ISSN 2816-8089

REVIEW ARTICLE

Revolutionizing Anti-Cancer Drug Discovery: The Role of Artificial Intelligence

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Abstract

This comprehensive review explores the integration of Artificial Intelligence (AI) in anticancer drug discovery, highlighting its transformative impact on streamlining the identification, design, and synthesis of novel drug molecules. Leveraging expansive datasets, AI and machine learning technologies enhance the understanding of cancer biology, facilitate target identification, and accelerate the design of molecules with desirable pharmacological properties. Despite promising advancements, challenges persist, including issues related to data quality, model interpretability, and the practical application of AI-generated findings in clinical settings. This review critically examines these challenges, proposes advanced AI models for drug combination predictions, and advocates for collaborative efforts to refine and implement AI methodologies in clinical oncology. The potential of AI to revolutionize anticancer drug discovery is immense, providing a new paradigm that merges precision with efficiency to push the boundaries of therapeutic innovation. Through rigorous validation and interdisciplinary cooperation, AI-driven strategies hold the promise to significantly shorten drug development timelines and improve clinical outcomes, ushering in a new era of personalized medicine in cancer treatment.

Key Words: *Drug design; Target identification; Machine learning; Biomarker discovery*

Highlights

Overview of AI-driven methods in target identification and validation.
Exploration of AI-driven molecular design and optimization of lead compounds.
Insights into drug repurposing strategies facilitated by AI technologies.
Examination of AI applications in cancer imaging and biomarker discovery.

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***Received Date**: April 22, 2024, **Accepted Date**: June 03, 2024, **Published Date**: July 22, 2024*

***Citation:** Bhuyana R, Tyagia E, Kumarib P, et al. Revolutionizing Anti-Cancer Drug Discovery: The Role of Artificial Intelligence. Int J Bioinfor Intell Comput. 2025;4(1):1-38.*

1. Introduction

Over the last decade, the landscape of cancer therapeutics has undergone a profound transformation, marked by a notable shift towards harnessing the capabilities of artificial intelligence (AI) and machine learning (ML) [1]. The integration of advanced computational techniques with traditional drug discovery processes has not only opened new frontiers but has also provided unparalleled opportunities for the identification and development of ground-breaking anticancer agents [2]. This review delves into the pivotal role played by AI and ML in simplifying the intricate landscape of anticancer drug discovery.

AI and ML have emerged as indispensable tools in analysing expansive biological datasets, empowering researchers to discern patterns, correlations, and potential targets that may have eluded conventional methods [3]. The amalgamation of genomics, proteomics, and other omics data facilitates a comprehensive understanding of cancer biology, enabling the identification of novel biomarkers and potential therapeutic targets [4]. This data-driven approach speeds up the early stages of drug discovery by offering insights into cancer's molecular mechanisms and helping prioritize candidate compounds [5]. Addressing a foremost challenge in anticancer drug discovery, the identification and validation of suitable molecular targets, AI and ML algorithms excel in analysing intricate biological networks. Such algorithms predict target-disease associations and elucidate complex interactions, offering a sophisticated computational approach to prioritize potential targets based on their relevance to specific cancer types, molecular pathways, and cellular processes. This targeted methodology not only reduces the likelihood of off-target effects but also augments the overall success rate of drug development [6,7].

The advent of AI-driven molecular design has ushered in a revolutionary phase in creating novel anticancer compounds. Generative models and deep learning algorithms significantly expedite the drug design phase by predicting molecular structures with desired pharmacological properties [8]. Furthermore, machine learning algorithms optimize lead compounds by predicting their bioavailability, toxicity, and other crucial parameters. This accelerates the drug development timeline and minimizes the resource-intensive aspects of experimental trial and error [9]. AI and ML methodologies propel the era of precision medicine in cancer treatment by analysing patient-specific data, including genetic profiles, clinical history, and treatment responses [10]. This analytical prowess tailors therapeutic regimens for individual patients by predicting responses and stratifying populations based on molecular characteristics [11].

While the integration of AI and ML in anticancer drug discovery holds immense promise, certain challenges, such as data quality, model interpretability, and the need for large, diverse datasets, necessitate meticulous consideration. Ongoing collaboration between computational biologists, pharmacologists, and clinicians is imperative to fully unlock the potential of these technologies and translate ground-breaking discoveries into clinically meaningful outcomes [12]. The evolving landscape of AI and ML applications in anticancer drug discovery provides a glimpse into a future where precision and efficiency converge, redefining the boundaries of therapeutic innovation.

