International Journal of Creative and Open Research in Engineering and Management
ISSN: **3108-1754 (Online)**
Volume 02 Issue 06 June-2026 | Impact Factor: 3.5

Revolutionizing Drug Discovery: The Evolving Role of Artificial Intelligence and Machine Learning

Harikrishna Bommala[1]

[1] Associate Professor, Department of Computer Science and Engineering, KG Reddy College of Engineering and Technology, Hyderabad, India.

Corresponding Author Email: haribommala@gmail.com, ORCID: https://orcid.org/0000-0002-9932-6152

How to Cite this Article:

Harikrishna Bommala. (2026). Revolutionizing Drug Discovery: The Evolving Role Of Artificial Intelligence And Machine Learning. International Journal of Creative and Open Research in Engineering and Management, 02(6). https://doi.org/10.55041/ijcope.v2i6.120

https://doi.org/10.55041/ijcope.v2i6.120

Abstract—

The recent surge in artificial intelligence and machine learning has been noteworthy. It has decreased the workload of humans significantly enhanced the quality of life. The article explains the application of artificial intelligence and machine learning in supporting drug discovery and drug development to make them efficient and accurate. In the present study, a systematic review of studies was conducted; these were identified based on earlier knowledge of the authors and keyword search in easily accessible databases which were filtered according to related context, abstract, methodology, and full text. This collection of work substantiated the role of machine learning and artificial intelligence in making drug development and drug discovery processes cost-effective or entirely eliminating clinical trials, due to the facilitation of the simulation process through these technologies. They also made it possible for researchers to investigate various molecules more comprehensively, without trials. The findings of the paper illustrate the common application of machine learning and artificial intelligence techniques in drug discovery, and point towards a bright future for these technologies; these findings should allow researchers, students, and the pharmaceutical industry to explore machine learning and artificial intelligence further in a drug discovery and development environment.

Keywords— Artificial Intelligence; Drug Discovery; Pharmaceutical; Polypharmacology; Machine Learning.

I. INTRODUCTION

Everything in life is always in a state of change, and one of the greatest human purposes is to manage these changes to our advantage; this is particularly true in the medicines and pharmaceutical sciences. These sciences include the manufacture or discovery of chemical compounds and blends and the application to alleviate physical and psychological pain. Drug product manufacture has been regulated for decades by a system of control that protects the quality of final products by raw material testing, in-process material testing, end-product attribute testing, batch-type operations and fixed process conditions [1]. The pharmaceutical and drug industries have been closed source of new and innovative technologies or equipment, and have led the development of new principles or interpretations in general chemical and mechanical engineering. The pharmaceutical business urgently requires mechanical innovation, simplifying the development of medications for human use. Development and production of complex process medications safe for use by human beings on a commercial scale, and integration into mainstream therapeutic practice, has been difficult, due to current constraints on technological resources [1]. Current drug prescribing practices are on a "one size fits all" basis; however, there are numerous critical areas of medicine that require new methods and thus new pharmacological development processes. Recent breakthroughs in genomics and diagnostics have made new and innovative pharmaceutical products and techniques an option, based on new tools for analysis and accurate portions. Medications such as these that are customized to the biology of the patient would make this business more efficient. The level of development of medical plans and construction of these items currently can't meet the requirements of customized medicine. New manufacturing structures to assemble and enable flexible assembly of customized technology and machinery are required in the pharmaceutical sector [1]. The use of artificial intelligence (AI) is becoming common, and will increasingly modify the nature of clinical examination and training. Doctors are able to assist in the development of this technology to be utilized in the pharmaceutical and medical sectors; this will assist in ensuring that the potential of AI to radically improve the delivery of medical care is brought into reality [2]. AI is currently utilized in the pharmaceutical sector in four manners. The first is in quantifying the severity of disease and predicting the effectiveness of treatment for a given patient, even before administration. Second, it is utilized in avoiding or rectifying complications that have developed during treatment. Its third major use is as an assistive technology to support treatment procedures or operations on patients. Lastly, it is utilized to determine the reason for the utilization of specific instruments or chemicals during treatment, and to develop or extrapolate new uses for instruments or chemicals to improve safety and efficacy. AI also has a more general use in the management and analysis of big data [3]. Big data is a new paradigm for describing the acquisition of very large data sets and marrying these with advanced analytics that enable new knowledge or insight into these data [4-5]. In the pharmaceutical sector, traditional data storage approaches are thus becoming obsolete as data volume grows. Big data provides a huge opportunity for more in-depth research as a result of data mining in this industry, and may augment pharmaceutical manufacturing, using a three-step data management process following acquisition involving the following steps: extraction and collation of big chunk of scattered and heterogeneous data; data configuration to ensure uniform formatting; and finally data analysis using various analytical platforms to yield a final output, the interpretation of which may inform decisions on which compounds or medicines to develop or which processes to use to maximise efficiency [5]. AI-enabled technology is actively being adopted to tackle minor yet crucial concerning issues in drug and development industries due to the advancements, growth and the adaption of surplus amounts of data available for generating meaningful insights. Therefore, the authors see a need to put together a comprehensive article scrutinizing AI, machine learning, and big data's contribution towards drug discovery and development, consisting of the latest technology, progress and novel studies done by the researchers in this field and what the future holds for the pharmaceutical industry when it practically incorporates the latest works of AI into it.

