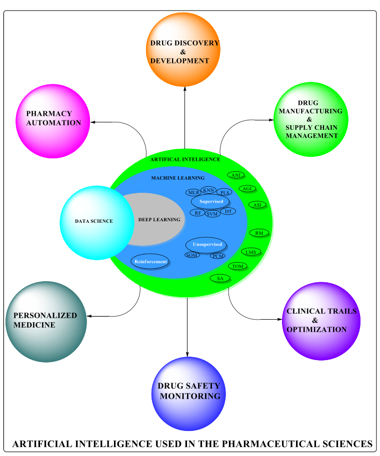
GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Artificial intelligence
Machine learning
Deep learning
Drug discovery
Virtual screening
Artificial neural networks
Hospital pharmacy

ABSTRACT

Drug discovery and development is an important area of research for pharmaceutical industries and medicinal chemists. This classical approach demanded significant investments of time and resources to bring a single drug to market. Furthermore, the complexity and vast scale of data from genomics, proteomics, microarrays, and clinical trials present significant challenges in the drug discovery pipeline. Nevertheless, bioinformatics, pharmacoinformatics, and cheminformatics technologies have been developed thanks to breakthroughs in computational methodologies and a surge in multi-omics data, drastically shortening the time it takes to create new drugs. Large amounts of biological data stored in global databases are the building blocks for machine learning and deep learning methods. They make it easier to find patterns and models that can help find therapeutically active molecules with less time, work, and money. Machine learning and deep learning technology are vital in drug design and development. We have applied these algorithms to various drug discovery processes such as protein structure prediction, toxicity prediction, oral bioavailability prediction, de novo design of new chemical scaffolds,

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https://doi.org/10.1016/j.ipha.2024.11.003
Received 17 October 2024; Received in revised form 28 November 2024; Accepted 29 November 2024
Available online 10 January 2025

structure-based and ligand-based virtual screening, pharmacophore modeling, quantitative structure-activity relationship, drug repositioning, and clinical trial design. Historical evidence underscores the successful implementation of AI and deep learning in this domain. Finally, we highlight some successful machine learning or deep learning-based models employed in the drug design and development pipeline. Furthermore, there has been a notable increase in interest regarding the application of AI technology in hospital pharmacy settings, which has been discussed in this review. This review will be invaluable to medicinal and computational chemists seeking DL tools for drug discovery projects and hospital pharmacies.

Abbreviations

AI	Artificial intelligence
ANNs	Artificial neural networks
QSAR	Quantitative structure-activity relationship
ML:	Machine learning
DL:	Deep learning
NN	Neural network
GNNs	Graph neural networks
SVM	Support Vector Machine
DTI	Drug-target interaction
DTBA	Drug-target binding affinity
DAE	Denoising autoencoder
CNN	convolutional neural network
SMILES	Simplified Molecular Input Line Entry System
LSTM	Long short-term memory
ECFP	Extended-connectivity fingerprint
CASP	Critical Assessment of Protein Structure Prediction
RL:	Reinforcement learning
DNNs	Deep neural networks

1. Introduction to artificial intelligence (AI)

Artificial Intelligence (hence referred to as AI) is integral to all pharmacological sciences. Artificial intelligence is a scientific discipline dedicated to intelligent machine learning, primarily encompassing advanced computer programs that replicate human cognitive functions.[1] This process generally encompasses data collecting, the development of efficient systems for data utilization, the formulation of accurate or approximate conclusions, and the implementation of self-corrections and changes.[2] Generally, Artificial intelligence is utilized to examine machine learning in a way that replicates human cognitive tasks, leading to more accurate analyses and meaningful interpretations.[3] AI technology integrates various statistical models and computational intelligence. AI technology has become an essential component across various technical and research fields, offering valuable applications.[4]

The process of bringing new treatments to market is still time-consuming and costly, even if our understanding of disease biology has advanced greatly and considerable technical development has been made. The high costs connected with clinical trials' high failure rates are the main cause of this.[5,6] This highlights the critical need for fresh perspectives, updated ideas about how drugs are discovered, and methods to increase access to treatments while decreasing their market price. The computer-aided drug design for small-molecules has been considered as a promising source.[7–9] Recent developments in data processing capabilities and new artificial intelligence (AI) techniques, such as Machine Learning and Deep Learning, have sparked a surge in interest in the topic.[10,11] The critical question now is whether these approaches can enable the faster design of superior small-molecule drug candidates.

The purpose of this article is to review AI-related topics, including the evolution of AI and the classification of AI, its applications in drug discovery and development, the pharmaceutical industry, and hospital pharmacy. The article also aims to raise awareness of AI as an integral part of future pharmaceutical sciences, encouraging medicinal chemists and pharmacists to embrace this advancement. By acquiring relevant skills, these professionals can contribute significantly to the anticipated progress in the field.

2. Significance of AI in different segments of pharmaceutical sciences

Artificial Intelligence (AI) is swiftly revolutionizing the pharmaceutical sector, creating new opportunities for enhancing medication discovery, patient care, and overall healthcare efficiency.[12–20] These are listed as.

- Drug Discovery and Development: Artificial intelligence expedites the discovery of novel pharmaceuticals by scrutinizing extensive databases, pinpointing prospective medication candidates, and forecasting their efficacy.
- Drug Interaction Analysing: By increasing the precision of predicting possible interactions, artificial intelligence (AI) can improve conventional drug interaction checking methods.
- Customizing Medicine: AI makes it possible to create personalized medical strategies, in which each patient receives a customized course of therapy based on their genetic composition, way of life, and surroundings.
- Drug Safety Monitoring: By facilitating better post-market medication safety monitoring, artificial intelligence (AI) significantly improves pharmacovigilance.
- Clinical Trials Optimization: Artificial intelligence (AI) is also transforming the way clinical trials are designed, piloted, and analyzed.
- Drug Manufacturing and Supply Chain Management: AI enhances supply chain administration, production efficiency, and quality control in pharmaceutical production.
- Pharmacy Automation: Artificial intelligence (AI) improves everyday pharmacy operations efficiency, which lowers mistakes and improves patient outcomes.

3. Artificial intelligence (AI)

The many definitions and interpretations of this word concur on three fundamental functionalities of artificial intelligence (about a computer or machine).

(A) **Resolving problems**,
(B) **Reflecting on past experiences and adjusting** and
(C) **Dealing with novel situations and problems (generalization).**

3.1. Classification of artificial intelligence

AI can be categorized into two forms.

a) Based on their caliber.
b) Based on their presence as shown in Fig. 1[21,22]

Based on their caliber, AI can be sub-divided as follows.

i. **Weak AI or Artificial Narrow Intelligence (ANI):** It executes a limited program, for example, face recognition, driving, chess practice, traffic signals, etc.
ii. **Strong AI or Artificial General Intelligence (AGI):** Artificial intelligence that emulates human performance in all tasks is referred to as human-level AI. It has the potential to make previously insurmountable mental tasks easier for humans to accomplish.
iii. **Artificial Super Intelligence (ASI):** It is a highly intelligent system that surpasses human intelligence and exhibits a far greater level of complexity in areas such as painting, mathematics, and space exploration.

