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Review article

Artificial intelligence, computational tools and robotics for drug discovery, development, and delivery

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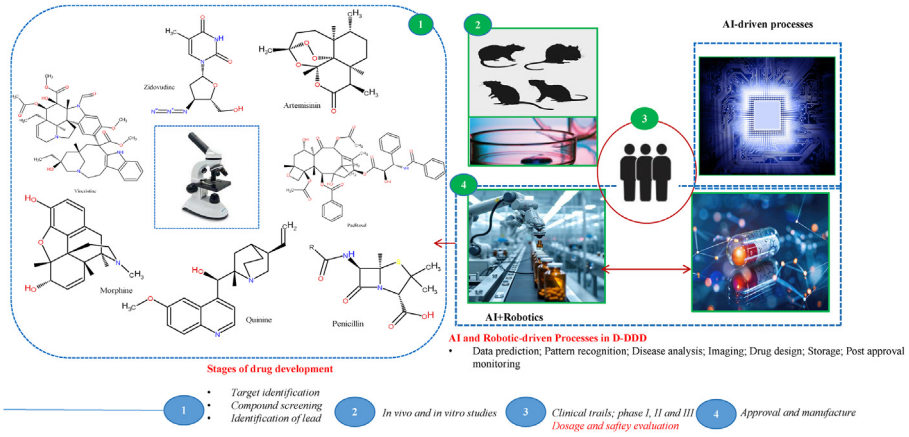
HIGHLIGHTS

- AI technologies accelerate target identification and drug repurposing through predictive modeling and data mining.
- Automated screening robotics enables efficient and large-scale compound testing with higher precision and consistency.
- AI and robotics optimize drug formulation, tailoring treatments based on patient-specific data.
- AI models improve the accuracy of toxicity and safety profiling of candidate drugs.
- AI and robotics will advance autonomous, end-to-end solutions for drug production.

GRAPHICAL ABSTRACT



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ABSTRACT

The integration of Artificial Intelligence (AI) and robotics into the pharmaceutical sector is rapidly transforming drug discovery, development, and delivery (D-DDD) processes. Traditional drug development is often characterized by lengthy timelines, high costs, and complex challenges associated with target identification, drug efficacy, and safety profiling. AI and robotics offer transformative solutions, bringing speed, precision, and scalability to various stages of D-DDD. In this review, we analyze cutting-edge advancements in AI-driven predictive modeling, machine learning algorithms for molecular screening, and data mining techniques that enable efficient drug target identification and toxicity prediction. We also explore robotics applications that enhance automation in high-throughput screening, compound synthesis, and patient-specific drug delivery systems. Through examining the applications, limitations, and future trends of these technologies, this review provides a comprehensive

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outlook on the potential of AI and robotics to streamline the drug pipeline and enable personalized therapeutic strategies. Our review reveals that the convergence of AI, robotics, and big data has potential to reshape pharmaceutical research, reduce costs, and pave the way for more accessible, effective therapies. This review thus serves as a critical resource for understanding the future trajectory of intelligent, technology-driven pharmacy and its implications for advancing healthcare.

1. Introduction

In the face of rising global health challenges, the pharmaceutical industry is experiencing an unprecedented era of transformation. Driven by the need to discover, develop, and deliver safe, effective, and affordable drugs, researchers are increasingly turning to Artificial Intelligence (AI) and robotics to accelerate each stage of the drug life-cycle. This paradigm shift is especially crucial given the escalating costs and time investments of traditional drug discovery and development, with estimates suggesting it can take over a decade and billions of dollars to bring a single drug to market.[1]

Historically, drug discovery has relied on trial-and-error approaches and labor-intensive screening methods, which, although valuable, have their limitations. These traditional methods often face challenges with accuracy, reproducibility, and efficiency, which can lead to high attrition rates of drug candidates.[2,3] In response, recent advances in AI have introduced powerful machine learning algorithms capable of analyzing vast chemical and biological datasets. These technologies can predict molecular interactions, optimize pharmacokinetics, and identify drug repurposing opportunities, transforming how researchers screen and evaluate potential drug candidates.[4,5,6] Complementing AI's data-driven precision, robotics has also introduced unprecedented automation in pharmaceutical processes—fromhigh-throughput screening to automated drug formulation—enabling not only speed but also enhanced reproducibility.[7,8] Yet, the future of pharmacy holds even more promise. Innovations at the intersection of AI, robotics, and big data suggest a future where these tools not only enhance but redefine drug development itself. Intelligent systems can now simulate human-like decision-making, envisioning multi-target therapies that consider patient-specific factors and complex disease pathways.[9,10] Robotics, too, is advancing beyond automation, moving toward creating adaptive, bioinspired systems capable of performing intricate tasks in drug delivery—such as navigating precisely to target sites within the body, releasing therapeutics in response to specific stimuli, and offering real-time feedback to medical teams.[11]

This intensive review explores the current state and future potential of AI and robotics in the D-DDD process, examining groundbreaking applications, limitations, and emerging trends. As the pharmaceutical field embraces intelligent, automated solutions, the boundaries between science fiction and clinical reality continue to blur, heralding a new era where personalized, data-driven therapeutics become not just feasible but the norm. Consequently, through syntheses of recent advancements, we aim to provide a roadmap for how these intelligent technologies could transform pharmacy, from data-driven drug design and predictive modeling to autonomous systems for targeted delivery.

The subsequent sections will cover: (i) Evolution of Drug Discovery, Development, and Delivery (ii) Traditional Methods (iii) Drug Delivery and Conventional Limitations (iv) AI and Robotics in Drug Discovery (v) Current Trends in AI (vi) Role of Robotics in Drug Discovery and Development (vii) Limitations, and (viii) Conclusion.

2. Evolution of Drug Discovery, development, and delivery: historical context

Medicines are essential for the well-being of both humans and animals, serving as diagnostic, prophylactic, curative, and palliative agents. Since antiquity, humans have sought ways to treat illnesses and diseases with various forms of medicine. The early history of drug discovery and development was largely based on natural sources.[12,13] Almost every ancient civilization practiced folk medicine. Notable traditional medicine practices include the cuneiform inscriptions on hundreds of clay tablets from Mesopotamia, dating back to around 2600 BC, Traditional Chinese Medicine (TCM),[14] Egyptian medicine as described in ancient medical papyri,[15] Ayurvedic medicine,[16] and Greek and Roman medicine.[14] Additionally, Hippocrates, a Greek physician, is believed to have established an ethical code for medical practice around 400 BC, although the concept of bioactive molecules as the healing principles from plants was not yet understood. The Medical Renaissance, spanning from 1400 to 1600 AD, laid the foundation for modern drug discovery and development, accompanied by advancements in human anatomy, physiology, medicine, and surgery.[17] During this period, the understanding of drug discovery evolved to recognize that secondary metabolites are responsible for the therapeutic efficacy of natural products.

As modern drug discovery progressed, initial efforts focused on the extraction of natural products. These extracts underwent a series of chromatographic techniques to separate and purify individual bioactive compounds. The chemical structures of isolated compounds were determined using various spectroscopic techniques, including ultraviolet spectroscopy (UV), infrared spectroscopy (IR), nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS)[18,19] (Fig. 1). After isolation, each compound was tested for biological activities, and their mechanisms of action were studied.

Some revolutionary isolation of bioactive compounds from natural products includes morphine for pains, penicillin for bacterial infections, quinine for malaria, podophyllotoxin for cancer.[19] In response to the successes of these discoveries, pharmaceutical industries established Research and Development (R&D) units to oversee drug discovery and development activities, including the development of new methodologies to expedite the drug discovery process. The monopharmacology-based medicine approach has recorded significant successes, with some molecules developed through this approach still in clinical use today (Fig.s 1 and 2). However, traditional drug discovery is a time-consuming, resource-intensive process that can take over ten years from start to approval. Moreover, drug discovery and development processes are difficult, challenging, and expensive. Before one drug is approved and brought to market, it is estimated that around 10,000 molecules are synthesized and tested for biological activity. The high cost of drug development is also notable, with estimates suggesting it costs approximately $ 2 billion dollars to discover and develop a single drug. Clinical trials account for over 60% of the costs.[20] Despite the costs, the attrition rate for drug development remains high, with around 93% of small molecule candidates and 89% of biologics failing during development.[21] The objective of modern drug discovery is to develop drugs that bind more effectively to specific disease-implicated protein targets than their natural substrates, thereby altering the biochemical reactions the target molecule facilitates.[22]

The modern drug discovery process for developing a new drug is illustrated in Fig. 3. This field is inherently multidisciplinary, involving experts in biology, medicinal and synthetic chemistry, pharmacology, pharmaceutics, drug formulation science, computational chemistry, and management, among others.[20] Drug discovery and development is a systematic process that translates a drug candidate from the laboratory to the clinic. Hence, the modern drug discovery process begins with the identification of unmet medical needs, followed by target selection, identification, and validation. High-throughput screening (HTS) and various *in vitro* assays are then employed to identify druggable ligands,

referred to as "hits." Subsequent optimization transforms these hits into leads, which exhibit adequate potency and selectivity toward the selected target. A promising drug candidate is subsequently subjected to clinical trials.[23]

Clinical trials are divided into two main categories: preclinical trials and clinical trials.

i. *Preclinical Trials*: This phase involves testing the drug candidate in experimental animals to gather information about its toxicity and safety profiles. Following preclinical studies, an Investigational New Drug (IND) application is submitted to the appropriate regulatory authority to request permission for the drug candidate to enter clinical trials.
ii. *Clinical Trials*: Clinical trials are further subdivided into three phases:

- Phase I: The drug is tested on a small group of healthy human volunteers, typically around 100, to gather data on its pharmacokinetics and pharmacodynamics.
- Phase II: This phase assesses the efficacy of the drug candidate in a larger group (about 50–500) of volunteered patients.
- Phase III: This is a confirmatory trial involving thousands of patients, focusing on both efficacy and safety.