II. SEARCH METHODOLOGY AND ARTICLE SELECTION

Since machine learning has been utilized to solve critical issues in drug development and drug discovery, we aimed to critically evaluate the existing technology, advancements, and novel researches conducted by researchers within this field. As studied and searched current literature in a systematic way by employing key words related to this field (e.g., ["Artificial Intelligence" or "Advanced Technology"] + "Machine Learning" + ["SVM or ANN"] + [Drug Discovery or

Drug Development]) in publicly available databases like Google Scholar (July 2016– July 2025), arXiv (July 2016– July 2025), Researchgate (July 2016– July 2025), ScienceOpen (July 2016– July 2025), IEEE Xplore (July 2016– July 2025) and PubMed (July 2016– July 2025). Approximately 106 studies were eligible to be included in our literature review after filtering by context, abstract, and methodology.

III. DRUG DISCOVERY

3.1 ADVANCED TECHNOLOGIES IN DRUG DISCOVERY

Our literature search brought us to the fact that there are a number of different technologies and methods that are currently in practice within the pharmaceutical industries to help with drug discovery as well as drug production. One of these technologies is the in silico absorption, distribution, metabolism, and excretion (ADMET) platform (Bayer, Leverkusen, Germany). This technology models pharmacokinetic and physicochemical endpoints for the manufacturing of new pharmaceutical medicines [6]. Hypothetically, two relatively different methodologies can be utilized in the application of this technology. The first measures these results in terms of the interaction between interest compounds and defined proteins [6]. The drawback of this methodology is that it utilizes single proteins with effects clearly correlated with the ADMET outcomes such as: change in cognition, safety, and cost-effectiveness measured; high definition and three dimensional (3D) imaging of the protein of interest is also required. The second methodology is the gathering and compilation of secondary data based on the above parameters, for a number of different compounds utilized to produce proteins; based on this data, complex/hybrid deep learning models can be thought of with the help of machine learning algorithms and AI [6]. However, this method requires heavy manual maintenance and accuracy; even the smallest blunders in design can create spurious results and conclusions, which consume a lot of time and money. Even without blunders, this method takes an enormous amount of time to be performed since enormous amounts of data have to be monitored, moderated, and deleted manually [6]. Another technology utilized in the pharmaceutical sector is blockchain. Blockchain is a data structure type based on the collection and collation of records and converting them into blocks and linking them to one another in chronological order creation to a chain; hence the name blockchain. There are several different traits of blockchain which make it applicable in the pharmaceutical sector. These include factors of permanence, decentralization, straightforwardness and recognisability [7]. Permanence is the immutable and unmodifiable character of the data in the blockchain. Decentralization is the fact that several entities can be tasked with data handling in the system. Straightforwardness is the openness of the data stored in a blockchain, and that a user can see all data stored in the entire blockchain. Recognizability is the fact that a blockchain user can trace the information stored in the blockchain with unchallengable timestamps. In a pharmaceutical scenario, these factors guarantee that manufacturers of drugs can see and trace their data and transactions at will [7]. As per various studies, blockchain has made drug testing and clinical trials easier to perform, and also made the distribution chain of pharmaceutical companies more effective and easy to trace [7]. Blockchain, however, has some drawbacks. For example, as it is a new and emerging technology, it carries enormous installation costs and maintenance costs which are still unaffordable by small companies, thus making it less useful. Due to the cost factor, very few people have experience with and can operate this kind of technology, making it applicable in only more affluent geographical areas. There is still much more to be achieved before expensive technologies such as blockchain can be used more extensively to realize their phenomenal potential [7]. A third high-tech technology used by the pharmaceutical industry today is 3D printing [8]. More advanced uses of this technology use blue rather than white light, which improves accuracy due to its higher capacity to transfer impedance. These technologies offer the possibility to install reproduction of objects incrementally; developments in 3D printing also allow the production of objects on-site and on-demand by a wide range of individuals and industries due to the omnipresence and ease of advanced 3D printing [9]. Overall, we saw a pattern of deficits and problems that affect the utility, effectiveness and overall impact of these new technologies used by the pharmaceutical industry. Future developments will likely address this by reducing cost, improving effectiveness, and improving consumer-friendliness, so increased use and adoption can be utilized to further human health.

