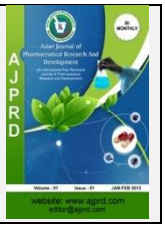
Available online on 15.04.2024 at http://ajprd.com

Asian Journal of Pharmaceutical Research and Development

Open Access to Pharmaceutical and Medical Research



Open Access

Review Article

The Impact of Artificial Intelligence on Drug Discovery; A Comprehensive Review

Muktai N.Rudrurkar *, Vishweshwar M. Dharashive, Dr. Sameer Shafi, Anis J. Kazi, Mohini A. Gurav, Sneha R. Patil, Punam V. Ritthe.

Shivlingeshwar College of Pharmacy, Almala Tq. Ausa Dist. Latur – 413520, Maharashtra, India.

A B S T R A C T

Artificial Intelligence (AI) is a technology that utilizes knowledge and learning to solve complicated problems. Recent advancements in computational power and AI technology have significantly increased its potential to revolutionize the drug development process. The pharmaceutical industry is among the primary beneficiaries of AI's recent applications in various sectors of society. In this review, we will discuss the primary causes of attrition rates in new drug approvals, explore how AI can improve the efficiency of the drug development process, and examine the collaboration between pharmaceutical industry leaders and AI-powered drug discovery firms.

Keywords: -Artificial Intelligence, Drug discovery, Drug development,AI based tools.

A R T I C L E I N F O: Received 24 Dec 2023; Review Complete 11 Jan 2024; Accepted 19 Feb.2024; Available online, 15 April. 2024

Cite this article as:

Muktai N.Rudrurkar*, Vishweshwar M. Dharashive, Dr. Sameer Shafi, Anis J. Kazi, Mohini A. Gurav, Sneha R. Patil, Punam V. Ritthe, The Impact of Artificial Intelligence On Drug Discovery; A Comprehensive Review, Asian Journal of Pharmaceutical Research and Development. 2024; 12(2):171-178. DOI: http://dx.doi.org/10.22270/ajprd.v12i2.1230

*Address for Correspondence:

Rudrurkar Muktai Naresh, Shivlingeshwar College of Pharmacy, Almala,Tq. Ausa Dist. Latur -413520, Maharastra MH, India.

INTRODUCTION:

Artificial intelligence (AI) refers to the process of simulating human intelligence by computers. This process involves the acquisition of information, development of rules for using it, concluding, and correcting itself. AI has become increasingly important in various sectors, including the pharmaceutical industry. It is used in many areas, from innovating educational methods to automating business processes. The idea of using AI in drug development has evolved from being hype to a hope. This review aims to discuss the potential applications of AI in drug development pipelines, pharmaceutical R&D efficiency, drug development strategies and processes, and the partnerships between AI and pharmaceutical companies.

AI, machine learning, and deep learning:

Artificial Intelligence (AI) is not a simple plug-and-play software. Instead, it is a complex and advanced set of clever technologies that are tailored to seek out and learn from data or experience. These technologies then perform tasks based on what they have learned while constantly improving through experience. AI is commonly defined as the use of techniques that enable computers to imitate human behavior.

Machine learning (ML) is a subfield of artificial intelligence (AI) that uses statistical methods to enable computer systems to improve their performance on a specific task over time [1-2]. There are three primary categories of machine learning: supervised learning, unsupervised learning, and reinforcement learning. In supervised learning, classification and regression techniques are used to develop a predictive model based on input and output data sources. The output from supervised machine learning includes disease diagnosis in the subgroup classification, and drug efficacy and ADMET prediction in the subgroup regression [3]. Unsupervised learning comprises clustering and feature-finding methods by grouping and interpreting data based solely on input data [4]. Unsupervised machine learning can achieve outputs such as discovering disease subtypes through clustering and discovering disease targets through feature-finding methods [5]. Reinforcement learning is a type of machine learning that focuses on making decisions and taking actions in a particular environment to improve its