Based on their presence, AI can be categorized as.

i. **Type 1** (Reactive machines)**:** Reactive machines are designed for specific, narrow-purpose applications and cannot utilize past experiences, as they do not possess a memory system. An example of a reactive machine is IBM's chess program, which can identify pieces on a chessboard and make predictions based on the current game state
ii. **Type 2 (**Limited memory system)**:** A limited memory system can utilize past experiences to address new problems. In autonomous vehicles, this system can make decisions based on previously recorded observations, which guide subsequent actions; however, these records are not stored permanently.
iii. **Type 3** (Theory of mind)**:** The "Theory of Mind" provides the foundation for it. This means that people's desires, ideas, and intentions play a role in their decision-making, which is something that AI systems can't achieve just now.
iv. **Type 4 (**Self-awareness)**:** This system possesses self-awareness, including a sense of self and consciousness, but such capabilities do not currently exist in AI.

4. Neural networks and ANNs

The learning algorithms for neural networks, based on input data, primarily take two distinct forms. The categories of neural networks are as follows:[23,24]

i. **Unsupervised learning:**In this context, the neural network is provided with input data that exhibits a known pattern and is utilized for organizational purposes. The unsupervised learning algorithm employed is the 'Self-Organizing Map' or 'Kohonen' network.[9,23] This approach is recognized as highly effective for identifying relationships within complex data sets.
ii. **Supervised learning:** This type of neural network is characterized by order of corresponding inputs and outputs, and it is employed to learn the relationships between these inputs and outputs. It proves useful in modeling the cause-and-effect connections between input and output variables. This is the most utilized form of artificial neural networks (ANNs), fully integrated with the backpropagation learning algorithm. This algorithm is widely regarded as an exceptional method for prediction and classification tasks.

The basic unit of a neural network is a mathematical processing item referred to as a neurone.[25] Every input is linked to a weight that signifies its relative significance, and the output is determined by calculating the weighted sum of all inputs. The output is subsequently sent to another neurone after undergoing modification by a transformation function. This entire process is referred to as a perceptron, a feed-forward mechanism. A neural network, consisting of several neurones, is organised into distinct network designs. The multilayer perceptron network is a prominent and efficient design. In this system, neurones are structured so that the outputs of one layer function as the inputs for the subsequent layer. One or many concealed layers may be included between the input and output layers. Theoretically, the quantity of hidden layers can be modified to satisfy particular requirements; but, in fact, several layers are frequently necessary for applications that include intricate nonlinear behaviour.

5. Artificial neural networks

Artificial neural networks are esteemed computer models that draw inspiration from the neuronal network architecture of the human brain. ANNs, in their most basic configuration, are fully linked networks or

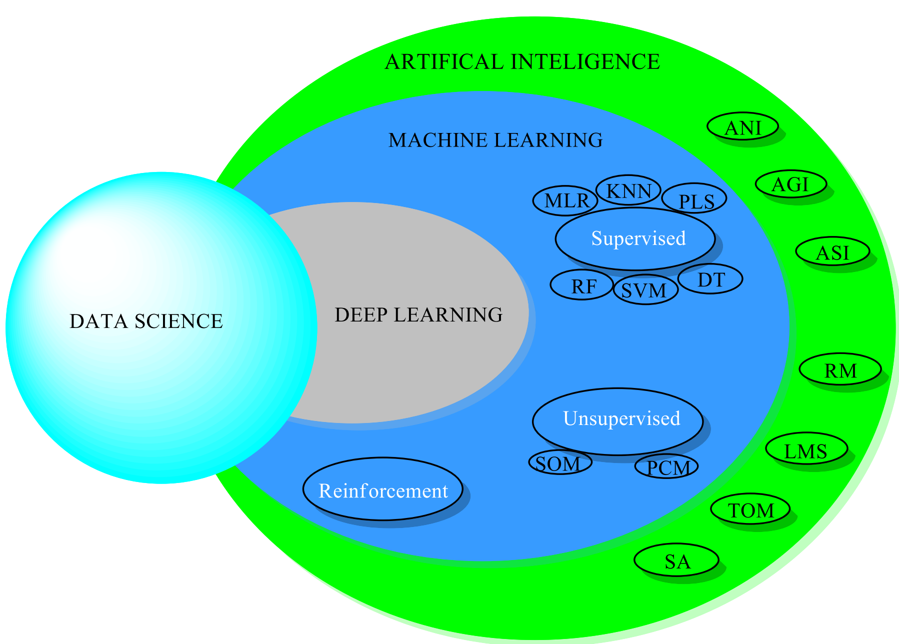

Fig. 1. Machine Learning and Deep Learning are subsets of Artificial Intelligence linked with data science.

feed-forward networks, including three layers: the input layer, hidden layer, and output layer. Each layer has distinct computational units called neurons, which operate as non-linear modifications of the incoming data. Figure 2 illustrates the progressive propagation of information via these levels, where each layer receives the output from the previous layer.

Artificial neural networks (ANNs) are computational models composed of numerous artificial neurons, which function as processing elements within the neural structure. These units work together to process information.[26] ANN methodologies offer a powerful modeling approach, especially for handling non-linear relationships often encountered in pharmaceutical research. Unlike traditional models, ANNs do not require prior knowledge of data sources but involve numerous weights that must be analyzed and require extensive training datasets. ANNs can integrate both literature and experimental data to solve complex problems.[27,28]

Recently, ANN models have been hybridized with simpler models to enhance their performance. For instance, a novel combination of neural networks and logistic regression enables the creation of hybrid linear/non-linear classification surfaces, helping to identify significant interactions between variables that define classification problems. These hybrid models have shown effective performance across various databases.[29]

Applications of ANNs in the pharmaceutical industry are wide-ranging, including data analysis and the modeling of pharmaceutical quality control. Artificial neural networks have shown to be highly useful in the field of drug design, namely in molecular modeling and quantitative structure-activity relationship (QSAR) investigations. Furthermore, ANNs are employed in the optimization of formulations for dose design and in the study of biopharmaceuticals, including pharmacokinetic modeling, pharmacodynamic modeling, and in-vitro, in-vivo correlation analysis.[30–32]

6. Basic principles of machine learning

The development of novel algorithms and models with the ability to comprehend massive volumes of data is the essence of machine learning.[33,34] Even though not all AI approaches are ML techniques, machine learning is defined as "an AI technique used to design and train software algorithms to learn from and act on data".[35]

By using a variety of algorithms, machine learning can predict the physical, biological, and chemical characteristics of new molecules. Two main types of learning—supervised and unsupervised—are used to do this. The goal of supervised ML is to train an algorithm to use existing data to generate predictions by identifying patterns and testing hypotheses [36]. Supervised learning is a method for training an algorithm to make predictions or classifications under controlled conditions by feeding it examples of those situations. Classification and regression algorithms are

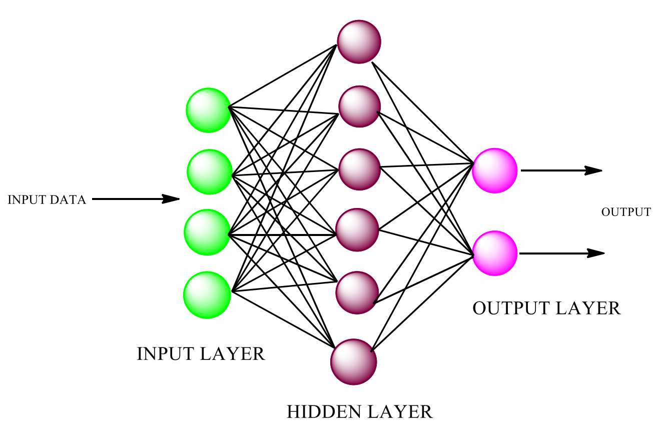

Fig. 2. Basic architecture of the artificial neural network.