3.2.MACHINE LEARNING IN DRUG DISCOVERY

Drug discovery is one of the many areas of the pharmaceutical industry where machine learning is being used more and more, which is helping the sector as a whole. The growing number of businesses where machine learning plays a major role in their organizational structure is evidence of machine learning's accomplishments. They claimed that big pharmaceutical companies have also looked into using machine learning techniques for drug research and development [10]. Future developments in the field of drug discovery must therefore incorporate machine learning due to its vast potential and practicality. Reducing the asset and work seriousness of medication disclosure is the aim of high-throughput screening technologies. Machine learning could the need for testing on live animals [10]. These studies show that machine learning is a very helpful tool for finding new drugs. In order to improve and advance machine learning technologies for drug discovery and development, certain chemical and biological information is required. The insights gleaned from data would aid in the design of increasingly sophisticated and precise systems [11]. Assays will be required to measure medicinal features like cytochrome P450 (CYP) inhibition values, pharmacokinetic endpoints, on-target activity, animal model efficacy, cellular toxicity, and cell structure heterogeneity in order to collect these data [11]. A condensed timeline of the steps involved in applying machine learning to the pharmaceutical sector, particularly in the development of [12] the need for in vivo animal testing [10]. These experiments show that machine learning is a very helpful tool in drug discovery.

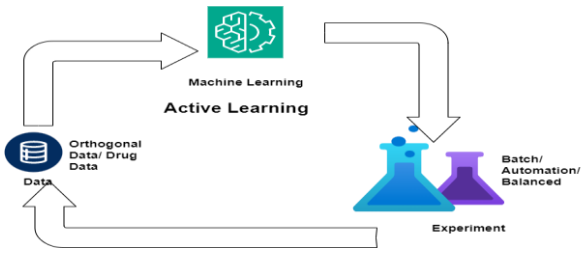

Figure 1: Machine learning in drug discovery

Some chemical and biological information factors are required to improve and create machine learning technologies for drug discovery and development. They would contribute to the design of more sophisticated and precise systems by the results from data [11]. To obtain these data, medicinal features like cellular toxicity, cell structure heterogeneity, animal model activity, on-target activity, pharmacokinetic endpoints, microsomal stability, and cytochrome P450 (CYP) inhibition values will have to be measured by assays [11]. Figure 1 illustrates a simplified cycle of the events that occur during the use of machine learning in the pharmaceutical industry, more specifically the development and manufacturing process of this industry, and also illustrates how machine learning works in general [12]. The data include different components, like orthogonal data and applicability domain and termination data. These data are fed into a pre-designed algorithm that considers model decisions, selection functions, and orthogonal calculations. The algorithm produces results as well as iterative improvements to the present methodology and procedures to make it efficient and reliable. The method is then adjusted, and the cycle is repeated until a final product is designed and manufactured. One experiment that illustrates the use of machine learning in the field of drug discovery was conducted by Margulis and others [13], which illustrates how intensely bitter molecules can be detected with the assistance of machine learning in the early stages of drug development. The aim was to see whether a certain algorithm employed in machine learning could be employed as a substitute for animal testing in an attempt to identify the bitterness of certain molecules employed in drugs. A total of 80% of the bitter molecules found were similar to those found from a brief access taste aversion (BATA) experiment, indicating that this experiment was successful. After the BATA experiment the findings indicated that the issue of toxicity and bitterness weren't always intertwined, as was initially thought. This indicates that machine learning was able to generate results that were accurate enough as well as generate new information. A study conducted by Raschka et al. [14-15] indicates how machine learning can be employed in G-protein coupled receptor (GPCR) ligand recognition, an integral part of the drug discovery process. The aim of their study was to see whether machine learning was capable of taking the place of the older technology employed in Sea Lamprey Receptor 1 (SLOR1) receptor signal inhibiting experiments, employing these experiments to crosscheck results obtained using the machine learning algorithm. Results from the algorithm were similar to the considered baseline performance, indicating that the new algorithm had potential to take the place of the