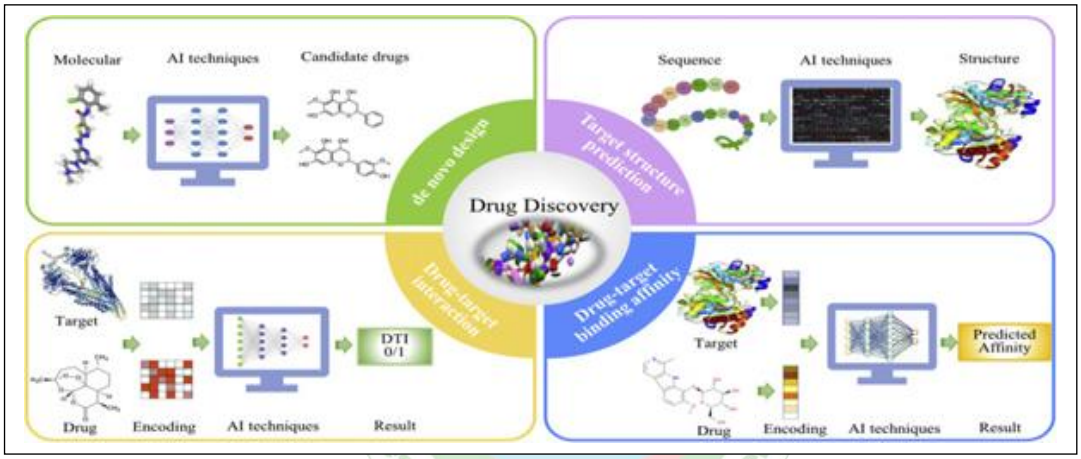
performance. This approach can generate new drug designs and execute experimental designs. Both objectives can be achieved through modeling and quantum chemistry [6].

Deep learning (DL), a subfield of machine learning (ML), utilizes artificial neural networks to adapt and learn from vast amounts of experimental data [2,7]. The use of big data, data mining, and various algorithmic methods can provide us with the ability to discover new compounds that could potentially become new drugs. Additionally, it can help us uncover or repurpose drugs that could be more potent when used alone or in combination. By leveraging genetic markers, personalized medicine can also be improved.

AI in drug discovery:

The huge chemical space, comprising> 1060 molecules, fosters the development of a large number of medicine molecules [8]. still, the absence of advanced technologies limits the medicine development process, making it a time-consuming and precious task, which can be addressed by using AI [9]. AI can fete megahit and lead composites, and give a hastily confirmation of the medicine target and optimization of the medicine structure design [8,10]. AI has multitudinous advantages, but it faces significant challenges when dealing with data, including the scale, growth, diversity, and query of the data. For case, datasets used in medicine development by pharmaceutical companies can contain millions of composites that traditional machine-literacy tools may not be suitable to handle.

Computational models based on Quantitative Structure-Activity Relationship (QSAR) are capable of predicting a large number of compounds or simple physicochemical parameters such as log P or log D quickly. However, these models may not always be accurate in predicting complex biological properties such as the efficacy and adverse effects of compounds.



QSAR-based models also face several challenges such as small training sets, experimental data errors in training sets, and a lack of experimental validations. To overcome these challenges, AI approaches such as Deep Learning (DL) and relevant modeling studies can be implemented for the safety and efficacy evaluation of drug molecules based on big data modeling and analysis.

Chemical space is a large virtual environment that represents a map of molecules, their distributions, and properties. The purpose of mapping chemical space is to collect information on the locations of molecules within the space to identify bioactive compounds. Virtual screening (VS) is a useful tool for selecting appropriate molecules for further testing. There are several open-access databases available for chemical space exploration, including Pub Chem, Chem Bank, Drug Bank, and Chem DB. Numerous in silico methods are used to virtually screen compounds from virtual chemical spaces, along with structure and ligand-based approaches. These methods provide a better profile analysis, faster elimination of no-lead compounds, and selection of drug molecules, all while reducing expenditure [8]. Drug design algorithms, such as coulomb matrices and molecular fingerprint recognition, consider physical, chemical, and toxicological profiles to identify the most promising compound[11].

Various methods, including predictive models, molecule similarity, generation, and in silico approaches, can be used to predict a compound's chemical structure [10,12]. Pereira et al. presented Deep VS, a new system for docking 40 receptors and 2950 ligands. It showed outstanding performance when tested against 95,000 decoys [13]. An automated replacement algorithm was used to optimize the potency profile of a cyclin-dependent kinase-2 inhibitor by assessing its shape similarity, biochemical activity, and physicochemical properties with a multi objective approach[14].

Table 1: Examples of AI tools used in drug discover

Tools	Details	Website URL
DeepChem	MLP model that uses a python-based AI system to find a suitable candidate in drug discovery	https://github.com/deepchem/deepchem
DeepTox	Software that predicts the toxicity of total of 12000 drugs	www.bioinf.jku.at/research/DeepTox
DeepNeuralNetQSAR	Python-based system driven by computational tools that aid detection of the	https://github.com/Merck/DeepNeuralNet-QSAR
ORGANIC	A molecular generation tool that helps to create molecules with desired properties	https://github.com/aspuru-guzik-group/ORGANIC
PotentialNet	Uses NNs to predict binding affinity of ligands	https://pubs.acs.org/doi/full/10.1021/acscentsci.8b00507
Hit Dexter	ML technique to predict molecules that might respond tobiochemical assays	http://hitdexter2.zbh.uni-hamburg.de
DeltaVina	A scoring function for rescoring drug–ligand binding	https://github.com/chengwang88/deltavina
Neural graph fingerprint	Helps to predict properties of novel molecules	https://github.com/HIPS/neural-fingerprint
AlphaFold	Predicts 3D structures of proteins	https://deepmind.com/blog/alphafold

Limitations of the Current Methods in Drug Discovery:

Currently, medicinal chemistry methods rely heavily on a hit-and-miss approach andlarge-scale testing techniques [15]. Large numbers of potential drug compounds are examined to identify those with desired properties. However, these methods can be slow, costly, and often yield results with low accuracy [16].