two subsets of supervised ML.[37] The training dataset is used by the classification algorithm to classify data. One typical use of classification algorithms in bioinformatics is the identification of genomic regions that code for genes. Because they employ numerous classification algorithms trained on provided datasets to categorize gene coding areas in a genome, these technologies achieve very high levels of accuracy.[38] The prediction of new targets or structures, like locations of protein–protein interactions, has seen heavy use of regression algorithms as of late. With an accuracy of more than 80% in recognizing structures in proteomics, studies on regression methods have shown encouraging results.[39]

Using an optimal decision boundary to train supervised learning algorithms is a major benefit. However, they also have several disadvantages, including the complexity and time consumption involved in classifying large datasets, the risk of overtraining decision boundaries due to a lack of appropriate examples, which can result in inaccurate test algorithm outputs, and the challenges in data preparation and preprocessing.[40]

Contrarily, unsupervised ML does not rely on predetermined labels or phenotypes to interpret or learn an abstract representation of the provided data. To extract useful biological information, it clusters data points into patterns. Two popular clustering techniques are hierarchical and k-means.[41] Based on their shared characteristics, the unlabeled dataset is divided into groups using the clustering technique. When working with massive datasets, k-means clustering is frequently employed to group small molecule profiles into clusters according to their degree of similarity.[42]

A major advantage of unsupervised learning techniques over supervised learning algorithms is their reduced complexity, as they do not require dataset training and are useful for sorting raw data and understanding different learning models in real-time. Additionally, it is easier to obtain unlabeled data automatically from a computer compared to labeled data, which requires human involvement.[43] However, unsupervised learning techniques also have significant disadvantages, such as imprecise data sorting due to the lack of labeled data, leading to less accurate and unpredictable results.

7. Application of machine learning tools for target identification

In conventional drug discovery, it is essential to identify target proteins associated with the pathophysiological aspects of the disease and establish a viable framework. Misinterpretation of target protein data can result in alterations in disease understanding, making target selection a critical and necessary step in the process.[44,45] Machine learning (ML) algorithms are employed to predict previously unobserved biological events and issues.[46] A computer model was built by Costa et al. to predict morbidity and discover druggable genes on a genome-wide scale. This model employed a data-driven method to uncover essential biological insights. The proposed model integrates classification functions including mRNA expression, gene vitalness, mutation appearance, and protein–protein interaction networks. The meta-classifier study yielded a 65 % recovery rate for established morbid genes and a 78% identification rate for previously undiscovered druggable genes.[47] Procedures including decision trees and rule-based systems evaluate aspects such as membrane localization and the control of different transcription factors to clarify biological characteristics.[48] Furthermore, these approaches also enable the comprehension and implementation of biosystem concepts employing reverse engineering.

To handle data for genome and cellular investigation, Volk et al. used ML approaches to model problems at the DNA, protein, and particular pathway levels.[49] In breast, pancreatic, and ovarian malignancies, Jeon et al.[50] used a Support Vector Machine (SVM) method to examine genomic alterations and systematic datasets, differentiating proteins according to their homologs or drug-binding capacity. Similarly, Momoshina et al.[51] used support vector machines (SVMs) with linear kernels and deep feature selection to tackle molecular elements of human aging by identifying therapeutic targets in complicated disorders, with a

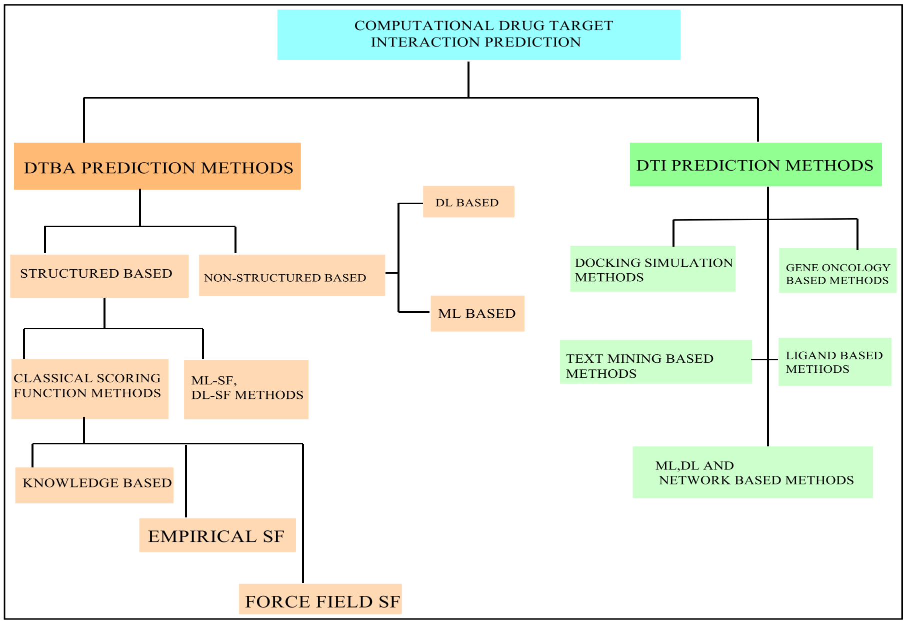

Fig. 3. Predictions of computational drug-target interactions represented by a branch diagram. The figure shows many DL methods for target identification and prediction. These methods are often categorized as either drug-target binding affinity prediction or drug-target interaction prediction.

focus on biomarkers in muscle tissue. Using Genotype-Tissue Expression (GTEx) data for gene expression, this model achieved an accuracy of 0.80.[52]

8. Application of machine learning tools for structure-based drug design

First steps in computational drug discovery include target identification, target evaluation, and candidate drug candidate discovery.[53,54] To comprehend disease biology, evaluate the druggability of lead compounds, and rank potential targets, target selection is essential.[55,56] The intricacy of human diseases necessitates all-encompassing approaches to target selection, which must combine disparate datasets, shed light on the molecular mechanisms driving disease manifestations, and detect individual differences across patients.[57] More and more, these problems are being solved by using advanced methods like machine learning (ML) and artificial intelligence (AI). As an example, DL algorithms make it easier to build new chemical structures and forecast retrosynthetic pathways for small compounds with required bioactivity.[58]

Use of neural network methods to unsupervisedly discretize input vectors into feature maps is at the heart of the self-organizing maps (SOM)-based prediction of drug equivalence relationships (SPiDER) ML technique.[59] While this method does not allow for target identification with certainty, it does allow for predictions of drug–protein interactions based on the similarity of descriptors to reference lead molecules within the same neuron.[60] In order to detect atoms that do not contain hydrogen, this method makes use of topological information and an existing set of pharmacophore descriptors, such CATS2. By using physicochemical characteristics to direct the analysis, self-organizing maps (SOM) are built using the topological feature autocorrelation of molecules.[61]

This software has been widely utilized in de novo approaches, particularly for the design of natural products with significant inhibitory potential. Numerous studies have reported the application of SPiDER in identifying drug targets such as the farnesoid X receptor (EC50 = 0.2 μM), 5-LOX (lipoxygenase) (EC50 = 11 μM), and PPAR-gamma receptor (peroxisome proliferator-activated receptor gamma) (EC50 = 8 μM).[62]