After the clinical trial process, monitoring may continue during the post-marketing phase, where surveillance is conducted for possible side effects and drug–drug interactions related to the drug.[23]

3. Traditional methods of drug discovery and development: efforts and limitations

Natural products have historically served as a vital source of drugs and continue to do so today. Traditionally, medicinal plants were utilized in the form of concoctions or macerates to treat various diseases. By the nineteenth century, drug discovery evolved from using crude extracts to isolating pure compounds. Advances in technology allowed for the separation of phytochemicals from natural sources in a bioactivity-guided manner and facilitated the resolution of their chemical structures.[19] These isolated compounds often serve as leads, with their structures modified through chemical reactions to create newer, more potent, or less toxic derivatives. The isolation of bioactive compounds from natural sources has demonstrated that nature functions as a vast chemical library, producing a diverse range of structurally and biologically distinct molecules. Biological organisms, including plants, bacteria, and fungi, synthesize secondary metabolites in response to environmental challenges such as stress or predation.[24]

Drug discovery is often serendipitous, meaning that drugs are found by chance while searching for unrelated substances.[25] A notable example of this is the discovery of the first antibiotics, which marked the beginning of the antibiotic golden era. In 1928, Alexander Fleming, a Scottish physician and microbiologist, observed that mold growing on Petri dishes he used to culture bacteria had inhibited the growth of *Staphylococcal* bacteria nearby. This mold, identified as *Penicillium chrysogenum*, produced a substance that could effectively kill bacteria and was subsequently characterized as penicillin [25]. This remarkable finding led to the

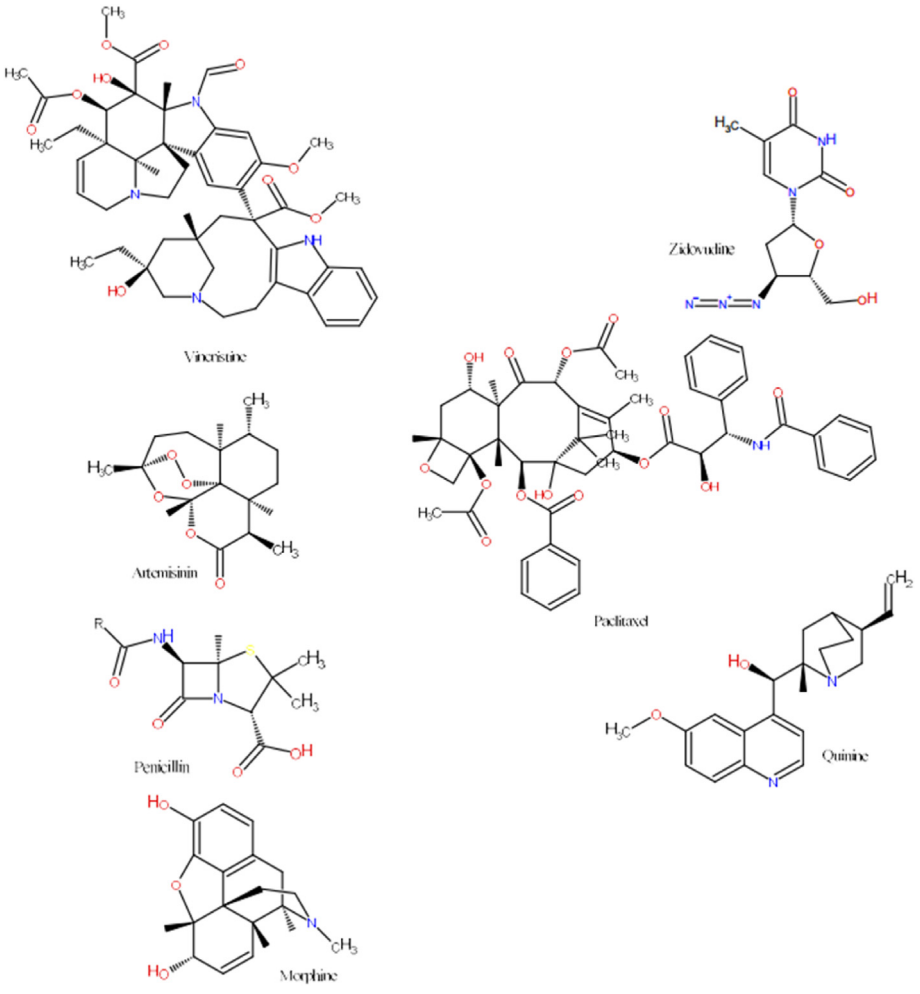

Fig. 1. Structures of some important drugs of natural product origin.

antibiotic revolution, transforming the treatment landscape for bacterial infections.[24] Another example of serendipitous drug discovery is sildenafil, which was initially investigated for its potential to treat angina pectoris. However, the clinical expectations for sildenafil's effectiveness in this area were not met. Instead, it was discovered to induce erections in some patients, redirecting its application from cardiovascular treatment to addressing erectile dysfunction.[26] Other drugs discovered through serendipity include chlorpromazine, chloral hydrate, iproniazid, meprobamate, and imipramine.[25]

Drugs derived from plants and microorganisms continue to serve as valuable leads or inspiration for the synthesis of small molecules. According to Newmann and Cragg,[27] between 1981 and 2019, unaltered natural products represented 3.8% of all new FDA-approved drugs, while natural product-derived (semisynthetic) drugs accounted for 18.9%. However, the drug discovery process involving natural products presents certain limitations. These challenges include difficulties in the isolation and purification of compounds, time-intensive processes, limited availability of naturally occurring compounds in small quantities, and the complexities associated with total synthesis or modification of intricate structures found in natural sources.[24]

Despite the significant value of natural products, there has been a noticeable shift in research focus towards technologically driven rational design, discovery, and development of drugs. The advent of HTS and combinatorial chemistry, which involves creating small molecule libraries or databases, has revolutionized the drug discovery landscape. In this approach, libraries of chemically synthesized compounds (small molecules, typically less than 500 g/mol) are assembled, allowing for the systematic evaluation of 5000 to 10,000 compounds per day for their biological activities *in vitro* against specific biological targets. This method offers speed and efficiency advantages over traditional approaches. However, HTS requires access to extensive libraries of small molecules and can be quite expensive.[28] Some disadvantages associated with automated HTS include the high cost of experiments and the time investment required. Additionally, while ultra-HTS can screen over 100, 000 compounds per day, the number of small molecules available via combinatorial chemistry that can be screened at any one time remains limited. Another drawback of HTS is the potential for generating false positive results, which can increase the failure rate in progressing from hits to leads.[28]

The 21st century has seen the emergence of computer-aided drug design (CADD), along with advances in molecular simulation, docking, and bioinformatics. These developments have been facilitated by progress in structural biology, which has made three-dimensional structures of proteins accessible through techniques such as NMR spectroscopy, X-ray crystallography, and electron microscopy.[29] The introduction of in silico models—utilizing computational algorithms to virtually screen larger libraries of compounds—too, has made it possible to reduce discovery time, enhance efficiency, and decrease the number of compounds that require subsequent *in vitro* assays.[30]

4. Drug delivery and the limitations of the conventional approach: an overview

Drug delivery encompasses the formulation approaches and manufacturing techniques designed to transport a drug product to its intended site of action in the body to achieve the desired therapeutic