In addition, they can be limited by the availability of suitable test compounds and the difficulty of accurately predicting their behavior in the body.Different AI algorithms, including supervised and unsupervised learning, reinforcement, evolutionary, and rule-based methods, can help solve problems. These methods are typically based on the analysis of large amounts of data that can be exploited in different ways [17–18]. For instance, the efficacy and toxicity of new drug compounds can be predicted using these approaches, with greater accuracy and efficiency than when using traditional methods [19,20].

Furthermore, AI-based algorithms can also be employed to identify new targets for drug development, such as the specific proteins or genetic pathways involved in diseases [21]. This can expand the scope of drug discovery beyond the limitations of more conventional approaches and may eventually lead to the development of novel and more effective medications [22]. Traditional methods of pharmaceutical research rely on trial-and-error experimentation and do not accurately predict the behavior of new bioactive compounds [23]. AI-based approaches can improve drug discovery efficiency and accuracy, leading to more effective medications.

The Role of AI in Predicting Drug Efficacy and Toxicity:

Artificial Intelligence (AI) techniques, together with Machine Learning (ML), can predict the effectiveness and toxicity of drug compounds used in medicinal chemistry. Traditional methods of drug discovery involve time-consuming experiments to assess the potential impact of a compound on the human body. Developing new bioactive compounds can be a slow and expensive process, with outcomes that are often uncertain and vary significantly. However, ML algorithms are capable of analyzing vast amounts of information and identifying patterns and trends that may not be apparent to human researchers. This allows for the identification of new bioactive compounds with minimal side effects in a much faster and more efficient manner. A Deep Learning (DL) algorithm was trained on a dataset of known drug compounds and their biological activity [24]. Machine learning algorithms have been intensively trained using large databases containing known toxic and non-toxic compounds to prevent potential drug compounds from being toxic. This has led to significant advancements in accurately predicting the activity of new compounds[25]. Artificial Intelligence (AI) plays a crucial role in the process of drug discovery. One of its applications is to identify drug interactions that can occur when different drugs are combined for the same or different diseases in a patient. These interactions can lead to altered effects or adverse reactions. By analyzing large datasets of known drug interactions, AI-based approaches can recognize patterns and trends to identify the issue accurately. Recently, a machine learning algorithm has been used to predict the interactions of novel drug pairs with high accuracy [26]. Artificial Intelligence (AI) plays a crucial role in identifying potential drug interactions while considering personalized medicine. It facilitates the creation of tailored treatment plans that minimize the risk of negative reactions. Personalized medicine focuses on delivering specific treatments based on individual patient traits, such as genetic profile and response to medication.

The Effect of AI on the Drug Discovery Process and Potential Cost Savings:

AI can be utilized in drug discovery to design new compounds with specific properties and activities. Traditional methods usually involve modifying existing compounds, which is a labor-intensive and time-consuming process. However, AI-based approaches can speed up the development of novel compounds with desired characteristics and activities. A deep learning algorithm has been trained using a dataset of known drug compounds and their properties. This algorithm can propose new therapeutic molecules with desirable characteristics like solubility and activity. This demonstrates the potential of these methods for designing new drug candidates rapidly and efficiently[27]. DeepMind developed AlphaFold, a software platform advancing our understanding of biology[28]. The use of protein sequence data and AI to predict the corresponding three-dimensional structures of proteins is a powerful algorithm. This breakthrough in structural biology is expected to have a major impact on personalized medicine and drug discovery. AlphaFold marks significant progress in the application of AI in life sciences and structural biology in particular.

Combining machine learning (ML) techniques and molecular dynamics (MD) simulations has become a popular approach in de novo drug design, as it improves efficiency and accuracy by leveraging the strengths of both methods[29]. The use of interpretable machine learning (IML) and deep learning (DL) techniques is also contributing to drug design efforts.