9. Basic principles of deep learning tools

A subfield of ML known as "deep learning," DL gradually extracts more complex characteristics from simpler input data by employing multi-layered artificial neural networks (ANNs). One of the most effective approaches in several branches of artificial intelligence (AI) research is DL, which, together with NN, can learn from both data and the environment.[63,64] In pharmaceutical research, it has lately become a very promising tool due to its performance, which surpasses other ML methods. Its use extends beyond bioactivity predictions and addresses several issues in drug design and discovery.[65] Some of the most used DL tools are listed in Table 1.[66]

When it comes to training and interpreting tiny datasets, neural networks are highly appreciated by deep networks due to their intricacy. The efficient learning of DL networks with more layers is frequently impeded by algorithmic challenges, such as vanishing gradients. The training efficiency of deep networks has been greatly enhanced, nevertheless, by developments in neural activation functions, initialization strategies, and gradient-based optimization algorithms. While RNNs learn spatial and local associations through filters, CNNs are making waves in image processing and can grasp temporal dependencies in sequence-level data. When dealing with unordered data, like in social network research, graph neural networks (GNNs) work well as representations for tiny molecules. Figure 5 shows the representation and distinction of these neural network types. DL is one of many subfields of ML that deal with the interconnection of artificial networks of computing devices.[68]

10. Application of deep learning tools in drug discovery

To exploit the immense capabilities of deep learning (DL) algorithms in the field of drug discovery and development, computer scientists and medicinal chemists have joined forces to build DL-based tools, predictive models, and algorithms specifically designed for this purpose. This paper presents a concise overview of many deep learning-based technologies that have been created to facilitate the process of drug discovery and development.

Table 1
Some of the most popular libraries for developing and testing deep learning algorithms[67].

Name of program	Platform	Useful links
TensorFlow	Python	TensorFlow
Torch	Lua	Torch
Theano	Python	Theano
Caffe	C++/Python	Caffe
DL4J	Java	DL4J
Paddle	Python	Paddle
Keras	Python	Keras
CNTK	C++/Python	CNTK
MxNet	R/Python/Julia	MxNet
AlexNet	MATLAB	AlexNet
PyTorch	Python	PyTorch
DeepChem	Python	DeepChem

11. Predicting drug-target interactions and binding affinities using deep learning techniques

A key component of drug discovery and development is drug-target interaction (DTI), which is the process by which chemical compounds interact with biomolecular drug targets in the human body to produce a therapeutic effect. Since there is a large disparity between known and unknown drug-target combinations due to the poor understanding of drug-target interactions gained from wet lab trials, there is a growing interest in creating effective DTI prediction algorithms.

Computational approaches have been shown to be more efficient than traditional methods for DTI prediction, which are limited by both time and money. Modern computational methods for DTI prediction encompass a wide range of techniques, including those based on ligands, docking simulations, chemogenomics, text mining, machine learning/ deep learning (DL), and networks. Figure 3 shows a schematic of different methods and tools.[69,70] Below, we will go over a few DL-based approaches to drug-target interaction.

There are a few of main categories into which computational approaches to drug-target interaction prediction fall: drug-target binding affinity (DTBA) prediction methods and DTI prediction methods. Methods for predicting DTIs range from docking simulations to those based on gene ontologies, ligands, text mining, and machine learning, deep learning, and networks. There are two subsets of DTBA-based methods: those that focus on structure and those that do not. Classical scoring function approaches and ML-SF/DL-SF methods are subsets of structure-based methods. One can further categorize classical scoring function methods as either knowledge-based, empirical, or force-field SF.[71]

12. Drug–target interaction & convolutional neural networks (DTI-CNN)

One kind of neural network that finds widespread application in image analysis is the convolutional neural network (CNN). An easy-to-understand deep learning tool for drug-target interaction prediction, DTI-CNN is said to surpass current state-of-the-art methods by combining three parts: (1) a feature extractor based on heterogeneous networks, (2) a feature selector based on denoising autoencoders, and (3) an interaction predictor based on convolutional neural networks.[72,73]

Building a heterogeneous network using a variety of drug and protein-related data sources and the random walk with restart (RWR) model to derive initial feature vectors for drugs and proteins is the primary stage in utilizing DTI-CNN for DTI prediction. Obtaining low-dimensional representations of the high-dimensional properties of medicines and proteins is the second stage in using the denoising autoencoder (DAE) model. Step last: positive and negative samples are created by dividing them according to known drug–protein interactions. After that, the convolutional neural network (CNN) model uses the feature vectors of the drug–protein pairs to forecast the relationship between every drug and protein. A CNN-based classifier for drug-target interaction prediction using autoencoder-based feature manipulation, FRnet-DTI is another DL-based tool.[74,75]

DeepCPI: It is an innovative paradigm for DTI prediction that combines deep learning with unsupervised representation learning.[76] Superior performance compared to traditional ML algorithms has been demonstrated by newly designed DL algorithms for drug-target binding affinity (DTBA). These deep learning algorithms take drug features and input data from sources such as the SMILES format, which is a compressed text representation of molecular structures with each chemical entity mapped to a single ASCII string of 20–90 characters; the LMCS format, which is a representation of ligand maximum common substructure; and the ECFP format, which is a representation of extended connectivity fingerprint. Plus, they use a variety of neural network types, each with its own set of advantages, so they can handle a lot of different tasks.[77]

DeepDTA: A non-structure-based method that employs SMILES as input data for medicines, DeepDTA was the first DL-based methodology for predicting drug-target binding affinity (DTBA).[78] Protein sequences and amino acid sequences are encoded in a similar fashion in SMILES. In order to learn latent characteristics, DeepDTA applies a convolutional neural network (CNN) to the drug embedding. This CNN is composed of three 1D convolutional layers followed by max-pooling functions. The protein embedding is subjected to a CNN block that is comparable to this one. Among the many hyperparameters that DeepDTA adjusts during validation are the batch size, optimizer, learning rate, number of filters, filter length for medicines and proteins, and the number of filters overall. The goal of the model is to train itself to provide DTBA values as close to the actual values as possible. Implementing other appropriate structures, like long short-term memory (LSTM), which can learn from long protein sequences, can overcome the model's limitations caused by CNNs.[79]

WideDTA: It is an additional convolutional neural network (CNN) DL model that takes four text-based inputs: (1) ligand SMILES (LS), (2) protein sequences (PS), (3) ligand maximum common substructure (LMCS), and (4) protein domains and motifs (PDM). Instead of representing LS and PS as full-length sequences, WideDTA uses sets of words. This is different from DeepDTA. Words in PS have three residues in the sequences, but words in LS have eight. Thanks to a word-based model instead of a character-based one, WideDTA is able to detect protein characteristics represented by shorter residue lengths, according to the

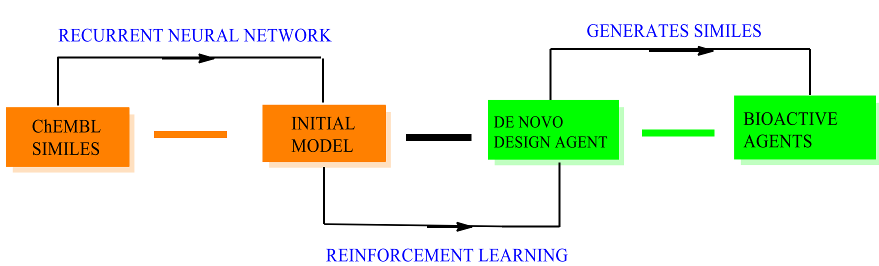

Fig. 4. A flow chart of ReLeaSE which stands for reinforcement learning for structural evolution.