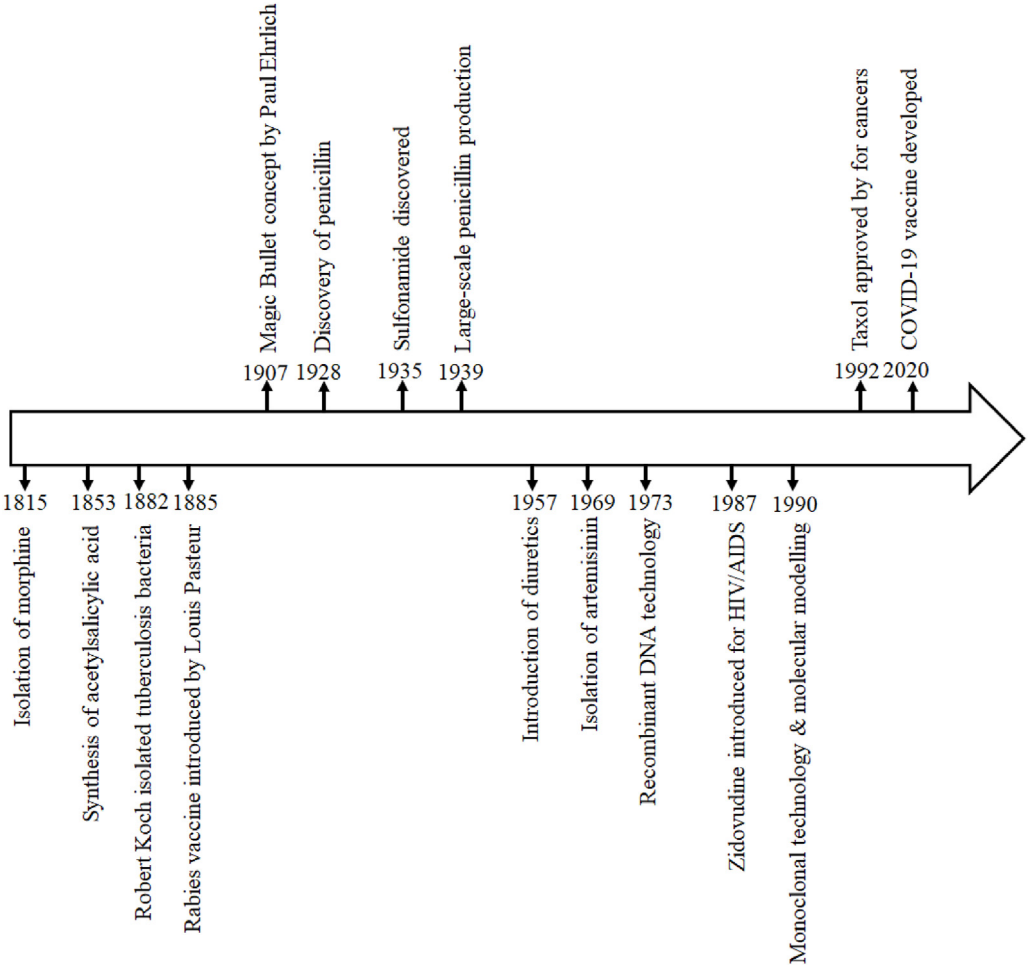

Fig. 2. Some milestones in drug discovery and development history.

effects.[31] Upon administration, a drug is distributed throughout the body via the bloodstream, often targeting multiple receptors. This nonspecific distribution may compromise its ability to achieve a specific pharmacological function. Therefore, new drug delivery technologies are being developed to minimize pharmacological promiscuity, thereby reducing toxicity, enhancing therapeutic outcomes, and improving patient compliance.[32]

Traditionally, therapeutic agents have consisted of bioactive compounds derived from natural products and synthetic small molecules. However, the scope of medicines has broadened to include monoclonal antibodies, proteins, peptides, biologics, and live cells.[32] A notable example is Onpattro® (Patisiran), developed by Alnylam Pharmaceuticals, Inc., which was approved by the FDA in 2018 as the first RNA interference (RNAi) drug delivered via lipid nanoparticles.[33] Conventional methods of drug delivery include tablets, capsules, caplets, syrups, mixtures, suspensions, emulsions (enteral), and injections (parenteral), as well as topical forms such as lotions, creams, and gels. In recent years, the focus of drug delivery has shifted towards smart or targeted drug delivery systems, as well as sustained or controlled drug delivery mechanisms. These advancements represent a maturation of drug delivery systems from basic pill formulations to molecular medicine, and from system-targeting to cell-targeting applications.

The concept of targeted drug delivery aims to selectively transport a drug and increase its concentration in specific tissues or organs of interest.[31] On the other hand, sustained or controlled drug delivery systems release active pharmaceutical ingredients (APIs) gradually over hours, days, or even months, thereby reducing the frequency of dosing and enhancing patient compliance.[32] Since the emergence of ALZA Corporation in the 1960s as a pioneering biotech company focused on therapeutic devices and drug delivery systems, the drug delivery industry has expanded to include several hundred additional companies.[34] Founded in 1968 by Dr. Alejandro Zaffaroni, ALZA Corporation has developed numerous innovative products, such as the first transdermal patches, ocular films for treating glaucoma, and minipills designed for controlled drug release over time. Among ALZA's early products were Ocusert, which consisted of pilocarpine formulated with poly(ethylene-co-vinyl acetate) for glaucoma and approved in 1974; Progestesert, a progesterone-based intrauterine contraceptive device also formulated with poly(ethylene-co-vinyl acetate) and approved in 1976; and Transderm Scop, which contained scopolamine formulated with polypropylene for motion sickness and was approved in 1979.[33]

The evolution of drug delivery can be categorized into various generations, as illustrated in Fig. 4. One of the landmark developments was Spansules®, produced in 1952 by Smith Kline and French Laboratories, which was the first controlled-release formulation of dexedrine, capable of delivering a drug over 12 h after oral administration.[35] This marked the beginning of modern drug delivery systems. In 1956, Riker Laboratories, Inc. introduced the first FDA-approved pressurized metered-dose inhaler.[36]

The two decades following (1950s–1970s) saw a significant increase in the application of polymeric materials for controlled drug delivery. By the 1980s, oral and transdermal formulations capable of delivering small molecules for extended periods of up to 24 h were introduced. The era of long-acting drug delivery systems (including injections and implants) began in 1989 with the introduction of Lupron Depot®, which could release drugs over several months. This was followed by advancements in drug delivery technologies that enabled long-term delivery of peptides and protein drugs, with products such as Adagen® being introduced in 1990. In 1995, the anticancer drug doxorubicin was reformulated as Doxil®, employing PEGylated liposome technology for long-term drug delivery. The year 2000 saw the introduction of antibody-drug conjugates, notably gemtuzumab ozogamicin, marketed as Mylotarg®.[37]

Initially, pharmaceutical research focused primarily on designing new chemical entities. However, over four decades ago, it became evident that the delivery of drugs within the body is just as important as the drug itself.[38] For instance, protein-derived drugs cannot be effectively formulated as oral preparations, while parenteral routes tend to be highly invasive. These limitations highlight the shortcomings of conventional drug delivery systems. Other significant limitations include the necessity of high drug doses, which can predispose patients to adverse effects and result in low patient compliance. Conventional drug delivery systems are often unsuitable for drugs with low solubility and poor stability. Additionally, drugs with low target specificity and a narrow therapeutic index are not optimally administered via traditional methods. Furthermore, drugs characterized by poor pharmacokinetic profiles—such as those with short half-lives or large volumes of distribution—also pose challenges in conventional delivery. Another notable drawback of traditional systemic dosage forms is the frequent dosing required. Upon administration, most drugs are rapidly released into the systemic circulation, leading to a significant drop in plasma concentration within just a few hours, particularly for those with short half-lives. This necessitates frequent dosing. While a rapid onset of action may sometimes be desired, effective and safe drug therapy is achieved when plasma concentrations are consistently maintained through controlled drug release.[38] In contrast, newer generations of drug delivery systems offer the advantage of directing drugs to specific areas within the body, thereby reducing toxicity and improving drug performance in terms of pharmacokinetics, pharmacodynamics, and pharmacotherapeutics.[39]

An emerging technology in drug delivery is three-dimensional (3D) printing. This innovative approach enables the fabrication of complex, personalized, and on-demand medications.[40] The 3D printing process involves a layer-by-layer technique that offers a time- and cost-effective design cycle for producing personalized medications. The method was first introduced in the 1980s, with the approval of the first 3D-printed drug product, Spritam (levetiracetam), for the treatment of epilepsy in 2015.[41] Utilizing computer-aided design software, along with magnetic resonance imaging or computed tomography scans, 3D-printed structures are created from a digital file. This allows for the on-demand manufacturing of medications tailored to individual patients.[42]

5. Introduction of AI and robotics to drug discovery, development, and delivery

AI and robotics have the potential to revolutionize drug discovery, development, and delivery in medicine. AI methodologies, including machine learning (ML) and deep learning (DL), utilize computer algorithms and specialized software to facilitate applications such as target identification, virtual screening, and drug design (Fig. 5). The drug discovery and development process is notoriously complex, costly, and time-consuming, with a high failure (attrition) rate. AI-assisted technologies and robotics can potentially reduce these costs, enhance speed, and improve precision throughout the drug discovery and delivery processes.[43]

Predictive AI employs models capable of making deductions or

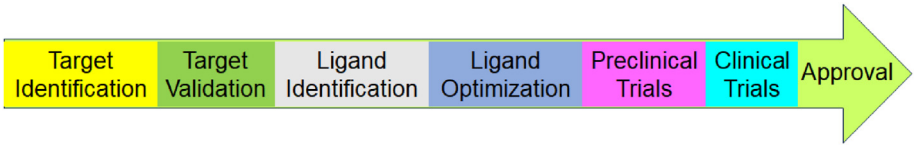

Fig. 3. Diagrammatic representation of modern drug discovery and development process.