Drug development process:

Drug development involves a feedback-driven process that begins by gathering existing results from multiple sources. These sources may include high-throughput compound and fragment screening, computational modeling, and literature reviews. The process alternates between induction and deduction to optimize the hit and lead compounds. Automating specific aspects of the cycle removes errors and randomness, thereby improving overall efficiency. For in silico compound synthesis, de novo design methods use organic chemistry knowledge. Additionally, virtual screening models can serve as surrogates for biochemical and biological efficacy and toxicity tests[30].

Figure: 2 Drug development process

In the initial stage of drug development, the first step is discovering new chemical compounds that have biological activity. This activity can result from the interaction of the compound with a specific enzyme or an entire organism. A compound that displays activity against a biological target is known as a "hit." Hits are often identified through the screening of chemical libraries, computer simulations, or examination of naturally occurring materials such as plants, bacteria, and fungi.

Identifying a lead molecule is the second most crucial step in the process of drug development. A lead molecule is a chemical compound that shows significant potential in treating a specific disease. These potential leads are then tested in cell-based assays and animal models to evaluate their efficacy and safety profile. Once a lead molecule is identified, scientists use its chemical structure as a starting point to explore different chemical modifications to discover new compounds that offer maximum therapeutic benefits with minimum potential for harm[32]

In the process of lead generation, scientists modify molecules that have the potential to hit biological targets. This modification aims to increase the activity and specificity of the molecules while also reducing their toxicity and unwanted effects. Compounds similar to the hit molecule and derived from it are called equivalents. This process is hit expansion [33]. Medicinal chemists play a critical role in the development of new drugs by using organic chemistry techniques to create a wide range of potential drug candidates. These candidates must be able to interact with the active site of the intended biological target, which is a specific region where the compound or substrate can bind through interaction forces.

Medicinal chemists use specific reactions to quickly assemble building blocks, which are compounds containing a reactive functional group and atoms that can interact with the biological target. To understand the binding of a substrate to the active site of the biological target, two models are utilized: the "lock and key" model and the "induced-fit" model. Both models help explain the molecular interactions between a drug candidate and its target, which aid chemists in the drug development process.

By using specific techniques, medicinal chemists can improve their chances of discovering an effective drug candidate. These techniques allow them to synthesize compounds more efficiently and test them for their ability to interact with the active site of the biological target. The ultimate goal is to discover a drug candidate that is safe and effective, and can be developed into a medicine for those in need.Medicinal chemists play a critical role in the development of new drugs by using organic chemistry techniques to create a wide range of potential drug candidates. These candidates must be able to interact with the active site of the intended biological target, which is a specific region where the compound or substrate can bind through interaction forces.

Medicinal chemists use specific reactions to quickly assemble building blocks, which are compounds containing a reactive functional group and atoms that can interact with the biological target. To understand the binding of a substrate to the active site of the biological target, two models are utilized: the "lock and key" model and the "induced-fit" model. Both models help explain the molecular interactions between a drug candidate and its target, which aid chemists in the drug development process.

By using specific techniques, medicinal chemists can improve their chances of discovering an effective drug candidate. These techniques allow them to synthesize compounds more efficiently and test them for their ability to interact with the active site of the biological target. The ultimate goal is to discover a drug candidate that is safe and effective and can be developed into a medicine for those in need[34]

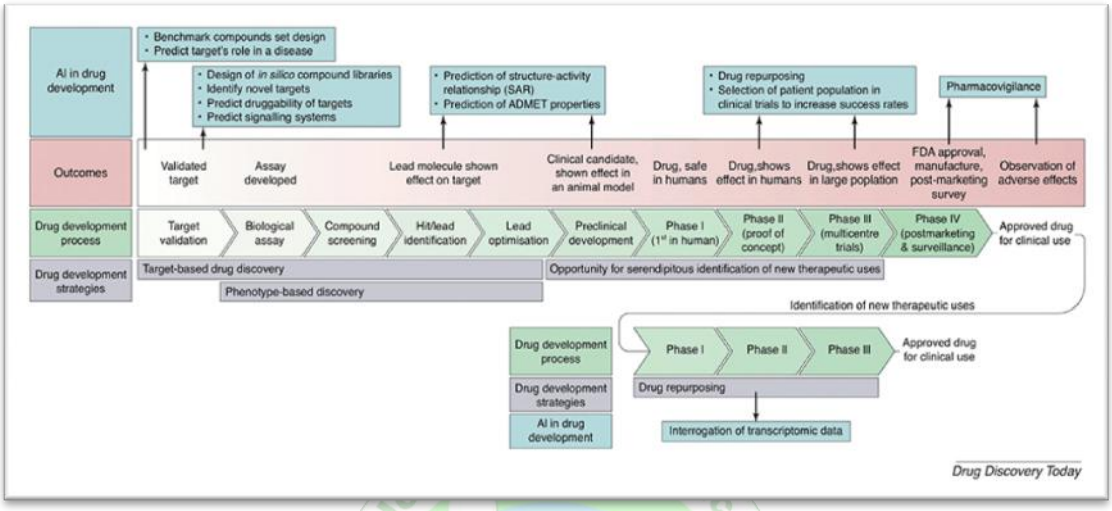


Figure: 3 Utilisation of artificial intelligence (AI) in the drug development process.