This paper explores the integration of artificial intelligence (AI) in anticancer drug discovery, focusing on its potential and current challenges. While AI has shown promise, gaps exist in predicting complex drug combinations and ensuring the practical application of research findings in clinical settings. The novelty of this work lies in proposing advanced AI models

for predicting drug combinations, emphasizing the need for interpretable models, and advocating for collaborative efforts to validate and implement AI solutions in clinical oncology. This research aims to address these gaps and contribute to the effective utilization of AI in anticancer drug discovery.

2. Stages of anticancer drug discovery

Drug discovery is a complex process encompassing various stages such as target identification, synthesis, characterization, screening, and efficacy assays (Figure 1). The timeline for developing a single drug molecule, from discovery to market availability, typically spans 12 to 15 years [13].The initial step involves identifying a target, achieved through data mining using bioinformatics, genetic association, expression profiling, pathway and phenotypic analysis, and functional screening [14]. Target validation is crucial, involving structural activity relationship (SAR) studies, generating drug-resistant mutants, and manipulating target genes through techniques like genetic manipulation, antibody interactions, chemical genomics, and viral transfection [15]. Chemical leads, meeting criteria of stability, feasibility, and drug-like activity, undergo a drug ability assessment to evaluate target binding and pharmacokinetics [16].

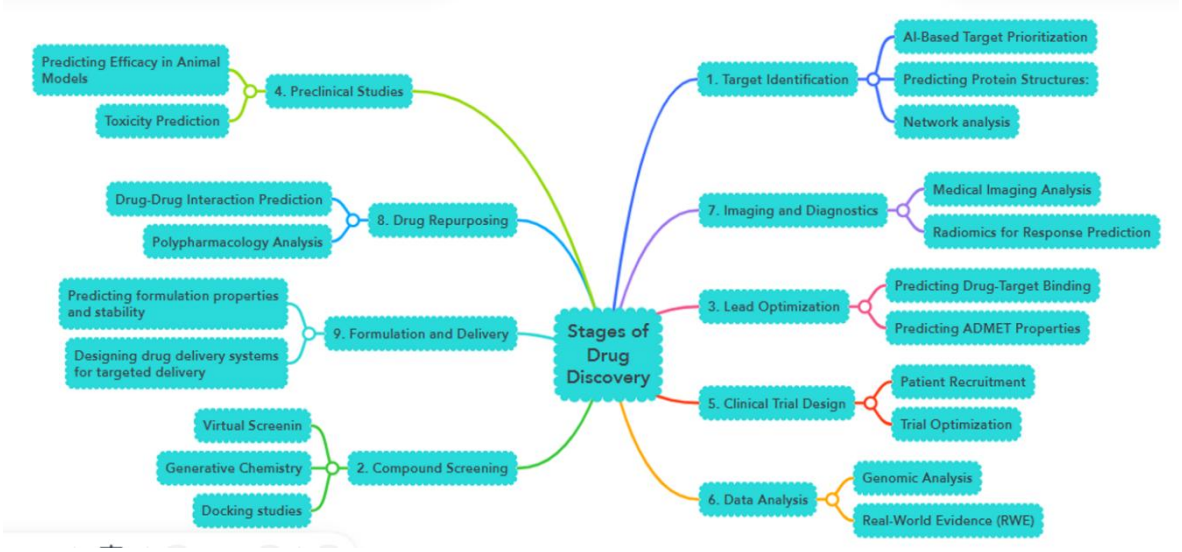

Figure 1: *Stages of drug discovery.*

Lead optimization, the final step in early-stage drug discovery, entails iterative synthesis and characterization to understand the relationship between chemical structure and activity [17]. Researchers use DMPK (Drug Metabolism and Pharmacokinetics) screens to predict *in vivo* pharmacokinetics and enhance drug potency and safety profiles [18]. Automated screening systems, MALDI imaging, and NMR Fragment-based Screening play pivotal roles in evaluating drug candidates [19].

Preclinical testing involves assessing safety and efficacy in animals through general pharmacology and toxicology studies [20]. Pharmacokinetic studies provide insights into absorption, distribution, metabolism, and excretion, while toxicological studies, conducted *in vitro* and *in vivo*, evaluate the drug's toxic effects. An Investigational New Drug application is filed with the FDA before commencing clinical research [21].

2.1. Clinical trials progress through phases

Phase 0 involves sub-therapeutic doses for pharmacokinetic data; Phase 1 assesses safety in healthy volunteers; Phase 2 evaluates drug efficacy in larger patient groups; and Phase 3 tests on a larger scale to prove action benefits. Phase 4 trials occur post-FDA approval, assessing real-world efficacy, cost-effectiveness, and safety [22–24]. To market a drug, a New Drug Application (NDA) is submitted, encompassing preclinical data to Phase 3 trial results. FDA review takes 6 to 10 months, and if the drug is deemed safe and effective, prescribing information is upgraded. Phase 4 trials are conducted post-approval to assess real-world impact [25].