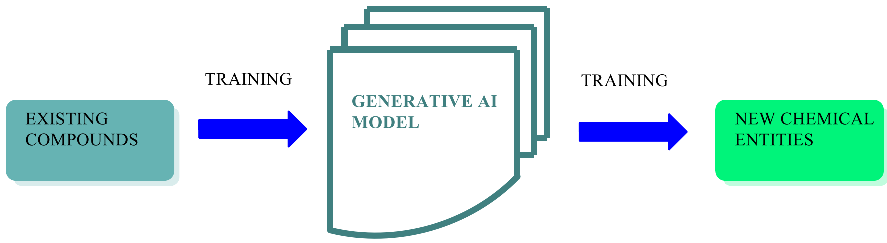

Fig. 5. Outline of generative artificial intelligence (AI)-based model.

inventors.[80,81] This is because full-length sequences have a low signal-to-noise ratio.

PADME: Protein and Drug Molecule Interaction Prediction is a deep learning-based approach to DTBA prediction that makes use of drug-target characteristics and fingerprints with several DNNs. We call this tool PADME-ECFP when we utilize the extended-connectivity fingerprint (ECFP) to represent medicines. One alternative, PADME-GraphConv, uses molecular graph convolution to extract latent drug characteristics from SMILES data including a second convolutional neural network for graphs. In both cases, the target proteins are represented by protein sequence composition descriptors, which provide a wealth of information. For each drug-target pair, a basic feedforward neural network is used to forecast the DTBA[82] after the feature vectors have been created.

DeepAffinity: It represents proteins by using a structural property sequence representation that efficiently annotates sequences with structural information. This method is more concise than other representations, providing structural details at a higher resolution, which significantly enhances the accuracy of regression tasks. The sequence data is encoded into an embedding form using a well-known RNN model, seq2seq. In the later stages of data processing, the RNN encoders are integrated with a CNN model. The output representations for both the drug and target are then concatenated and fed into fully connected (FC) layers to produce the final drug-target binding affinity (DTBA) values. The entire model, encompassing data representation, embedding learning, and joint supervised learning, is trained from end to end.[83]

Deep Docking: The drug discovery and development process is greatly expedited by the virtual prediction of protein-ligand interactions using docking.[84,85] Virtual screening-based drug-target interaction (DTI) prediction, on the other hand, has its limitations due to the gigantic chemical libraries that include billions of chemicals. By retaining the majority of possible virtual hits, deep docking aims to narrow this massive database down to a manageable selection of a few million chemicals. Docking studies or other virtual screening approaches can be used to refine these findings and focus the data on more promising candidates for future investigation. In deep docking, deep neural networks (DNNs) are used, where the training set is gradually increased with hit molecules predicted in earlier iterations, and stricter cutoffs are used in the last stages of the computation. To systematically exclude compounds that are unlikely to provide favourable docking scores, it uses quantitative structure-activity relationship (QSAR) models trained on docking scores from chemical library subsets to forecast docking outcomes for untested compounds. With powerful computer resources and detailed QSAR descriptors such as 2D chemical fingerprints,[86] deep docking accomplishes a 100-fold enhancement in virtual screening time and a 6000-fold improvement in detecting highly rated compounds, hence reducing the loss of potential virtual hits.[87,88]

DeepBAR: The tool is a deep learning simulation designed by MIT researchers to estimate binding affinities by combining chemistry and machine learning techniques.[89,90] Binding free energy measures the strength of attraction between a drug molecule and its target. The most efficient medication is the one with the lowest binding free energy, as it most effectively interferes with the specific activity of the target protein. The abbreviation "BAR" in DeepBAR denotes the Bennett acceptance ratio approach, which is a previous methodology used to compute binding free energy. DeepBAR improves upon this approach by integrating data from several endpoints and intermediate stages.

13. Application of AI tools for Protein structure prediction

Proteins are essential biomolecules that perform diverse functions in organisms, such as enzyme function, receptor interactions, cell signaling, hormonal regulation, and intracellular movement. Well-established drug targets are protein molecules, and their dysfunction results in pathological conditions. Understanding protein function necessitates knowledge of protein structure, as structure typically determines function, activity, and pathological conditions. However, determining protein structure is complex, requiring experimental techniques such as X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy, which take a lot of time and are often hard. To bridge the gap of numerous unknown protein structures, accurate computational approaches are essential, enabling large-scale structural bioinformatics.[91] To simplify protein structure determination, scientists have leveraged deep learning (DL) techniques, which can predict protein structures with high confidence, as discussed below.

AlphaFold: A novel computational approach for predicting protein structures by analyzing covariation in homologous sequences.[92] To improve structural insights, the first step is to train a neural network to accurately estimate the lengths between pairs of residues. By optimizing the potential of mean force using a simple gradient descent method, AlphaFold achieves improved accuracy without sophisticated sampling techniques[93] for sequences with less homologous sequences. AlphaFold detects mutations that have happened over evolutionary timeframes in response to other mutations and assembles the most plausible pieces based on multiple sequence alignment analysis. It interprets spatial closeness. Managing the deep neural networks (DNNs) that detect evolutionary trends in protein structure sequences concerning contact distributions and angular constraints is an extremely computationally intensive process. Moreover, AlphaFold can generate a statistical potential for a protein by utilizing DL algorithms, which allow for the use of a 'learned reference state' rather than a physical-based reference state. As a result, AlphaFold gives scientists a potent resource for predicting protein structures.[94,95]

CASP: The goal of the Critical Assessment of Protein Structure Prediction (CASP) is to create tools that can identify protein sequences and use them to build their three-dimensional structure.[96–98] The availability of a template structure determines the primary approach, however there are two main ways to accomplish this: (1) template-based models and (2) template-free models. To make it more mature and accessible to less experienced researchers, template-based modeling is favored when a decent template is available. It employs the known protein structure as a basis for prediction. It is possible to construct the building without a template by using template-free modeling. Two examples of template-free modeling are de novo folding and fragment-based assembly. It uses fundamental physics to generate three-dimensional structures from scratch. De novo folding requires an accurate energy function to find the lowest energy state conformation and distinguish native-like structures from decoys. But, when no good template is available, fragment-based assembly is still the go-to method for protein structure prediction because of how accurate it is.

14. Application of deep learning tools for compound de novo design

De novo design refers to the process of generating novel molecules based on drug-target binding affinity (DTBA) or drug-target interaction (DTI) data, or pharmacophore data. A pharmacophore is defined as the minimum structural features necessary for a molecule to exhibit biological activity.[99] The goal of de novo design is to discover new drug-like compounds. Traditional de novo algorithms utilized structure-based approaches to develop ligands that fit the target binding site both sterically and electronically. However, a significant drawback of these approaches is that the generated molecules often exhibit poor drug metabolism and pharmacokinetic properties and are synthetically impractical.[100] With the advent of big data and the development of deep learning algorithms, de novo methodologies based on deep reinforcement learning have emerged. These methodologies facilitate the generation of compounds with desirable physical, chemical, and bioactivity properties.[101,102] These RL algorithms analyze potential actions and estimate the statistical relationships between actions and outcomes, aiming to find the most desirable results.