The outcomes and the strategies of the various components of the drug development process are defined. The applications of AI at each stage of drug developmentare also displayed.

AI has become a versatile tool that can be applied ubiquitously in various stages of drug development. It can help in identifying and validating drug targets, designing new drugs, repurposing existing drugs, improving R&D efficiency, aggregating and analysing biomedicine information, as well as refining the decision-making process to recruit patients for clinical trials [35–36]. AI can minimize bias and human intervention in drug development [37].The other uses of AI in drug development include the prediction of feasible synthetic routes for drug-like molecules [38], pharmacological properties [39], protein characteristics as well as efficacy [40], drug combination and drug–target association [41] and drug repurposing [42]. Also, the identification of new pathways and targets using omics analysis becomes possible via the generation of novel biomarkers and therapeutic targets, personalised medicine based on omics markers and discovering the connections between drugs and diseases [43,44]. DL has demonstrated outstanding success in proposing potent drug candidates and accurately predicting their properties and the possible toxicity risks [45]. Circumventing past issues in drug development, such as analysing large datasets, screening compounds while minimizing standard error, and requiring substantial R&D costs and time of over US$2.5 billion and a more than a decade [46] – are now possible using AI methods [47]. With AI technology, new studies can be carried out in assisting the identification of new drug targets, rational drug designing and drug repurposing [48,49].

AI in advancing pharmaceutical product development:

Dosage form with desired delivery characteristics. In this area, AI can replace the older trial-and-errorapproach [50]. Various computational tools can resolve problems encountered in the formulation design area, such as stability issues, dissolution, porosity, and so on, with the help of QSPR [51]. Decision-support tools use rule-based systems to select the type, nature, and quantity of excipients based on the physicochemical attributes of the drug, and The discovery of a novel drug molecule requires its subsequent incorporation in a suitable operation through a feedback mechanism to monitor and modify the entire process intermittently. [52]. Guo et al. integrated Expert Systems (ES) and ANN to create a hybrid system for the development of direct-filling hard gelatine capsules of piroxicam in accordance with the specifications of its dissolution profile. The MODEL EXPERT SYSTEM (MES) generates decisions and recommendations for formulation development based on input parameters. By contrast, ANN uses backpropagationlearning to link formulation parameters to the desiredresponse, jointly controlled by the control module, to ensure hassle-free formulation development [50]. Various mathematical tools, such as computational fluid dynamics (CFD), discrete element modeling (DEM), and the Finite Element Method have been used to examine the influence of the flow property of the powder on the die-filling and process of tablet compression [53,54]. CFD can also be utilized to study the impact of tablet geometry on its dissolution profile [55]. The combination of these mathematical models with AI could be immensely helpful in rapidly producing pharmaceutical products.

AI-based advanced applications:

- **AI-based Nanorobots for drug delivery**

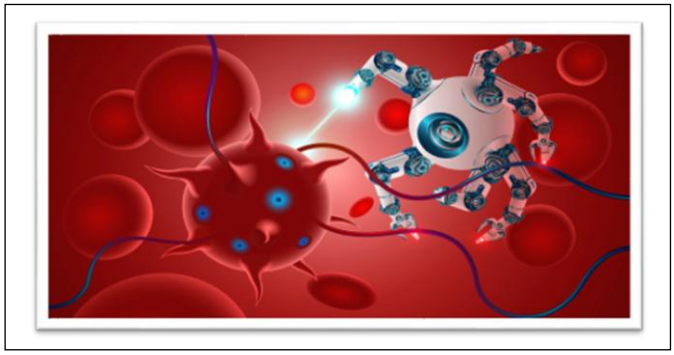


Figure: 4 AI-based Nanorobots for drug delivery

Nano robots consist of integrated circuits, sensors, power supply, and data backup mechanisms, all of which are maintained using computational technologies like AI [56,57]. They are designed to avoid collisions, identify targets, detect and attach, and ultimately excrete from the body. Advancements in nanorobotics and microrobotics have given them the ability to navigate to specific sites based on physiological conditions, such as pH, resulting in improved efficacy and reduced systemic adverse effects [57]. The development of implantable nanorobots for controlled drug and gene delivery requires consideration of parameters such as dose adjustment, sustained release, and controlled release. The release of drugs requires automation controlled by AI tools such as NNs, fuzzy logic, and integrators [58]. Microchip implants are also used for programmed release and to detect the location of the implant in the body.