older technology in identifying other molecules' traits. It also indicated that machine learning had the potential to be employed on a lot of different things (like multimedia, medicine, petroleum industry etc.), indicating its potential in drug discovery. Another study indicating the employment of machine learning in this section was conducted by Pereira and colleagues. The aim of the study was to see whether a machine learning algorithm had potential to identify and rank docking receptors with the correct corresponding ligands among other things or compounds. The results showed that the machine learning algorithm was more efficient compared to the traditional ranking mechanism of the docking receptors. This also showed that machine learning can be utilized for other applications like the synthesis of molecular libraries and databases and the identification of the pharmacokinetic properties of novel drugs. They tested to predict the antifungal activity and antibacterial activity of various drugs and molecules based on their action on various fungi and bacteria. A linear description analysis algorithm was combined with an array of heterogeneous descriptors like stimulants, depressants, hallucinogens, dissociative, opioids, inhalants and cannabis. The results showed that this identification process of drug characteristics was more effective compared to other non-linear approaches, contributing to the evidence base for the utilization of machine learning to create drugs. Another study in appreciating the virtue of machine learning attempted to identify whether machine learning algorithms and deep learning (neural networks) could be combined and utilized in an analysis of the restorative and remedial activities of various drugs on genes. Results showed that the prediction accuracy of drug categories improved considerably from the baseline model, and they were classified more accurately resulting in a greater accuracy percentage. Thus, the improved accuracy shows that combining deep learning neural networks with machine learning algorithms improved the efficiency of this classification system of drugs and classified drugs more accurately with heterogeneous pharmacodynamic and pharmacokinetic properties. Two studies, by Rantanen and Khinast [16] and Turki and Taguchi [17], respectively, represent two distinct subcategories of machine learning, and can be meaningfully compared. Turki and Taguchi utilized reinforcement learning (one of the three paradigms of machine learning, the other two being supervised learning and unsupervised learning) to accelerate the process utilized to identify potentially useful drugs, while Zhavoronkov and Mamoshina utilized transfer learning (a machine learning (ML) problem that is concerned with storing knowledge gained during the solution of a problem and transferring it to a related but different problem) in a bid to predict reactions of patients suffering from multiple myeloma to a drug that had already been discovered. Turki and Taguchi demonstrated that the drug discovery process took 46 days, a huge difference from time taken using the traditional approach. The outcome of Zhavoronkov and Mamoshina's study indicated predictability above their baseline readings. Turki and Taguchi determined that there is still some margin for improvement, as far as coding the algorithm, so that synthesized compounds have different formulas with regard to existing market products; while Zhavoronkov and Mamoshina determined that the scope of the algorithm needs to be extended (by utilizing hybrid models and deep learning models) since data collected for individuals cannot be utilized for a cluster of individuals [18–22].

3.3. ARTIFICIAL INTELLIGENCE IN DRUG DISCOVERY

V. CONCLUSION

Summarize the key findings of your research and their implications for theory, practice, or policy. Highlight the significance of your contribution and suggest areas for future work. Avoid repeating sentences from the abstract.

ACKNOWLEDGMENT

We extended our sincere thanks to the KG Reddy College of Engineering and Technology for their outstanding support.

REFERENCES

[1]. Rantanen J, Khinast J. The future of pharmaceutical manufacturing sciences. J Pharm Sci 2015;104(11):3612–38. doi:10.1002/jps.24594.

[2]. Greenhill AT, Edmunds BR. A primer of artificial intelligence in medicine. Tech Innov Gastrointest Endosc 2020;22(2):85–9. doi:10.1016/j.tgie.2019.150642.

[3]. Solanki P, Baldaniya D, Jogani D, et al. Artificial intelligence: new age of transformation in petroleum upstream. Pet Res 2021. doi:10.1016/j.ptlrs.2021.07.002.

[4]. Kshirsagar A, Shah M. Anatomized study of security solutions for multimedia: deep learning-enabled authentication, cryptography and information hiding. Adv Secur Solut Multimed 2021. doi:10.1088/978-0-7503-3735-9CH7.