ReLeaSE: One deep RL method that allows for the construction of chemical libraries with desired features is ReLeaSE, which stands for reinforcement learning for structural evolution. The Simplified Molecular Input Line Entry System (SMILES) is used to represent molecules, which is a distinctive aspect of this technique.[105] Two steps of training are used in the ReLeaSE approach for deep neural networks (DNNs): one for generative models and another for prediction models. The initial step is to train the models independently using various techniques. In the second phase, the RL method is used to train the models simultaneously. The generating model creates new chemicals that can be chemically tested, and the predictive model measures how well the generative model did its job by giving each generated molecule a numerical reward or penalty, as checked in Fig. 4.

Generative Artificial Intelligence (AI)-Based Model: This model is predicated on generative AI, which autonomously designs novel chemical compounds using knowledge of known bioactive compounds and their inherent bioactivity and synthesizability.[103] The approach comprises two steps: first, creating a generic model that learns the structure of drug-like molecules from a large, unfocused compound set; second, refining this model based on specific molecular characteristics from a small, target-focused library of active compounds. A deep recurrent neural network is employed to train the generic model as shown in Fig. 5.[104]

DeepScaffold: Using DeepScaffold, the goal of drug design is to find new compounds that have good pharmacological characteristics. To produce promising therapeutic candidates, it is helpful to keep some scaffolds as key components. To aid in the process of discovering new drugs, DeepScaffold is a molecular generative model that uses scaffolds to produce molecules. Core molecular structures, or scaffolds, can take several forms, such as cyclic skeletons, Bemis-Murcko scaffolds, or scaffolds endowed with desirable side-chain characteristics. By applying the previously acquired chemical laws to each given scaffold, DeepScaffold can generalize the process of scaffolding. Drug design problems such as de novo drug design of possible drug candidates with specific docking scores and generating compounds with a given scaffold are both addressed by molecular docking evaluations of the produced molecules to D2 dopamine receptor (DRD2) targets.

AIScaffold: It is an AI-based tool that mainly uses a deep generative model to diversify scaffolds.[105] Unlike other tools that rely on molecular scaffold information for development, AIScaffold generates up to 500,000 molecules in minutes and recommends the top 500 or 0.1% of molecules. It also provides extra features like site-specific diversification, as outline in Fig. 6. The AI-based tool AIScaffold is available at iaidrug.stonewise.cn.

DESMILES: A novel drug design model is proposed, which utilizes a deep neural network (DNN) based on machine learning (ML) and employs a recurrent neural network (RNN) architecture.[106] The main goal of DESMILES is to synthesize a sequence of tiny molecules that mirror the chemical composition of a specific input molecule. The mechanism utilizes molecular fingerprints as input and associates them with matching SMILES strings to establish a correlation between the fingerprint and the SMILES string. Incorporating DESMILES into the first phases of drug design and discovery allows for its usage in conjunction with diverse molecular screening methods to uncover novel scaffolds for prospective therapeutic candidates.

15. DL tools for hit identification using virtual screening

To find tiny compounds with a better chance of binding to a medicinal target, virtual screening is an in-silico approach used in drug discovery to search through large libraries of potential candidates. This method makes use of the physicochemical, topological, and biological features of the chemical substances and their targets. There are mainly two types of virtual screening methods: (I) structure-based, which models and visualizes interactions using the 3D structures of chemical substances and targets.[107,108] Both X-ray crystallography and nuclear magnetic resonance (NMR) can provide the three-dimensional structure. The interactions between a target and a chemical can be determined using docking techniques once 3D structural data is available. (II) Non-structure-based approaches, which can be further divided into (a) proteochemometric modeling, which integrates non-structural descriptors with targets at the input level[109] and (b) ligand-based virtual screening, which uses the molecular features of compounds to model and analyze their interactions with targets.[110,111] Virtual screening and quantitative structure-activity relationship (QSAR) research both make use of the DL-based techniques listed below.

DeepVS: An approach to virtual screening based on docking. It leverages the output of the docking program to extract pertinent features from existing data on protein-ligand complexes. It models the compound as a set of atom contexts and uses atom and amino acid embeddings to create distributed vector representations of the complexes. DeepVS then processes these representations using a convolutional layer. One advantage of DeepVS is that it doesn't require feature engineering.[112]

The SIEVE score: The Similarity of Interaction Energy Vector Score (SIEVE) is an innovative artificial intelligence (AI)-based virtual screening tool.[113,114] This technique is regarded as a very promising approach for identifying hits, to systematically select potentially active chemicals from a vast chemical library for biological research.

Similarity searching: One approach that has proven useful in the search for chemical analogues of biologically active substances is similarity searching.[115,116] By building a network of interconnected neural circuits using chemical signatures as vectors, this deep-learning model follows the tenets of ligand-based drug design. Predicting bioactivity, water solubility, and toxicity from the structure of the investigated molecule is an important part of hit identification, and this method shows promise in this regard. Using a two-step de novo method based on PERL scripts, similarity search takes specific inputs into account to improve the efficiency of the output. To score compounds for virtual screening or to predict their affinity for a given target, this method combines deep neural networks (DNN) with machine learning (ML) techniques. With this approach, it is possible to test a single chemical against several targets, or a large number of compounds against a single target.[117]

16. Application of DL tools for pharmacokinetic property prediction

Pharmacokinetics encompasses the examination of a drug's absorption, distribution, metabolism, and excretion inside the body. ADMET

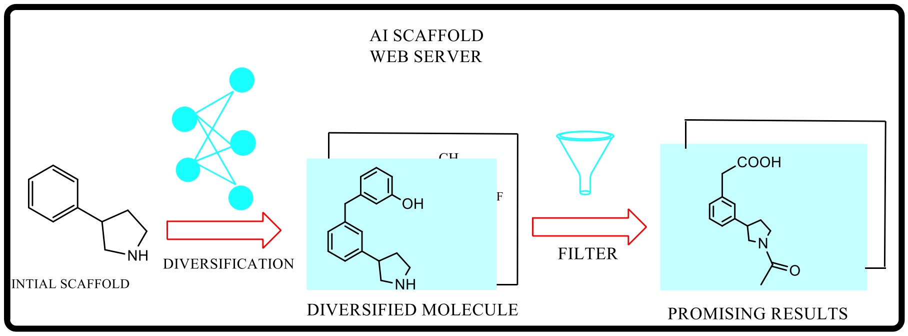

Fig. 6. Outline of AIScaffold.

includes all pharmacokinetic parameters and the toxicity profile of xenobiotics (ADMETox). Thus, the ADME-Tox profile of lead chemical entities can profoundly influence its effectiveness and safety. The need for effective predictive tools for ADMET attributes is rising to fulfil two primary objectives: firstly, to facilitate the initial selection of novel compounds and compound libraries, thereby minimizing the risk of late-stage attrition; and secondly, to enhance screening and testing by forecasting the ADMET profiles of lead compounds in drug discovery. In this regard, machine learning techniques are frequently utilized for ADME-Tox prediction. These predictions are feasible due to the availability of extensive pharmacokinetic data, which facilitates the development of models for ADMET in-silico modeling. These models can predict various properties, such as dose size, dose frequency, oral absorption, bioavailability, and blood–brain barrier (BBB) penetration.[118,119] Table 2 represents the ADMET properties that use ML algorithms and Table 3 shows some of the Machine learning algorithms used in ADMET predictions.