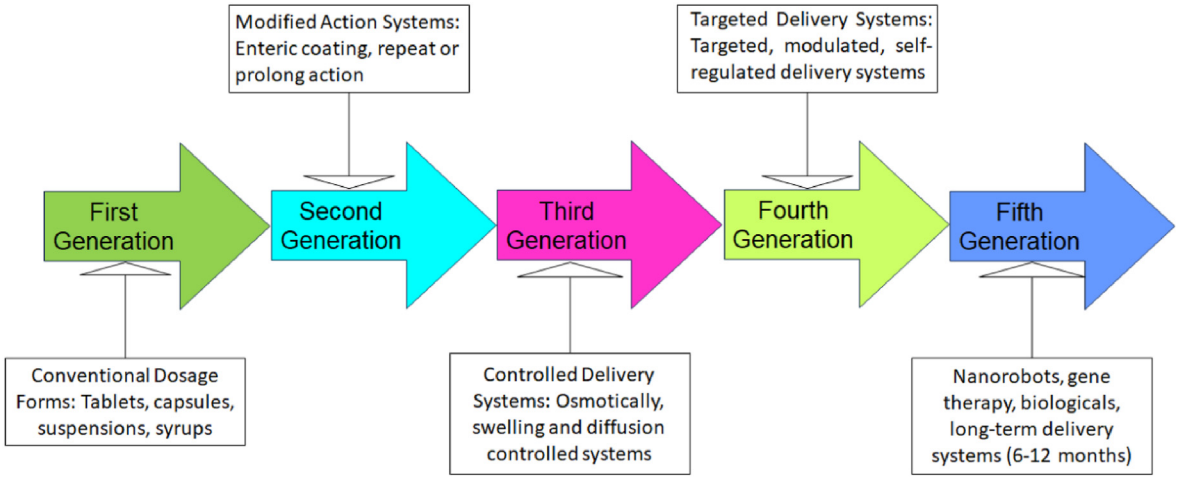

Fig. 4. Generations of drug delivery systems (Modified from[20]).

Fig. 5. A flow chart of the role of AI in drug development.[339]

predictions based on provided data. For instance, in the context of quality-by-design (QbD) for pharmaceutical products, AI can analyze vast and intricate biological and medical datasets from various sources to identify critical quality attributes (CQAs) and predict the absorption, distribution, metabolism, and excretion (ADME) as well as toxicity profiles of products. In contrast, active AI systems, such as robotic arms, can automate specific laboratory tasks, including *in vitro* sample preparation, sorting, and analysis.[43] ML is a pivotal AI technique that can predict molecular properties, identify potential drug candidates, and optimize the structures of lead compounds. This technological innovation significantly aids in designing molecules that fit specific protein targets and facilitates the rapid translation of discoveries from the laboratory to clinical settings.

The early integration of AI in medicine dates back to the 1970s with the introduction of computer-aided diagnosis (CAD) systems for medical imaging, alongside the development of the expert system MYCIN, which was designed to diagnose bacterial infections. By the 1980s, AI algorithms began to be applied to the interpretation of medical imaging, including MRI, X-rays, and CT scans. A landmark development occurred in 1999 with the introduction of AI- and robotic-assisted surgical systems, such as the da Vinci Surgical System created by the American biotechnology firm Intuitive Surgical, Inc. This robotic surgery system integrates AI and robotics to facilitate minimally invasive surgical approaches.[44] Additionally, the applications of AI and robotics in medicine extend to AI-enhanced prosthetics that significantly improve the quality of life for patients, including amputees, and the automation of laboratory processes.[43,45]

As previously discussed, the drug discovery and development process begins with the recognition of an unmet medical need. To design and develop a drug candidate for a specific disease, it is essential to first identify and validate its biomolecular targets, such as receptors, enzymes, or nucleic acids. Target identification and validation involve elucidating the roles and functionalities of a biological target in the initiation and progression of a disease. Following this, it must be established that modulating or manipulating the target—whether through agonistic or antagonistic probes—has therapeutic significance. In the search for potential biological targets, AI-assisted techniques can analyze extensive genomic, proteomic, and metabolomic databases, offering significant insights for drug discovery.[43] One notable AI application is AlphaFold, which predicts and determines the three-dimensional shapes of protein structures based on their amino acid sequences.[46] This technology has proven invaluable; for instance, in 2020, AlphaFold was utilized to predict the structures of five SARS-CoV-2 (COVID-19) targets.

Once a target has been validated—confirming its direct involvement in disease pathogenesis and therapeutic relevance—the next step is lead identification. This can be achieved, as earlier mentioned, through HTS of compound libraries or structure-based virtual screening of compound databases. AI technologies such as ORGANIC are employed to create molecules with desired properties, while DeepChem, a Python-based AI technique, aids in detecting suitable molecules in drug discovery.[47] In

addition, AI-powered methods offer predictive and simulative capabilities regarding a molecule's potential interaction with a biological target, thus eliciting a pharmacological response.[43] Machine learning techniques, including Bayesian docking approximations and reinforcement learning (RL), are used for molecular docking to simulate ligand interactions within the three-dimensional space of target proteins. Tools like DeltaVina also serves as scoring functions for protein-ligand interactions, while PotentialNet employs neural networks to compute ligand binding affinity.[47]

The anticipated effects of these molecules on biological functions, dynamics, and the structures of selected proteins can be validated experimentally. Additionally, computational algorithms can aid in designing and optimizing molecules of interest into drug candidates, enhancing efficacy while reducing toxicity through structure–activity relationship (SAR) studies.[48] An example of this is DeepNeuralNetQSAR, a deep learning technique that predicts biological activity based on molecular structures.[47] Additionally, automated and optimized AI platforms have the potential to identify new structural scaffolds for treating certain diseases more rapidly than traditional drug discovery methods, such as high-throughput screening (HTS) and combinatorial chemistry. The identification of new scaffolds can significantly reduce both the time and cost associated with the drug discovery process, increasing its efficiency and effectiveness. AI-driven technologies also add value to clinical trials by assisting in patient recruitment (selecting specific populations for Phase II and III clinical trials), utilizing electronic hardware for virtual clinical trials, identifying biomarkers, monitoring trial progress, and managing as well as analyzing data.[49] A notable example is INS018_055, the first fully AI-generated drug developed by InSilico Medicine, which is currently in late-stage clinical trials. This drug is indicated for the treatment of idiopathic pulmonary fibrosis. Another example, Pembrolizumab, developed by Merck & Co., is used to treat various cancers, including head and neck cancers, lung cancer, and melanom

Another interesting application is nanorobots, which are computer-controlled, engineered nanoscale devices designed to deliver therapeutic substances to specific sites within the body. These nanorobots leverage physiological conditions, such as pH levels, to navigate to their targeted locations. They can be engineered for various purposes, including targeted delivery, enabling them to traverse complex physiological environments to interact with specific targets, or controlling the release of drugs over time.[48,49] Nanorobots offer advantages in precision and timing compared to traditional drug delivery systems. Microfabrication, also, are techniques are utilized to enhance the efficacy and control of drug delivery, which can improve bioavailability and achieve targeted delivery. Furthermore, AI tools are employed to develop nanocarriers and advanced smart devices for innovative drug delivery solutions. Microfabricated drug delivery systems can function as drug reservoirs and self-regulate plasma drug concentrations.[50] For instance, an AI-based neural network model (ANN) and a central composite design (CCD) system were employed to design orodispersible tablets of moxifloxacin.[51] These engineered formulations are optimized for performance and have the potential to improve patient compliance and therapeutic effectiveness.

6. Current Trends in computational techniques and AI for drug development

As mentioned in previous sections, drug development is a complex, cost intensive and time consuming process that involves several stages.[52] It has also been emphasized that owing to its potentials in accelerating drug discovery, enhancing design, optimizing clinical trials, and enabling drug repurposing while significantly reducing cost of multiple trials, implementing AI in drug development has gained traction in recent times. This section provides elaborate discussion of AI-integrated techniques, including computational modelling and simulations, applied in drug development and their areas of application.