- **AI in combination drug delivery and synergism/antagonism Prediction**

Several drug combinations are approved and marketed to treat complex diseases such as tuberculosis and cancer as they provide a synergistic effect that enables quick recovery [59,60]. To create a collection of effective drug combinations, a large number of drugs need to be screened through a high throughput process. This can be a tedious procedure, especially for cancer therapy which requires six or seven drugs as a combination therapy. To streamline this process, ANNs, logistic regression, and network-based modeling techniques can be used to screen drug combinations and improve overall dosage regimens [59,61]. Rashid et al. developed a quadratic phenotype optimization platform for the finding of optimal combination therapy for the treatment of bortezomib-resistant multiple myeloma using an assembly of 114 FDA-approved drugs. This model suggested the mixture of decitabine (Dec) and mitomycin C (MitoC) as the best two-drug mixture and Dec, Mito C, and mechlorethamine as the superior three-drug combination [60].

- **AI emergence in nanomedicine**

Nanomedicines are a blend of nanotechnology and medicine that help diagnose, treat, and monitor complex diseases such as HIV, cancer, malaria, asthma, and various inflammatory diseases. In recent years, the use of nanoparticle-modified drug delivery has become crucial in the field of therapeutics and diagnostics as it enhances treatment efficacy. Combining nanotechnology and AI has the potential to solve several challenges in formulation development.

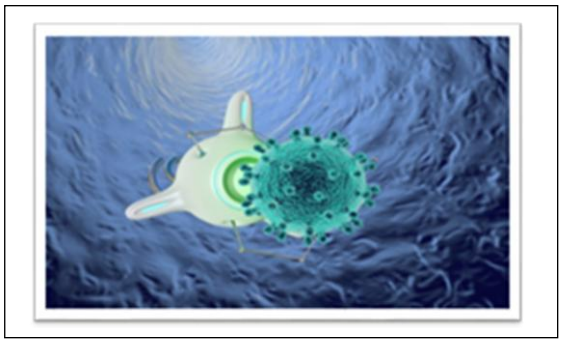


Figure: 5 Nanomedicine

CONCLUSION:

Artificial intelligence has the potential to significantly improve and reshape the process of drug development. With the advancement of technology, collaborations between AI experts, bioinformaticians, and pharmaceutical researchers are likely to become crucial for unlocking the full potential of AI in creating safer and more effective drugs. It is advisable to stay updated regularly on the latest developments in the field due to the rapid pace of advancements in AI and drug development.