3. AI in Biological data analysis

Big Data, characterized by its immense volume and complexity, has become a transformative force in drug discovery, drawing insights from diverse disciplines such as chemistry, pharmacology, and bioassays. The integration of Artificial Intelligence (AI) into this domain has ushered in a new era, alleviating human workloads and expediting target achievement [26].

Genome sequencing initiatives yield a plethora of potential target hypotheses, necessitating meticulous prioritization [27]. AI contributes significantly to this process by refining computational models in subsequent optimization rounds. This paradigm shift involves reasoning, knowledge representation, solution search, and machine learning. For example, IBM Watson an AI tool capable of disease detection within a remarkably short timeframe [28]. Chu et al., 2019, conducted a study to uncover the ceRNA network in gastric cancer (GC) associated with *Helicobacter pylori* (Hp) infection. By analyzing RNA expression profiles from the TCGA database, they compared 20 GC cases with Hp infection to 168 cases without. They identified differentially expressed lncRNAs, miRNAs, and mRNAs, constructing a lncRNA-miRNA-mRNA ceRNA network. Key findings included 32 differentially expressed miRNAs, 27 lncRNAs, and 257 mRNAs, with 10 miRNAs, 11 lncRNAs, and 219 mRNAs forming the ceRNA network. GO and KEGG pathway analyses revealed significant roles in extracellular exosomes and the P13K-Akt signaling pathways. PPI network analysis highlighted six hub genes: NTS, APOC3, OTX2, KRT13, CALCA, and GNG4. Survival analysis linked four lncRNAs and four miRNAs to overall survival in Hp-positive GC patients. Real-time PCR confirmed higher levels of specific lncRNAs in Hp-positive cases [29].

Further, Umar et al., 2023, explored the potential of Albizia lebbeck methanolic (ALM) extract in combating breast cancer metastasis. The study investigated the phytochemical compositions and the cytotoxic, anti-proliferative, and anti-migratory effects of ALM extract on MDA-MB 231 and MCF-7 human breast cancer cells. The researchers employed artificial neural networks (ANN), adaptive neuro-fuzzy inference systems (ANFIS), and multilinear regression analysis (MLR) to predict cell migration in response to various extract concentrations. While lower concentrations (10, 5, 2.5 µg/mL) showed no significant impact, higher concentrations (25, 50, 100, 200 µg/mL) significantly inhibited cell proliferation and motility ($p<0.05$; $n\geq3$). The study revealed that both traditional MLR and AI-based models effectively predicted metastasis in the cancer cells [30].

In drug discovery, AI plays a pivotal role, across virtual screening to Quantitative Structure-Activity Relationship (QSAR) modelling, expediting drug design and reducing costs (Figure

2). The digitalization of pharmaceutical data has facilitated AI's capacity to handle large datasets with enhanced automation, promising a transformative impact on societal work cultures [31]. Rehman and Najmi 2023, investigated potential inhibitors for the Epidermal Growth Factor Receptor (EGFR), relevant in treating cancers like non-small cell lung cancer (NSCLC) and breast cancer. They screened 2734 FDA-approved compounds for EGFR kinase inhibition, selecting the top 30 based on binding affinity scores.

The strongest potential of compounds indicating it could lead to new EGFR kinase inhibitors, highlighting the effective use of computational methods in drug discovery [32]. Mellado et al., 2022, addressed the limited efficacy of traditional chemotherapy for neuroblastoma, a common cancer in infants, by developing new compounds with enhanced activity and selectivity. The study synthesized 21 chalcones and evaluated their antiproliferative activity against the neuroblastoma cell line SH-SY5Y. Using three-dimensional quantitative structure–activity relationship models with high statistical values ($q2 > 0.7$; $r2 > 0.8$; $r2pred > 0.7$), they identified promising candidates based on IC50 and selectivity index data. Further, they designed and synthesized 16 new molecules, three of which exhibited higher selectivity indexes than reference drugs 5-fluorouracil and cisplatin. These three compounds also demonstrated significant proapoptotic effects, indicated by increased caspase 3/7 activity, altered Bcl-2/Bax mRNA levels, and DNA fragmentation [33].