6.1. Computational modeling and simulations

Computational modeling and simulation refers to the process by which a product is created using computer tools, and the product is then subjected to real life conditions in which it would function when made.[53] This enhances prediction of the responses and behavior of the product to environmental conditions. At instances when the outcome of such testing is undesirable, computational modeling and simulation allows for iterations of processes after adjustment of process parameters that determine the outcome.[54] By so doing, it significantly eliminates the costs that would have been incurred if such product were to be built and tested every time process parameters change.[55] In drug development, computational modeling and simulation has been shown to drastically reduce drug development time, since it does not require waiting long hours for reactions to completely take place and for the product to be tested.[56] The implication of this is that drugs can now be developed, improved and produced at a faster rate to meet emergency demands like in the case of COVID-19.[57]

One important application of computational modeling and simulation in drug development is in assessing drug-target residence time and enhancing lead optimization. Drug-target residence time τ is a critical parameter that influences both the efficacy and safety of drugs.[58,59] In a study conducted by Kokh et al.,[60] a drug-τ RAMD (Random Acceleration Molecular Dynamics) computational method was utilized to predict the residence times of 70 diverse drug-like compounds targeting the N-terminal domain of HSP90α. The study aimed to establish a relationship between the compounds' structures and their pharmacokinetics. The results demonstrated that approximately 78% of the compounds had relative residence times computed with an accuracy of about 2.3τ, and less than 2.0τ within congeneric series. This research highlights the effectiveness of τRAMD as a valuable tool for improving residence times during lead optimization. Lead optimization not only enhances the efficacy of a developed lead molecule through structural modifications but also improves various parameters, including target–lead interactions, toxicity, binding affinity, pharmacokinetics, and thermodynamic properties. Other computational modeling and simulation tools, along with their applications in drug development, are summarized in Table 1.

6.2. Clinical trial design, data mining and analysis

Many drugs presented for clinical trials often fail between Phase I and regulatory approval, resulting in significant losses in resources and time.[234] Understanding the mechanisms that govern drug response is crucial for the success of drugs during clinical trials.[235] However, this understanding can be complex, cumbersome, and time-consuming, as it involves processing large datasets to identify and extract relevant patterns associated with various drug discovery and development processes.[52] AI and ML can leverage large clinical datasets, commonly referred to as big data, to derive insights that enhance patient outcomes and facilitate drug discovery, even before the initiation of these processes.[236] Research has shown that data mining, applied to clinical big data, can generate effective, value-driven information that accelerates drug discovery and development.[237,238] Data mining enables the extraction and identification of patterns from clinical, pharmaceutical, and pharmacological big data through the application of machine learning and AI techniques, further supporting drug development and discovery efforts.[239] Table 2 summarizes the applications of AI and ML in drug discovery and development.

6.3. Machine learning algorithms

ML algorithms have revolutionized the field of drug discovery, enabling the prediction of a compound's chemical, biological, and physical properties.[293] Pharmaceutical companies have benefited significantly from this advancement at various stages of drug development, including molecule bioactivity optimization, drug repurposing,

Table 1
Applications of computational modeling and simulations in drug discovery and development.

Computational Tool	Purpose	Applications	References
Molecular Docking (AutoDock, Glide, GOLD)	Predict drug-target binding	Virtual screening, binding affinity prediction	[61–64]
Molecular Dynamics (MD) Simulations (GROMACS, AMBER, CHARMM, NAMD)	Study molecular behavior over time	Drug optimization, protein flexibility analysis	[65–71]
Quantitative Structure–Activity Relationship (QSAR) (MOE, PyMOL, ChemAxon)	Correlate chemical structure with biological activity	Predict biological activity of new compounds	[72–78]
Pharmacophore Modeling (LigandScout, Phase)	Identify features necessary for biological activity	Drug discovery, virtual screening	[79–81]
Structure-Based Drug Design (SBDD) (Schrodinger Maestro, OpenEye, AutoDock)	Design drugs based on 3D target structure	Lead discovery, rational drug design	[82–86]
AI & Machine Learning (ML) (DeepChem, Atomwise, Chemprop)	Analyze large datasets for drug discovery	Predict drug-target interactions, drug repurposing	[87–92]
High-Throughput Screening (HTS) Data Analysis (KNIME, Pipeline Pilot)	Process large biological datasets	Hit identification, compound screening	[93,94]
In Silico ADMET Prediction (ADMET Predictor, pkCSM, QikProp, OptADMET)	Predict pharmacokinetics and toxicity profiles	Early elimination of poor candidates, lead optimization	[95–102]
Cheminformatics (RDKit, ChemAxon, Open Babel)	Manage chemical data for drug discovery	Chemical property prediction, data mining	[103–108]
Virtual Screening (ZINC, DrugBank, Chembl)	Screen large libraries of compounds against biological targets	Discover novel drug candidates quickly	[109–113]
Computer-Aided Drug Design (CADD) (Schrodinger Suite, Discovery Studio, OpenEye)	Design drug candidates using computational methods	Lead optimization, structure-based design	[72,113, 114]
De Novo Drug Design (LUDI, LigBuilder, AutoGrow)	Generate novel molecules from scratch	Creation of new drug candidates	[115–120]
Metabolomics and Proteomics Tools (MetaboAnalyst, XCMS, MaxQuant)	Analyze metabolite and protein data	Biomarker identification, drug effect studies	[121–124]
Pharmacokinetic (PK) and Pharmacodynamic (PD) Modeling (Simcyp, GastroPlus, NONMEM)	Simulate drug absorption, distribution, metabolism, excretion, and effects	Dosage optimization, clinical trial simulation	[125–132]
Cryo-Electron Microscopy (Cryo-EM) Data Analysis (RELION, CryoSPARC, ChimeraX)	Analyze high-resolution structures obtained from Cryo-EM	Structural drug design, molecular assembly studies	[133–139]
Ensemble Docking (RosettaDock, AutoDock Vina, FlexX)	Dock ligands against multiple conformations of a target	Predicting flexible protein-ligand binding	[140–144]
Protein–Ligand Interaction Fingerprinting (PLIP, Schrodinger's Maestro)	Generate fingerprints of protein-ligand interactions	Drug-target interaction analysis, lead optimization	[145–201]
Fragment-Based Drug Design (AstexViewer, MOE FBDD, FTMap)	Build drugs from smaller fragments that bind to the target	Lead generation, fragment-to-lead transitions	[202–206]
Toxicogenomics (ToxPi, OpenTG-GATEs, Tox21)	Study gene expression changes caused by drugs to predict toxicity	Predicting adverse reactions, understanding drug toxicity mechanisms	[207–210]
Chemical Space Exploration (ChemGPS, ChemSpace Navigator)	Explore and analyze vast chemical compound libraries	Novel compound identification, chemical space analysis	[211–215]
Virtual Clinical Trials (Certara, PhysioLab, Archimedes Model)	Simulate clinical trials computationally	Predicting clinical outcomes, optimizing trial designs	[216–221]
Quantum Chemistry (Gaussian, ORCA, Q-Chem)	Calculate electronic properties of molecules	Predict binding affinities, study reactivity and metabolism	[222–229]
Evolutionary Algorithms (AutoGrow, EvoDesign, EvoDock)	Optimize drug candidates by simulating natural evolutionary processes	Lead optimization, scaffold hopping	[119, 230–234]

virtual screening, predictive modeling, pharmacokinetics and pharmacodynamics, clinical trial optimization, and drug–protein interaction prediction.[294] Techniques such as Random Forest (RF), Naive Bayesian (NB), and Support Vector Machine (SVM) are frequently employed due to their ability to manage large datasets, identify patterns, and make predictions that are challenging to interpret with conventional methods. Additionally, deep learning approaches like recurrent neural networks (RNNs) and convolutional neural networks (CNNs) are gaining traction in drug development.[240,261] These models excel at deciphering complex biological data, including 3D protein and chemical structures and genetic sequences. For instance, RNNs can generate novel chemical compounds with desired features, while CNNs can accurately predict the binding affinity between drugs and their targets.[295]

ML algorithms are generally classified into supervised learning, unsupervised learning, and deep learning methods. Supervised learning utilizes labeled data to predict outcomes, making it suitable for applications such as predicting drug efficacy. In contrast, unsupervised learning identifies patterns in unlabeled data by using dimensionality reduction techniques like Principal Component Analysis (PCA).[262] This approach is particularly beneficial for clustering similar molecules or discovering new drug candidates from large, unannotated datasets. Furthermore, hybrid approaches such as semi-supervised learning—combining a small amount of labeled data with a larger quantity of unlabeled data—and reinforcement learning, which allows models to learn optimal actions through trial and error, enhance the impact of ML across divergent datasets.[263] These combined strategies are notably effective in drug development, enabling more precise projections and uncovering hidden correlations within complex biological data.