REFERENCES

1. Bishop, C.M. (2013) Model-based machine learning. Philos. Trans. A Math. Phys. Eng. Sci. 371
2. Lee, J.-G. et al. Deep learning in medical imaging: general overview. Korean J. Radiol. 2017;18:570–584
3. Gun9car, G. et al. An application of machine learning to haematological diagnosis. Sci. Rep. 2018; 8:411
4. Koohy, H. 2018 The rise and fall of machine learning methods in biomedical research. F1000 Res. 6
5. Young, J.D. et al. Unsupervised deep learning reveals prognostically relevant subtypes of glioblastoma. BMC Bioinf. 2017; 18: 381
6. Chen, H. et al. The rise of deep learning in drug discovery. Drug Discov. Today 2018; 23, 1241–1250
7. Grys, B.T. et al. (2017) Machine learning and computer vision approaches for phenotypic profiling. J. Cell Biol. 2017; 16:65–71
8. Mak, K.-K. and Pichika, M.R. (2019) Artificial intelligence in drug development: present status and future prospects. Drug Discovery Today 24, 773–780
9. Vyas, M. et al. (2018) Artificial intelligence: the beginning of a new era in pharmacy profession. Asian J. Pharm. 12, 72–76
10. Sellwood, M.A. et al. (2018) Artificial intelligence in drug discovery. Fut. Sci. 10, 2025–2028
11. Chan, H.S. et al. (2019) Advancing drug discovery via artificial intelligence. Trends Pharmacol. Sci. 2019; 40 (8):592–604
12. Brown, N. (2015) Silico Medicinal Chemistry: Computational Methods to Support Drug Design. Royal Society of Chemistry
13. Pereira, J.C. et al. Boosting docking-based virtual screening with deep learning. J. Chem. Inf. Model. 2016; 56:2495–2506
14. Firth, N.C. et al.MOARF, an integrated workflow for multiobjective optimization: implementation, synthesis, and biological evaluation. J. Chem. Inf. Model. 2015; 55:1169–1180
15. Wess, G.; Urmann, M.; Sickenberger, B. Medicinal Chemistry: Challenges and Opportunities. Angew. Chem. Int. Ed. **2001**; 40, 3341–3350. [CrossRef]
16. Pu, L.; Naderi, M.; Liu, T.; Wu, H.C.; Mukhopadhyay, S.; Brylinski, M. EToxPred: A machine learning-based approach to estimate the toxicity of drug candidates. BMC Pharmacol. Toxicol. **2019**; 20:2. [CrossRef]
17. Chen, R.; Liu, X.; Jin, S.; Lin, J.; Liu, J. Machine learning for drug-target interaction prediction. Molecules **2018**; 23:2208. [CrossRef] [PubMed]
18. Hansen, K.; Biegler, F.; Ramakrishnan, R.; Pronobis, W.; Von Lilienfeld, O.A.; Müller, K.R.; Tkatchenko, A. Machine learning predictions of molecular properties: Accurate many-body potentials and nonlocality in chemical space. J. Phys. Chem. Lett. **2015**; 6:2326–2331. [CrossRef]
19. Gawehn, E.; Hiss, J.A.; Schneider, G. Deep Learning in Drug Discovery. Mol. Inform. **2016**; 35:3–14. [CrossRef]
20. Lysenko, A.; Sharma, A.; Boroevich, K.A.; Tsunoda, T. An integrative machine learning approach for prediction of toxicity-related drug safety. Life Sci. Alliance **2018**; 1: e201800098. [CrossRef]
21. You, J.; McLeod, R.D.; Hu, P. Predicting drug-target interaction network using deep learning model. Comput. Biol. Chem. **2019**; 80:90–101. [CrossRef]
22. Liu, X.; IJzerman, A.P.; vanWesten, G.J.P. Computational Approaches for De Novo Drug Design: Past, Present, and Future. In Methods in Molecular Biology; Humana Press Inc.: Totowa, NJ, USA, 2021; 21 (90):139–165.
23. Bannigan, P.; Aldeghi, M.; Bao, Z.; Häse, F.; Aspuru-Guzik, A.; Allen, C. Machine learning directed drug formulationdevelopment.Adv. Drug Deliv. Rev. **2021**;175:113806. [CrossRef]
24. Hansen, K.; Biegler, F.; Ramakrishnan, R.; Pronobis, W.; Von Lilienfeld, O.A.; Müller, K.R.; Tkatchenko, A. Machine learning predictions of molecular properties: Accurate many-body potentials and nonlocality in chemical space. J. Phys. Chem. Lett. **2015**; 6:2326–2331. [CrossRef]
25. Santín, E.P.; Solana, R.R.; García, M.G.; Suárez, M.D.M.G.; Díaz, G.D.B.; Cabal, M.D.C.; Rojas, J.M.M.; Sánchez, J.I.L. Toxicity prediction based on artificial intelligence: A multidisciplinary overview. Wiley Interdiscip. Rev. Comput. Mol. Sci. **2021**, 11, e1516. [CrossRef]
26. Jang, H.Y.; Song, J.; Kim, J.H.; Lee, H.; Kim, I.W.; Moon, B.; Oh, J.M. Machine learning-based quantitative prediction of drug exposure in drug-drug interactions using drug label information. npj Digit. Med. **2022**; 5:100. [CrossRef] [PubMed]
27. Gómez-Bombarelli, R.; Wei, J.N.; Duvenaud, D.; Hernández-Lobato, J.M.; Sánchez-Lengeling, B.; Sheberla, D.; Aguilera Iparraguirre, J.; Hirzel, T.D.; Adams, R.P.; Aspuru-Guzik, A. Automatic Chemical Design Using a Data-Driven Continuous Representation of Molecules. ACS Central Sci. **2018**; 4:268–276. [CrossRef]
28. Nussinov, R.; Zhang, M.; Liu, Y.; Jang, H. AlphaFold, Artificial Intelligence (AI), and Allostery. J. Phys. Chem. B **2022**;126:6372–6383. [CrossRef] [PubMed]