[5]. Anthony CC. Big data in medicine: the upcoming artificial intelligence. Prog Pediatr Cardiol 2016;43:91–4. doi:10.1016/j.ppedcard.2016.08.021.

[6]. Göller AH, Kuhnke L, Montanari F, et al. Bayer's in silico ADMET platform:a journey of machine learning over the past two decades. Drug Discov Today 2020;25(9):1702–9. doi:10.1016/j.drudis.2020.07.001.

[7]. Abu-Elezz I, Hassan A, Nazeemudeen A, et al. The benefits and threats of blockchain technology in healthcare: a scoping review. Int J Med Inform 2020;142:104246. doi:10.1016/j.ijmedinf.2020.104246.

[8]. Park BJ, Choi HJ, Moon SJ, et al. Pharmaceutical applications of 3D printing technology: current understanding and future perspectives. J Pharm Investig 2018;49(6):575–85. doi:10.1007/S40005-018-00414-Y.

[9]. Zimmerling A, Chen X. Bioprinting for combating infectious diseases. Bioprinting 2020;20:e00104. doi:10.1016/j.bprint.2020.e00104.

[10].Elbadawi M, Gaisford S, Basit AW. Advanced machine-learning techniques in drug discovery. Drug Discov Today 2021;26(3):769–77. doi:10.1016/j.drudis.2020.12.003.

[11].Bender A, Cortes-Ciriano I. Artificial intelligence in drug discovery: what is realistic, what are illusions? Part 2: a discussion of chemical and biological data. Drug Discov Today 2021;26(4):1040–52. doi:10.1016/j.drudis.2020.11.037.

[12].Reker D. Practical considerations for active machine learning in drug discovery. Drug Discov Today Technol 2019;32-33:73–9. doi:10.1016/j.ddtec.2020.06.001.

[13].Margulis E, Dagan-Wiener A, Ives RS, et al. Intense bitterness of molecules: machine learning for expediting drug discovery. Comput Struct Biotechnol J 2020;19:568–76. doi:10.1016/j.csbj.2020.12.030.

[14].Raschka S, Kaufman B. Machine learning and AI-based approaches for bioactive ligand discovery and GPCR-ligand recognition. Methods 2020;180:89–110. doi:10.1016/j.ymeth.2020.06.016.

[15].Raschka S. Automated discovery of GPCR bioactive ligands. Curr Opin Struct Biol 2019;55:17–24. doi:10.1016/j.sbi.2019.02.011.

[16].Rantanen J, Khinast J. The future of pharmaceutical manufacturing sciences. J Pharm Sci 2015;104(11):3612–38. doi:10.1002/jps.24594.

[17].Turki Turki, Taguchi YH. Machine learning algorithms for predicting drugs–tissues relationships. Expert Syst Appl 2019;127:167–86. doi:10.1016/j.eswa.2019.02.013.

[18].Popova M, Isayev O, Tropsha A. Deep reinforcement learning for de novo drug design. Sci Adv 2018;4(7):eaap7885. doi:10.1126/sciadv.aap7885.

[19].Taroni JN, Grayson PC, Hu Q, et al. MultiPLIER: a transfer learning framework for transcriptomics reveals systemic features of rare disease. Cell Syst 2019;8(5):380–94 e4. doi:10.1016/j.cels.2019.04.003.

[20].Li L, He X, Borgwardt K. Multi-target drug repositioning by bipartite block-wise sparse multi-task learning. BMC Syst Biol 2018;12(Suppl 4):55. doi:10.1186/s12918-018-0569-7.

[21].Weng Y, Lin C, Zeng X, et al. Drug Target interaction prediction using multi-task learning and co-attention. In: Proceeding of the IEEE international conference bioinformatics and biomedicine BIBM; 2019. p. 528–33. doi:10.1109/BIBM47256.2019.8983254.

[22].Han L, Zhang Y. Learning multi-level task groups in multi-task learning. Proceeding of the twenty-ninth AAAI conference on artificial intelligence; 2015. Available from https://www.aaai.org/ocs/index.php/AAAI/AAAI15/paper/view/9510 .

[23].Mak KK, Pichika MR. Artificial intelligence in drug development: present status and future prospects. Drug Discov Today 2019;24(3):773–80. doi:10.1016/j.drudis.2018.11.014.