6.3.1. *Supervised learning algorithms*

i. Support vector machines

Support Vector Machines (SVMs) have become invaluable tools in drug discovery, particularly for applications such as virtual screening, quantitative structure–activity relationship (QSAR) modeling, and toxicity prediction. Their ability to manage high-dimensional data and model complex, non-linear relationships makes them highly effective in categorizing compounds as either active or inactive against specific biological targets. This capability is especially crucial in virtual screening, where SVMs facilitate the rapid filtering of irrelevant compounds from extensive chemical libraries, thereby reducing the necessity for exhaustive laboratory testing.[296] A significant advantage of SVMs is their functionality in high-dimensional feature spaces, which allows them to determine optimal hyperplanes for data separation, even when linear separation is not possible in lower dimensions.[297]

In QSAR modeling, Heikamp and Bajorath[298] emphasize the effectiveness of SVMs in predicting biological activity based on various molecular descriptors. Their performance with small datasets is noteworthy, as SVMs maximize class margins and help reduce overfitting, elucidating the relationships between molecular features and biological activity. This capability ultimately supports the development of new therapeutic

Table 2
Applications of AI in clinical trial design, data mining and analysis for clinical outcomes.

AI Application	Data Mining Tool	Purpose	Reference
Drug Target Identification	Machine Learning Models	Identifies biological targets for drugs	240–242
		Predicts likely effectiveness of drug compounds	243–245
Predicting Drug Efficacy	Neural Networks	Classify drugs to therapeutic categories based on their transcriptional profiles	246
	Fingerprint Graph Neural Network	Predicting and discovering better molecules with desired functions or properties	247
Toxicity Prediction	Deep Learning Algorithms	Assesses toxicity potential of new drug candidates	248–251
Drug–Drug Interaction Analysis	Association Rule Mining	Analyzes interactions to minimize adverse effects	252–254
Optimizing Drug Formulation	Clustering Techniques	Groups compounds to identify optimal formulation strategies	255–259
Patient-Specific Response	Decision Trees	Tailors treatments to individual patient profiles	260–265
Predictive Modeling	Support Vector Machines (SVM)	Models drug behavior and distribution in the body	266–271
Drug Repositioning	Text Mining & NLP	Analyzes literature and clinical data to find new uses for existing drugs	272–279
Clinical Trial Data Analysis	Random Forests	Evaluates trial data to improve clinical outcomes and predicting drug sensitivity	256, 280–282
Side Effect Prediction	Bayesian Networks	Predicts potential side effects of drug candidates	283–288
Drug Target Inference	Siamese spectral-based graph convolutional network (SSGCN)	Inferring protein targets of chemical compounds from gene transcriptional profiles	289–292

candidates. Additionally, SVMs play a vital role in toxicity prediction by enabling the early detection of potentially harmful compounds during drug development. By training on datasets containing known toxic and non-toxic substances, SVMs can minimize reliance on prolonged animal testing, thus expediting the drug development process and reducing associated costs.[299–301]

The adaptability of SVMs to various kernel functions—such as radial, polynomial, and linear—further enhances their utility in chem-informatics and computational biology. Applications include the use of Radial Basis Function (RBF) SVMs for identifying compounds for cancer treatment and Biased SVMs for detecting drug-target interactions. Moreover, Regression-SVMs evaluate target–ligand interactions, ensemble SVMs predict therapeutic sensitivity, and linear SVMs are applied in kinase mutation analysis and anti-cancer compound classification.[302] Numerous studies confirm that SVMs are a robust tool for classification and prediction in drug development, significantly improving the efficiency and precision of identifying potential drug candidates. The technique demonstrates remarkable predictive accuracy, often ranging between 85% and 90%.[296] SVMs excel particularly in scenarios with limited data—an all too common challenge in pharmaceutical research—while maintaining high levels of predictive accuracy.

ii. Random Forest

Random Forest has emerged as a popular and effective ensemble method in drug discovery, primarily due to its versatility and high predictive accuracy. This technique generates multiple decision trees, with each tree constructed using a random subset of the training data, usually two-thirds of the dataset, while the remaining data is reserved for internal validation.[302] During the tree-building process, a random selection of predictors is considered at each split, with the best predictor chosen to optimize that split. After all trees are built, predictions for new data are made by aggregating the results through a majority vote across the ensemble. This methodology allows Random Forest to effectively manage complex biological data and achieve high levels of accuracy in both classification and regression tasks.[303]

One significant application of Random Forests in drug discovery is predicting drug activity. By analyzing chemical descriptors alongside genetic mutation data, researchers can accurately forecast the efficacy of small molecule drugs against cancer cells.[304] This capability has particularly benefitted personalized oncology, where the approach consistently demonstrates validation across diverse datasets. Furthermore, another crucial application involves Drug–Target Interaction (DTI) prediction, which aims to identify potential interactions by analyzing chemical structure characteristics and evolutionary data. Random Forests also excel when dealing with high-dimensional biomedical datasets, such as those containing genetic and proteomic features. This strength makes it easier to pinpoint critical factors that influence drug safety and efficacy.[305] The method's feature importance capability is particularly valuable, allowing researchers to isolate molecular characteristics that are most predictive of drug interactions, thus guiding the selection of therapeutic candidates. Additionally, Random Forest can be effectively combined with other methods, such as Lasso Regression, to enhance prediction accuracy by capturing complex biological interactions.[306–308]

In a study by Rahman et al.,[306] Random Forests were employed to enhance dose–response predictions through the inclusion of functional data. They stored dose–response profiles in the leaf nodes and leveraged genomic information to improve the prediction of drug efficacy against specific cancers. In virtual screening, Cano et al.[307] utilized Random Forests to refine ligand-protein affinity predictions, selecting molecular descriptors that were appropriately tailored to particular enzyme types, such as kinases. Another investigation by Plewczynski et al.[308] incorporated Random Forests with flexible docking techniques for high-throughput screening, achieving an impressive 90% hit rate and successfully identifying 60% of active compounds by docking only 10% of the ligands. Additionally, Wan and Pal[309] improved drug susceptibility predictions using a multivariate Random Forest model that correlates various drug responses, thereby increasing prediction accuracy. These studies collectively demonstrate the flexibility and effectiveness of Random Forests across numerous tasks in drug discovery, such as virtual screening, sensitivity prediction, and structure–activity relationship modeling. Their adaptability and robustness make them an optimal choice for researchers focused on enhancing therapeutic outcomes and streamlining the drug development process.

iii. Gradient boosting

Gradient boosting is an advanced ensemble learning technique that incrementally constructs a strong predictive model by aggregating multiple weak learners, usually in the form of decision trees. The method optimizes the model by minimizing a loss function, which quantifies the difference between the predicted and actual values, adjusting subsequent models to address the residual errors of earlier models. Owing to their robust predictive abilities and efficiency in various applications, gradient boosting algorithms have become pivotal in the drug development process.[310] When compared to other machine learning models such as Random Forest, Support Vector Machines, and neural networks, gradient boosting models—especially Extreme Gradient Boosting (XGBoost)—have demonstrated outstanding performance in capturing intricate biological relationships. These models excel in drug development scenarios

due to their capability to manage imbalanced datasets and accommodate a diverse array of chemical structures, making them particularly suitable for high-throughput screening tasks.[310,311] A newer entrant, LightGBM, enhances this framework by improving scalability and predictive accuracy while concurrently decreasing computation time, rendering it ideal for handling extensive molecular libraries and frequent model retraining.[312]

Gradient boosting algorithms—including Stochastic Gradient Boosting (SGB) and Gradient Tree Boosting (GTB)—are particularly effective in predicting synergistic drug combinations by integrating biological, chemical, and pharmacological data. They utilize features derived from heterogeneous networks and employ methods to reduce redundancy during feature selection, ultimately yielding more insightful and accurate predictions than traditional classifiers.[313] In the realm of DTI prediction, Gradient Boosting Decision Trees (GBDT) and similar methodologies have proven successful in achieving high accuracy. These models enhance predictions by constructing drug-target networks, extracting topological information through methods like random walks, and addressing class imbalance with negative sampling techniques to bolster robustness.[314,315] Noteworthy advancements like AutoDock Koto, which merges gradient boosting with differential evolution, leverage gradient boosting in molecular docking to optimize search functionality and docking accuracy, identifying potential treatments for diseases such as COVID-19.[316] Similarly, SXGBsite combines XGBoost with SMOTE (Synthetic Minority Over-sampling Technique) to predict protein-ligand binding sites, helping reduce overfitting while delivering rapid, high-quality predictions based on sequence information.[317] Another model, Drug-LXGB, utilizes Light eXtreme Gradient Boosting (LXGB) and incorporates multiple feature descriptors, achieving high predictive accuracy for discovering druggable proteins and aiding the identification of novel therapeutic targets.[318]