29. Bai, Q.; Liu, S.; Tian, Y.; Xu, T.; Banegas-Luna, A.J.; Pérez-Sánchez, H.; Huang, J.; Liu, H.; Yao, X. Application advances of deep learning methods for de novo drug design and molecular dynamics simulation. Wiley Interdiscip. Rev. Comput. Mol. Sci. **2022**;12:e1581. [CrossRef]
30. Yuan, Y. et al.Lig Builder 2: a practical de novo drug design approach. J. Chem. Inf. Model. 2011;51:1083–1091
31. Zhu, T. et al. Hit identification and optimization in virtual screening: practical recommendations based on a critical literature analysis. J. Med. Chem. 2013; 56,6560–6572
32. Anderson, A.C. (2012) Structure-based functional design of drugs: from target to lead compound. Methods Mol. Biol. 2012; 823:359–366
33. Hall, D.R. et al. Hot spot analysis for driving the development of hits into leads in fragment-based drug discovery. J. Chem. Inf. Model. 2012; 52, 199–2091 34
34. Alanine, A. et al. Lead generation-enhancing the success of drug discovery by investing in the hit to lead process. Comb. Chem. High Throughput Screen. 2003; 6:51–66
35. Huang, Z. et al. (2017) Data mining for biomedicine and healthcare. J. Healthc. Eng. 2017 http://dx.doi.org/10.1155/2017/7107629 Article ID 7107629, 2 pages
36. Mamoshina, P. et al. Applications of deep learning in biomedicine. Mol. Pharm. 2016; 13:1445–1454
37. Seddon, G. et al. Drug design for ever, from hype to hope. J. Comput. Aided Mol. Des. 2012; 26:137–150
38. Merk, D. et al.De novo design of bioactive small molecules by artificial intelligence. Mol. Inform. 2018; 37:1700153
39. Klopman, G. et al. ESP: a method to predict toxicity and pharmacological properties of chemicals using multiple MCASE databases. J. Chem. Inf. Comput. Sci. 2004; 44:704–715
40. Menden, M.P. et al. (2013) Machine learning prediction of cancer cell sensitivity to drugs based on genomic and chemical properties. PLoS One 8, e61318
41. Nascimento, A.C.A. et al. (2016) A multiple kernel learning algorithm for drug-target interaction prediction. BMC Bioinf. 17, 46
42. Schneider, G. Automating drug discovery. Nat. Rev. Drug Discov. 2017; 17:97–113
43. Matthews, H. et al. (2016) Omics-informed drug and biomarker discovery: opportunities, challenges and future perspectives. Proteomes 4 http://dx.doi.org/ 10.3390/proteomes4030028
44. Hamet, P. and Tremblay, J.Artificial intelligence in medicine. Metabolism 2017; 69:S36–S40
45. Hughes, J.P. et al. Principles of early drug discovery. Br. J. Pharmacol. 2011; 162:1239–1249
46. Mohs, R.C. and Greig, N.H.Drug discovery and development: role of basic biological research. Alzheimers Dement. 2017; 3:651–657
47. Katsila, T. et al. (2016) Computational approaches in target identification and drug discovery. Comput. Struct. Biotechnol. J. 14, 177–184
48. Emig, D. et al.Drug target prediction and repositioning using an integrated network-based approach. PLoS One 2016; 8: e60618
49. Duch, W. et al. Artificial intelligence approaches for rational drug design and discovery. Curr. Pharm. Des. 2007; 13: 1497–1508
50. Guo, M. et al. A prototype intelligent hybrid system for hard gelatin capsule formulation development. Pharm. Technol. 2002; 6:44–52
51. Mehta, C.H. et al.Computational modeling for formulation design. Drug Discovery Today 2019; 24:781–788
52. Zhao, C. et al. Toward intelligent decision support for pharmaceutical product development. J. Pharm. Innovation 2006; 1:23–35
53. Rantanen, J. and Khinast, J.The future of pharmaceutical manufacturing sciences. J. Pharm. Sci. 2015; 104:3612–3638
54. Ketterhagen, W.R. et al. Process modeling in the pharmaceutical industry using the discrete element method. J. Pharm. Sci. 2009; 98:442–470
55. Chen, W. et al. Mathematical model-based accelerated development of extended-release metformin hydrochloride tablet formulation. AAPS PharmSciTech 20165; 17:1007–1013
56. Hassanzadeh, P. et al.The significance of artificial intelligence in drug delivery system design. Adv. Drug Delivery Rev. 2019; 151:169–190
57. Luo, M. et al.Micro-/nanorobots at work in active drug delivery. Adv. Funct. Mater. 2018; 28:1706100
58. Fu, J. and Yan, H.Controlled drug release by a nanorobot. Nat. Biotechnol. 2012; 30:407–408

59. Calzolari, D. et al. (2008) Search algorithms as a framework for the optimization of drug combinations. PLoSComput. Biol. 4, e1000249
60. Wilson, B. and KM, G.Artificial intelligence and related technologies enabled nanomedicine for advanced cancer treatment. Future Med. 2020; 15:433–435
61. Tsigelny, I.F. Artificial intelligence in drug combination therapy. Brief. Bioinform. 2019; 20:1434–1448
62. Ho, D. et al. Artificial intelligence in nanomedicine. Nanoscale Horiz. 2019; 4:365–377
63. Sacha, G.M. and Varona, P.Artificial intelligence in nanotechnology. Nanotechnology 2013; 24:452002