[24].Paul D, Sanap G, Shenoy S, et al. Artificial intelligence in drug discovery and development. Drug Discov Today 2021;26(1):80–93. doi:10.1016/j.drudis.2020.10.010.

[25].Dnyaneshwar K, Gaurav S, Debleena P, et al.. Artificial intelligence in the pharmaceutical sector: current scene and future prospect. the future of pharmaceutical product development and research. Elsevier; 2020. p. 73–107. doi:10.1016/B978-0-12-814455-8.00003-7.

[26].Cui RB, Zhu F. Ultrasound modified polysaccharides: a review of structure, physicochemical properties, biological activities and food applications. Trends Food Sci Technol 2021;107:491–508. doi:10.1016/J.TIFS.2020.11.018.

[27]. Lusci A, Pollastri G, Baldi P. Deep architectures and deep learning in chemoinformatics: the prediction of aqueous solubility for drug-like molecules. J Chem Inf Model 2013;53(7):1563–75. doi:10.1021/ci400187y.

[28].Polykovskiy D, Zhebrak A, Vetrov D, et al. Entangled Conditional adversarial autoencoder for de novo drug discovery. Mol Pharm 2018;15(10):4398–405. doi:10.1021/acs.molpharmaceut.8b00839.

[29].Daynac M, Cortes-Cabrera A, Prieto JM. Application of artificial intelligence to the prediction of the antimicrobial activity of essential oils. Evid Based Complement Altern Med 2015:561024 2015. doi:10.1155/2015/561024.

[30].Pu L, Naderi M, Liu T, et al. eToxPred: a machine learning-based approach to estimate the toxicity of drug candidates. BMC Pharmacol Toxicol 2019;20(1):2. doi:10.1186/s40360-018-0282-6.

[31].Kadurin I, Rothwell S, Ferron L, et al. Investigation of the proteolytic cleavage of α 2 δ subunits: a mechanistic switch from nhibition to activation of voltage-gated calcium channels? Biophys J 2017;112(3):244a. doi:10.1016/j.bpj.2016.11.1335.

[32].Maram Y, Hamdy H. The role of artificial intelligence in revealing the results of the interaction of biological materials with each other or with chemicals. Mater Today Proc 2021;45:4954–9. doi:10.1016/j.matpr.2021.01.387.

[33].Unterthiner T, Mayr A, Klambauer G, et al. Toxicity Prediction using deep learning. 2015. 1-10. Available from: https://arxiv.org/abs/1503.01445v1.

[34].Avdagic Z, Begic Fazlic L, Konjicija S. Optimized detection of tar content in the manufacturing process using adaptive neuro-fuzzy inference systems. Stud Health Technol Inform 2009;150:615–19.

[35].Zhavoronkov A, Ivanenkov YA, Aliper A, et al. Deep learning enables rapid identification of potent DDR1 kinase inhibitors. Nat Biotechnol 2019;37(9):1038–40. doi:10.1038/s41587-019-0224-x.

[36].Lee H, Kim W. Comparison of target features for predicting drug-target interactions by deep neural network based on large-scale drug-induced transcriptome data. Pharmaceutics 2019;11(8):377. doi:10.3390/pharmaceutics11080377.

[37]. Putin E, Asadulaev A, Ivanenkov Y, et al. Reinforced adversarial neural computer for de novo molecular design. J Chem Inf Model 2018;58(6):1194–204. doi:10.1021/acs.jcim.7b00690.

[38]. Henstock PV. Artificial intelligence for pharma: time for internal investment. Trends Pharmacol Sci 2019;40(8):543–6. doi:10.1016/j.tips.2019.05.003.

[39].Chan HCS, Shan H, Dahoun T, et al. Advancing drug discovery via artificial intelligence. Trends Pharmacol Sci 2019;40(8):592–604. doi:10.1016/j.tips.2019.06.004.

[40].Wang LL, Ding JJ, Pan L, et al. Artificial intelligence facilitates drug design in the big data era. Chemom Intell Lab Syst 2019;194:103850.doi:10.1016/j.chemolab.2019.103850.

[41].Kshirsagar A. Bio-remediation: use of nature in a technical way to fight pollution for a long run. ResearchGate 2018. doi:10.13140/RG.2.2.26906.70088.Rantanen J, Khinast J. The future of pharmaceutical manufacturing sciences. J Pharm Sci 2015;104(11):3612–38. doi:10.1002/jps.24594.