17. Tox_(R)CNN

Pharmaceutical-induced cytotoxic effects result in cellular and nuclear morphological modifications, which are distinctive of particular cell-death pathways.[120] Traditionally, these alterations are detected by visualising nuclei using distinct microscopic methods. Tox_(R)CNN is a modern method specifically developed to identify cytotoxicity present in microscopic pictures of fluorescently labeled nuclei, without the need for explicit toxicity labelling. This tool utilizes deep learning (DL) models, renowned for their outstanding proficiency in addressing computer vision problems.[121] Tox_(R)CNN utilizes two convolutional neural networks (CNNs): Tox_CNN classifies cells by processing nucleus pictures by segmentation and cropping, and Tox_RCNN automates cell identification and classification. The networks present very sensitive screening results that can identify pre-lethal toxicity, therefore establishing the model as a reliable screening tool for the purpose of drug development.

18. Metabolite Prediction

Approximately 25% of chemicals are discontinued from the market or clinical studies because of metabolic, pharmacokinetic, or toxic concerns, leading to substantial financial setbacks for firms. The demanding nature of experimental approaches for discovering and investigating drug metabolic pathways, in terms of equipment, knowledge, expense, and time, has led researchers to explore computational alternatives. Metabolic sites (SOMs) and metabolite structure are two key research fields that crucially assist and guide computer-aided metabolic prediction approaches. Metabolite prediction is achieved by the model by the initial establishment of a database including extensive metabolic reaction rules encoded using SMARTS. Subsequently, it retrieves chemical fingerprints of compounds in order to develop a classification model based on deep learning algorithms. This model is capable of detecting reaction types that have a greater likelihood of occurring.[122,123]

Table 2
ADMET parameters that are adapted using Machine Learning algorithms

Parameters	Measurement
Clearance	Rodent in vivo pix PK
Permeability	Caco-2, PAMPA, MDCK
Solubility	Kinetic solubility
Drug–drug interactions	CYP450s, transporters
Metabolic stability	Hepatocytes and liver microsomes
Transporters such as P-gp	Transporters overexpressing cell lines
Cardiotoxicity (hERG)	Binding or flux in different cell types
Blood–brain barrier (BBB)	Mouse brain endothelial cell line

Table 3
Machine learning algorithms which are utilized in ADMET prediction

Algorithm	In a nutshell
Neural network	A simple neural network which has input, hidden and output layers
Random forest (RF)	An ensemble learning technique that generates multiple decision trees and produces a class prediction, or an average prediction based on the aggregated outcomes.
Support vector machine (SVM)	A supervised learning approach where data points are plotted in a multidimensional space, and the classes are divided by a hyperplane.
Deep learning (DNN)	Utilizes multiple layers within a neural network, where each layer processes the output from the preceding one. This approach enables the model to learn and represent data at various levels of abstraction.
K nearest neighbors (KNN)	A non-parametric technique that classifies objects based on the majority vote of the K nearest training examples in the feature space, or in the case of regression, uses the average of the values from the closest examples.
Naive Bayes (NB)	A probabilistic classifier that assumes each feature independently contributes to the overall probability.

19. Oral bioavailability Prediction

Oral bioavailability is crucial in determining a drug's absorption in the body. Predicting bioavailability, which is challenging due to its dependence on complex factors and processes, would significantly streamline the prioritization of drug candidates in the drug discovery process.[124]

OpenChem: Designed to make it easier to create DL models for computational chemistry and drug design research, OpenChem is a DL toolkit with a PyTorch backend that may be found freely in the GitHub repository.[125] Use this toolbox to keep tabs on the training set, see assessments visually, and project embeddings into lower-dimensional space. Because it is multi-GPU compatible, it speeds up the training process and helps with data preprocessing. New models can be constructed using only configuration files, thanks to the user-friendly toolkit. Data classification, regression analysis, and model generation for ADME property prediction of lead compounds are all made easier with OpenChem as represented in Fig. 7.

20. Tools for drug activity Prediction

Deep Learning tools can identify chemical aspects in drug scaffolds and predict the activity of known scaffolds, including their pharmacological activity. One such DL-based tool is MultiCon.

MultiCon: Semi-supervised learning algorithms can be used to improve model efficacy while reducing the workload associated with big amounts of supervised data. Save time and money by utilizing a semi-supervised learning system to forecast a drug's therapeutic uses based on its structural formula. Medications are grouped into 12 groups in the MultiCon toolbox according to their therapeutic uses and structural formula image analysis as shown in Fig. 8.[126] Due to its rational data balancing, limited labeled data, online augmentations of input of drug images during training, and the simultaneous application of multi-contrastive loss and consistent regularisation, MultiCon outperforms other existing semi-supervised learning algorithms in terms of prediction accuracy, according to studies.

21. Application of DL in clinical trial design

The clinical trial phase is the next stage in the drug development process, which is a multi-billion-dollar business focused on assessing the efficacy of drugs by testing lead compounds on human subjects.[127] One of the main goals of a clinical researcher is to ascertain the safety and efficacy of a novel therapy, such as a medication, dosage form, or medical device (e.g., a pacemaker), for human use. Furthermore, they formulate doses to attain the most effective treatment outcomes with the least quantity of medication required to produce a reaction.[128] Typically, it takes about 10–15 years and incurs a cost of 1.5–2 billion USD for a novel pharmaceutical compound to be introduced to the market. Evidence suggests that around 50% of the time, human resources, and financial resources in the process of developing new drugs are specifically allocated to the phases of clinical trials. The remaining 50% include the procedures of preclinical lead compound discovery, optimization, and regulation.[129] Prior research has emphasized the considerable capacity of artificial intelligence (AI) and sophisticated analytics tools to implement automation in clinical trial procedures, therefore enhancing their cost-efficiency.[130] Several artificial intelligence (AI) solutions now accessible for clinical trial preparation are analyzed here.

Trials.ai: The startup known as Trials.ai uses artificial intelligence (AI) methods such as natural language processing to aid in the design of clinical trial procedures. Journal articles, medication labels, and private hospital records are just a few of the sources that the software scours for information. Research on clinical trial outcomes, including costs and participant retention rates, as well as the strength of eligibility requirements, can be informed by this data.[131]

AICURE: Clinical trial participants can use their smartphones to film videos of themselves taking medication using AICURE, an AI-based platform. The AICURE program can check if the patient has taken their medicine using computer vision techniques. In addition to helping with therapy creation, this instrument may evaluate facial expressions to track how patients respond to treatment.[132]

22. Success narratives about the application of deep learning in pharmaceutical discovery and development

With the advancement of deep learning (DL) methodologies, major pharmaceutical companies are increasingly adopting artificial intelligence (AI), moving away from traditional methods to enhance patient outcomes and their own profitability. AstraZeneca's growth exemplifies the potential of integrating AI with medical science. Their ongoing efforts to expand AI usage are evident in their collaborations with other AI-based companies, such as their partnership with Alibaba subsidiary Ali Health to develop AI-assisted screening and diagnostics platforms in China.[133]

The SARS-CoV-2 outbreak has pressured numerous companies to identify effective drugs rapidly. Below are some notable success stories of companies that have identified potential leads against the COVID-19 virus.