In summary, gradient boosting algorithms, particularly XGBoost and LightGBM, have proven invaluable across a plethora of drug discovery applications. These include molecular docking, drug-ligand binding site identification, druggable protein discovery, synergistic drug combination prediction, biological activity prediction, and drug-target interaction analysis. The scalability, efficiency, and prediction accuracy of these techniques have rendered them indispensable tools in modern drug discovery.

iv. Unsupervised learning algorithms

Clustering: Clustering algorithms play a crucial role in the drug development process by organizing molecules based on their chemical characteristics, biological data, and drug interactions. This approach enables researchers to efficiently evaluate a more manageable subset of compounds by selecting a few from each cluster, rather than assessing a vast number of compounds at random.[319] For example, clustering can help in identifying structurally similar molecules that may exhibit comparable biological activities, thus aiding in the discovery of lead compounds that could serve as viable drug candidates. Moreover, clustering ensures that each cluster is adequately represented, contributing to the selection of a diverse array of compounds for screening. It also helps in optimizing ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties by identifying compounds with desirable pharmacokinetic profiles.[320] Furthermore, the analysis of clustered fragments bound to protein binding sites can guide lead optimization and pharmacophore mapping efforts.[321]

Among the most commonly utilized clustering techniques in drug development are K-Means and Hierarchical Clustering.[319] K-Means clustering divides compounds into a specified number of clusters (k) based on their chemical characteristics, such as molecular weight, boiling point, density, and pKa, assuming a linear correlation between compounds and their clusters.[321] This method can categorize pharmaceutical datasets into three groups based on usage—high, medium, and low. In contrast, Hierarchical Clustering organizes compounds into a hierarchical structure represented by a dendrogram, thus providing a more detailed view of the dataset and enabling the identification of compounds with similar structural properties. For instance, researchers have successfully clustered large datasets (e.g., 16,000 chemicals) into approximately 100 clusters using a combination of K-Means and hierarchical methodologies. Other clustering approaches, including model-based and density-based clustering, are also employed based on the specific requirements of the analysis.[319,322,323] In addition, clustering algorithms prove to be valuable in drug repositioning and can work alongside AI techniques like GraphSAGE to uncover novel drug–disease associations. This integration can enhance predictive capabilities, allowing researchers to discover previously unidentified relationships between existing drugs and new therapeutic targets, which is particularly beneficial for identifying potential treatments for diseases like COVID-19.[53,316]

Applications of clustering algorithms extend into protein–protein interaction (PPI) network analysis, virtual screening, and drug repositioning. PPIs are essential for identifying pharmacological targets and understanding mechanisms of action. Different clustering algorithms can yield varying results in PPI analyses, with some, such as Walktrap, showing superior performance in specific contexts, making them valuable tools for target identification.[295] Clustering is also beneficial for managing extensive chemical libraries. Techniques such as incremental algorithms and 2D fingerprinting enable rapid clustering and efficient handling of large datasets comprising millions of compounds, which is crucial for high-throughput screenings where both speed and accuracy are imperative.[324]

Integrative clustering algorithms that combine chemical and biological data enhance the understanding of compounded potency and structural properties, significantly increasing the chances of discovering novel therapeutics. By leveraging multiple data types, these strategies can identify compounds that share aligned features.[325] Hierarchical clustering methods, like Ward's method, are extensively used in drug development due to their capability to handle large datasets efficiently. These algorithms can be implemented in parallel to reduce computation time, making them suitable for large-scale studies that have limited computational resources. Non-hierarchical clustering techniques, such as Jarvis-Patrick, are favored for their rapid processing capabilities. Nevertheless, recent modifications to these algorithms have been introduced to enhance their accuracy by reducing the inclusion of outlier compounds, thereby ensuring that the clusters generated are more meaningful and relevant to the drug development context.[326,327]

Dimensionality Reduction: Dimensionality reduction techniques are crucial in the drug discovery process, particularly when handling complex high-dimensional datasets. These techniques simplify data while retaining vital information, making analysis and interpretation simpler.[328] Researchers employ them at various stages of drug discovery, such as predicting how drugs and targets interact. By focusing on the most critical data, these models improve their predictive capabilities.[329] For instance, a multi-kernel approach that incorporates dimensionality reduction has shown success in predicting DTIs, which significantly benefits the drug discovery process.

AI and ML models often rely on dimensionality reduction techniques to transform large datasets into more manageable forms.[330,331] This step is vital when training ML models to forecast how well drugs will work and how safe they will be. Methods such as PCA and T-distributed Stochastic Neighbor Embedding (t-SNE) effectively reduce the data dimensionality, making them more suitable for analysis and interpretation. Recent advancements in deep learning have enabled the integration of dimensionality reduction methods into generative models, enhancing their ability to generate novel molecular structures while handling complex data efficiently.[332] These models can now create new molecules by leveraging dimensionality reduction techniques, making them more effective in drug design tasks. Dimensionality reduction is also essential in creating QSAR models, which link chemical structure to biological activity.[330] Methods such as PCA are commonly employed to predict how

drugs and targets interact, identify biomarkers, and visualize complex biological systems. PCA reduces the number of variables while retaining the dataset's variance, thereby boosting the model's predictive capabilities. Other dimensionality reduction techniques, such as Uniform Manifold Approximation and Projection (UMAP), Feature Selection methods, Independent Component Analysis (ICA), Linear Discriminant Analysis (LDA), and linear embedding (LLE), are also used to minimize data in drug discovery.[332]

Precisely, dimensionality reduction techniques play a pivotal role in the following applications in drug discovery:

1. Predicting Drug–Target Interactions (DTIs): Methods such as PCA and multi-kernel approaches are useful in predicting DTIs, which is crucial for understanding drug interactions and mechanisms.
2. QSAR Model Creation: Dimensionality reduction techniques like PCA are employed to create QSAR models, which relate chemical structure to biological activity.
3. Gene Expression Data Analysis: Techniques like t-SNE and UMAP are used to analyze high-dimensional gene expression data, facilitating the discovery of novel biomarkers and therapeutic targets.
4. Generative Models for Drug Design: Dimensionality reduction methods are integrated into generative models to enable the creation of novel molecular structures while handling complex data efficiently.

Deep learning algorithms: Convolutional Neural Networks (CNNs) play a significant role in drug discovery, particularly in the analysis of structured data such as images and molecular graphs. These networks excel at identifying patterns and features in two-dimensional data, making them useful for analyzing molecular structures and biological images, such as histological slides, to pinpoint potential drug targets and assess the efficacy of therapeutic compounds.[333,334] For instance, Hirohara et al.[333] demonstrated how a CNN could utilize SMILES strings, which are representations of chemical structures, to identify crucial binding sites on proteins, facilitating the search for novel drug candidates. Similarly, Matsuzaka and Uesawa[334] leveraged CNNs with 3D representations of chemical compounds to accurately predict their interactions with the constitutive androstane receptor, outperforming traditional methods.

In contrast, Recurrent Neural Networks (RNNs) are adept at handling sequence data, making them particularly suitable for predicting the behavior of biological sequences or drug-like compounds based on their chemical structures. RNN variants, such as Long Short-Term Memory (LSTM) networks, can model complex temporal relationships in time-series data, which is especially relevant in pharmacokinetics and pharmacodynamics studies. These models are frequently employed in drug discovery to understand how drug compounds interact with biological targets. Research indicates that LSTM-RNNs can effectively predict the activity of drug compounds based on their sequences, showcasing their ability to handle time-based dependencies intrinsic to biological data.[335,336]

Graph Neural Networks (GNNs) offer a unique approach by representing molecules as graphs, where atoms are treated as nodes and chemical bonds as edges. This perspective aligns closely with the way chemical interactions occur, enabling GNNs to learn from the relationships and connectivity between molecular components.[337,338] For instance, Nguyen et al.[339] developed a model known as GraphDRP that employs GNNs to predict drug efficacy by analyzing gene expression data from cancer cell lines, highlighting the capability of GNNs to interpret complex biological interactions.[339] Similarly, Generative Adversarial Networks (GANs) are revolutionizing the field of drug discovery by generating novel molecular structures based on existing datasets. GANs consist of two neural networks—the generator and the discriminator—operating in competition, which drives the generator to produce increasingly realistic data. This capability allows GANs to create new compounds with desired properties, significantly streamlining the process of de novo drug design. One notable example is the druGAN model, which combines GANs with autoencoders to generate new molecules that meet specific drug-related criteria. This innovative approach enables researchers to explore vast chemical spaces and uncover potential drug candidates that traditional methodologies might overlook.[337]

7. Robotics in Drug Discovery, development, formulation, and production processes

The advent of robotics has significantly impacted many industrial processes since the industrial revolution, and drug discovery and development are no exceptions.[338,339] Processes traditionally involving human labor are increasingly being replaced by machines, which offers numerous benefits. In various upstream and downstream drug production processes, including discovery, development, formulation, and production, reduced human contact helps ensure the ultra-high purity required for pharmaceuticals. Additionally, robotics promotes quicker and more efficient synthesis, testing, and throughput of compounds, enabling a faster response to urgent medical needs, as witnessed during the COVID-19, Ebola, Polio, and Cholera outbreaks.[340] Table 3 highlights specific examples of automated processes and robotics tools used to facilitate pharmaceutical operations.

Furthermore, robotic systems automate the transport of microplates between different instruments and storage locations, significantly reducing manual handling time and enabling continuous, unattended screening over extended periods.[340,341] Robotics integrated with advanced detection tools—such as plate readers, imagers, and high-content screening systems—enhances the collection and analysis of extensive datasets.[342] Paired with specialized software, these systems can process, analyze, and store large volumes of data rapidly, accelerating the identification of active compounds and the advancement of potential drug candidates.[342,343,345] Importantly, the modular design of robotic platforms allows for scalable workflows, enabling researchers to adjust capacity based on specific project needs. The synergy between robotics and ML accelerates the discovery of potential candidates and predicts how molecular modifications may influence compound performance, ultimately optimizing lead compounds.[346,347] One of ML's strengths lies in its ability to learn and adapt based on new data, improving prediction accuracy and strategic planning as robotic systems accumulate more information. Moreover, ML integrated with cloud technology enables real-time data analysis, providing researchers with the capability to monitor experiments and make data-driven decisions instantaneously, which enhances flexibility and responsiveness in drug discovery.[344,348]

For example, companies like Recursion Pharmaceuticals showcase the effectiveness of robotic and AI integration in drug discovery. Robots at Recursion handle the treatment, staining, and imaging of millions of cell samples, automating these processes for machine learning algorithms to analyze changes in cell morphology quickly and efficiently.[349] Similarly, Evotec, in collaboration with Exscientia, demonstrated the significant impact of robotics on small-molecule drug development by identifying a novel anticancer compound in just eight months—a process that traditionally extended over four to five years.[350] Arctoris has revolutionized automation further by employing robotic systems across the complete drug discovery pipeline, from high-throughput screening to compound management and data analysis, facilitating rapid and precise experimentation.[351] Insilico Medicine combines robotics with AI and deep learning to design and optimize new drug candidates through predictive modeling, while Pfizer employs automation for high-throughput screening and data analysis, enhancing the accuracy and speed of hit selection.[352] A key insight from the integration of robotics and ML is the significant potential to enhance the success rates of pharmaceutical projects by automating critical tasks and providing robust data analysis, predictive modeling, and experimental design. Furthermore, the integration of robotics with advanced detection tools—such as plate readers, imagers, and high-content screening systems—has transformed the drug discovery landscape by enabling the

Table 3
Applications of robotics in drug development, formulation and production processes.

Application	Robotics Tool	Purpose	Reference
Drug Discovery	Automated High-Throughput Screening (HTS) Systems	Rapidly screens large compound libraries for activity against disease targets.	[312–315]
Drug Discovery	Automated Compound Synthesis Robots	Synthesizes novel compounds with minimal human intervention	[316–318]
Development & Data Collection	Lab Automation Platforms	Coordinates laboratory equipment to optimize workflow and collect high-quality data	[319–321]
Drug Formulation & Personalization	Robotic Arm with AI Integration	Optimizes drug formulation and dosing for personalized medicine approaches	[322–324]
Production & Manufacturing	Automated Quality Control Systems	Ensures consistency and accuracy in drug production quality control processes	[325,326]
Assay Preparation	Robotic Liquid Handlers	Precisely dispenses reagents for bioassays and cell culture experiments	[326–328]
High-Throughput Screening	Microplate Handlers	Manages microplates in screening processes to maximize efficiency	[329–331]
Preclinical Testing	Cell Culture Robots	Automates cell culture preparation and maintenance for testing candidate drugs	332
Preclinical/Clinical Testing	Automated Sample Preparation Systems	Prepares biological samples consistently for more accurate testing results	[333–335]
Compound and Sample Management	Automated Storage and Retrieval Systems	Organizes and retrieves samples efficiently, thereby reducing storage time and enhancing lab safety	[336,337]

efficient collection and analysis of extensive datasets.[342] When coupled with specialized software, these robotic systems can rapidly process, analyze, and store large amounts of data, accelerating the identification of active compounds and the progression of potential drug candidates.[342,343] The modular design of these robotic platforms allows for scalable workflows, empowering researchers to tailor their capabilities according to specific project requirements.

The synergy between robotics and ML not only accelerates the discovery of potential drug candidates but also aids in forecasting how molecular modifications might impact compound performance, thereby optimizing lead compounds.[346,347,348]

8. Drawbacks of AI and robotic systems in drug development

Although AI and robotics have brought numerous benefits to drug discovery, development and delivery processes, their implementation comes with some limitations. One of the main limitations of the Vinci Surgical System, for example, is its cost, which can be prohibitively expensive for some hospitals and healthcare institutions. The high cost of the system can limit its accessibility and availability, which can be a significant barrier to adoption. AI is effective in the presence of trained and consistent information-rich databases to solve problems. Paucity of big databases with consistent information is a hurdle to AI implementation in drug discovery and delivery.[353] Lack of accurate data may lead to incorrect or inconsistent predictions or skewed conclusions by AI. This means that reliably accurate, unbiased, representative, and high-quality datasets are required for training AI-assisted models for drug discovery.[43] Another important consideration for AI used in drug discovery and delivery is the choice of AI algorithms for an intended problem. The use of wrong AI algorithms to solve a particular problem will give inaccurate results. Therefore, the use of AI requires that researchers know the appropriate computer algorithms for a specific chemical or biological task. The interpretation of and reasons behind AI-generated results is equally important. Scientists must be able to interpret the results generated by AI algorithms.[45]

AI models, particularly those used in robotics for pharmaceutic tasks, like other areas of application, often rely on vast amounts of personal or sensitive data to function effectively. Ensuring data privacy while gathering, storing, and processing this information remains a significant ethical and technical challenge.[354,355] Secure data handling practices are essential, yet they can also limit the volume and type of data available for training and improving models. Furthermore, AI is frequently needed in robotics applications to enable quick, real-time modifications in response to shifting conditions or unforeseen hurdles. A recurring technological challenge is striking a balance between computational efficiency and the accuracy of AI-driven judgments, which is frequently limited by hardware constraints and the requirement for strong sensor integration. Because it requires quick processing rates and reliable algorithms that can handle dynamic data, real-time adaption is difficult.[356,357]

Finally, AI is developed essentially to make useable predictions based on patterns in the input datasets. However, the AI predictions need to be experimentally validated. For instance, AI models could predict biological activity of a series of chemical derivatives based on their structural features (SAR); AI-driven platforms can also explore the conformational space of a target protein to predict its binding interaction with a small molecule probe. Either of activity predicted based on chemical structures or activity predicted based on binding affinity still must be subjected to biological testing, but this has the implications of being capital-intense and time-consuming.[43]

9. Summary and conclusions

In this intensive review, we have traced the profound impact of AI, computational tools and robotics on D-DDD landscape, illustrating their potential to reshape traditional pharmaceutical processes. We discussed that, historically, drug discovery and development have been constrained by lengthy timelines, high costs, and complex processes that limit rapid advancements. Traditional methods have offered groundbreaking contributions but also revealed inherent limitations, particularly in terms of efficiency, precision, and scalability. The introduction of AI and robotics into D-DDD represents, however, significant shift, offering solutions to these longstanding challenges. From computational modeling and machine learning algorithms in molecular screening to robotics-driven automation in compound synthesis and personalized delivery systems, the field is witnessing a surge in transformative innovations.

We provided current applications of AI, including predictive modeling, clinical trial design, and advanced data mining, to emphasize its role in enhancing drug efficacy, safety, and target identification. Robotics further complements these advancements by enabling high-throughput screening and optimizing drug formulations. Together, these technologies allow for accelerated development cycles, precise formulation adjustments, and tailored delivery methods that can adapt to individual patient needs. Despite the clear benefits, we noted the limitations of both AI and robotics in D-DDD—such as data privacy concerns, model interpretability, and the complexities of real-time adaptation, which highlight areas for further refinement and development.

Looking to the future, the convergence of AI, robotics, and big data in the pharmaceutical sector promises a paradigm shift toward intelligent, adaptive drug development and delivery. As these technologies evolve, there is immense potential to advance beyond personalized medicine to a proactive and preventive healthcare model, where therapies are not only tailored but also anticipated and optimized for individual health profiles. We believe that through continuous refinement of AI algorithms, enhanced robotic precision, and fostered interdisciplinary collaborations, the industry can pave the way for a more efficient, accessible, and patient-centered approach to healthcare.

CRediT authorship contribution statement

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Data availability

Not applicable.

Declaration of competing interests

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.

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