MT-DTI: The Molecule Transformer Drug–Target Interaction Model (MT-DTI) is a deep learning model created by Deargen, a business located in the Republic of Korea. It is designed to predict the intensity of drug–protein interactions using simpler chemical sequences instead of 2D or 3D molecular structures. This model, when applied to FDA-approved antiviral medications, has shown that Atazanavir, an HIV treatment, is very likely to bind to and block a crucial protein of the SARS-CoV-2 virus.[134,135]

Benevolent AI: It is a biotechnology firm located in London that strategically utilizes biological data, artificial intelligence (AI), and machine learning (ML) to expedite research in the health industry. The firm has found six prospective pharmaceuticals, among which Ruxolitinib is now being evaluated in clinical trials for COVID-19. The FDA has approved their proposed use of Baricitinib in combination with Remdesivir for treating COVID-19 patients.[136]

The intersection of medical science and AI is also driving innovation in dermatology. A significant number of smartphone apps for skin cancer detection have been launched, offering a technological solution for individuals with suspicious lesions to determine the need for medical consultation. Between 2014 and 2017, approximately 235 dermatology smartphone apps were developed.[137] One successful example is the SkinVision app.[138]

23. AI in hospital pharmacy

AI has numerous applications within hospital pharmacy-based healthcare systems, including the organization of dosage forms tailored to individual patients, the selection of appropriate or available administration routes, and the formulation of treatment strategies.

Maintaining of medical records: Maintaining patient medical records is a complex task, involving data collection, storage, normalization,

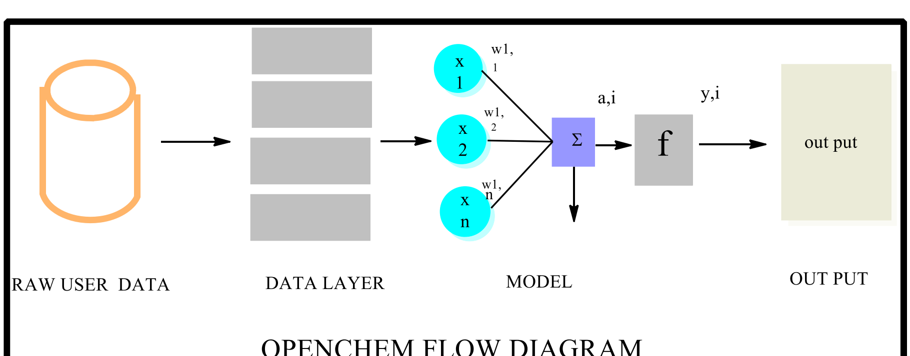

Fig. 7. Flow chart of OpenChem in which PyTorch used as a DLtoolkit to carry out the drug design.

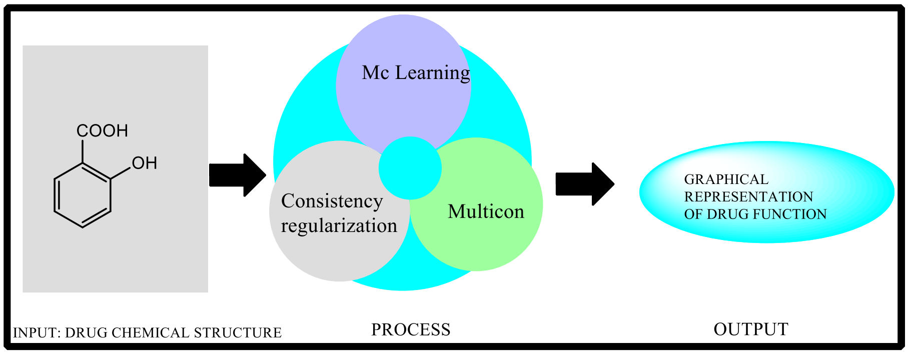

Fig. 8. Overview of the MultiCon toolkit.

and tracking. The implementation of AI systems has streamlined these processes. Google's DeepMind Health project, for instance, facilitates rapid extraction of medical records, enhancing the efficiency of healthcare delivery. This project has proven particularly valuable in improving eye care at Moorfields Eye Hospital NHS.

Health support and medication assistance: In recent years, the application of AI technology has proven to be highly effective in health support services and medication assistance. For instance, Molly, a virtual nurse developed by a start-up, features a friendly voice and a personable interface designed to assist patients by guiding their treatment and providing support for chronic conditions between medical appointments. Similarly, Ai Cure, an app available on smartphones, uses the device's webcam to monitor patients and help them manage their health conditions.

AI helps to people in health care system: It is capable of gathering and analyzing data through social awareness algorithms.[139] The extensive data accumulated within the healthcare system encompasses patients' medical histories, including their treatment profiles from birth, as well as their habits and lifestyles.

The Treatment plan designing: The development of effective treatment plans can be significantly enhanced through the application of AI technology. When a patient presents with a critical condition and selecting an appropriate treatment plan becomes challenging, AI systems are essential for managing the situation. These systems take into account all available data, including historical records, reports, and clinical expertise, to assist in formulating a treatment strategy. For example, IBM Watson has introduced a program specifically designed to support oncologists in this process.

Assisting in repetitive tasks: AI technology aids in the execution of repetitive activities, including the analysis of X-ray pictures, radiography, ECHO (Echocardiogram), and ECG (Electrocardiogram), with the purpose of detecting and identifying illnesses or problems. Developed by IBM, the Medical Sieve algorithm operates as a "cognitive assistant" equipped with sophisticated analytical and reasoning skills. Optimizing patient results necessitates the use of deep learning techniques with medical data via specialized medical start-ups. Dedicated computer programs are accessible for the analysis of certain anatomical regions and the treatment of particular medical disorders. Numerous imaging analyses, such as X-ray, CT (computed tomography) scans, ECHO, and ECG, may be effectively used using deep learning models.[139]

Conclusions: In the field of contemporary pharmaceutical research and hospital pharmacy, this approach is generally well-respected. It has great potential for improvement thanks to new deep learning (DL) tools. It is clear that contemporary DL techniques will be pivotal in the age of big data search and analysis for medication design and discovery, given the recent results and its adoption by pharmaceutical corporations to improve drug development. Getting a therapeutic candidate to the clinical trials stage has always been a difficult and time-consuming step in the drug discovery and development process. AI has made great strides in improving the success rate of this process, which in turn has decreased research expenses. The ecology of in silico drug creation necessitates the participation of specialists in data science, chemistry, biology, and other related disciplines in order to develop these algorithms. It is imperative that pharmacists have access to continuing education opportunities that help them learn about artificial intelligence. To better equip pharmacists to participate in the creation, regulation, and use of artificial intelligence, there has to be access to data science courses or residency programs that concentrate on AI-related subjects. To keep up with the fast-paced changes in these technologies and make sure our profession is ready to lead the way in care transformation, pharmacy schools need to be flexible.

CRediT authorship contribution statement

Saleem Javid: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Abdul Rahmanulla:** Resources, Formal analysis, Data curation. **Mohammed Gulzar Ahmed:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Investigation. **Rokeya sultana:** Writing – review & editing, Supervision, Software, Methodology, Formal analysis, Aishwarya Susil, Software, Resources, Methodology, Investigation, Data curation. **B.R. Prashantha Kumar:** Writing – review & editing, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Data curation, Conceptualization.

Conflicts of interest

The authors declare that they have no conflicts of interest with the article's contents.

Data availability

Data available will be made available on request.

Funding statement

The authors have not received any funding from any source.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

We greatly appreciate the support for this review article provided by Yenepoya Pharmacy College & Research Centre, Mangalore, Karnataka, India. The authors are thankful to the Yenepoya Pharmacy College & Research Centre, Mangalore, Karnataka, India and JSS Academy of Higher Education & Research, Mysore, Karnataka, India for supporting collaborative writing of review article.

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