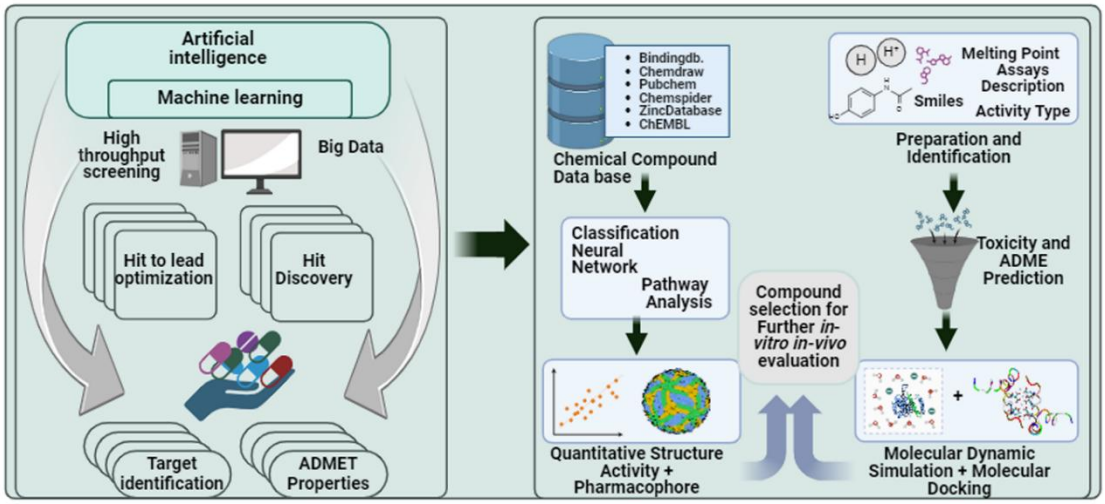

Figure 2: *AI and machine learning methods in advancing drug design.*

Functional genomics has witnessed a remarkable transformation due to AI, offering innovative solutions to unravel intricate gene-function relationships. Machine learning algorithms analyse extensive genomic datasets to predict gene functions, leveraging diverse biological data sources like gene expression profiles and protein-protein interactions [34]. Deep learning models, such as convolutional neural networks, excel in identifying regulatory elements within the genome, enhancing our understanding of gene functions and regulatory mechanisms [35]. An exemplary case involves the utilization of NCI's CellMiner Cross Database and Lantern Pharma's RADR® platform, showcasing the effectiveness of AI and machine learning in elucidating biological insights and identifying potential indications for specific drugs. Multi-omics analysis, a cornerstone of precision medicine, demands the profiling and interpretation of various omics data types at an individual level [36]. AI proves instrumental in constructing models for non-canonical data analysis, addressing the fast-growing landscape of multi-omics data [37]. This interdisciplinary endeavor requires

collaboration between biologists and computer scientists, with AI offering advanced analytical methods and predictive capabilities [38].
Machine learning, a subset of AI, involves training algorithms using a significant portion of the dataset, followed by validation with the remaining data [39]. Supervised learning maps input data to output using labelled examples, while unsupervised learning operates through reinforcement. Integrating multi-omics data involves model-based, concatenation-based, and transformation-based approaches [40]. Researchers spend countless hours searching for relevant literature and sifting through various data sources to assemble information relevant to a particular research question. AI will eventually solve this problem by collecting and assembling this data using text mining, semantic analysis, and missing link prediction [41].

AI and ML are being applied to infectious diseases, such as COVID-19, to improve control, forecasting, and treatment. Supercomputing models can help us understand the potential of AI in epidemiology [42]. AI infrastructure is growing, but there are still challenges such as limited computational input/output capability and ethical implications [43,44].

4. Target Identification and Validation

In the domain of Target Identification and Validation, Artificial Intelligence (AI) has emerged as a potent tool for predicting drug-target interactions and assessing their binding affinity [45]. Various machine learning (ML) and deep learning (DL) methodologies, including KronRLS, SimBoost, DeepDTA, PADME, DeepAffinity, and MANTRA, have been leveraged to elucidate Drug-Target Binding Affinity (DTBA) [46]. Furthermore, unsupervised ML techniques such as PREDICT offer the capability to prediction the therapeutic efficacy of drugs and target proteins. AI-driven tools like XenoSite, FAME, and SMARTCyp play pivotal roles in delineating drug metabolism sites [47,48]. McInerney et al., 2022, explored new therapeutic targets for glioblastoma (GBM), a challenging adult brain tumor with limited treatment options. They investigated the role of the isocitrate dehydrogenase 1 (IDH1) enzyme, which is overexpressed in GBM. Using artificial intelligence and evolutionary algorithms, they analyzed IDH1-wildtype gliomas from the TCGA LGG-GBM cohort, identifying 90 genes associated with IDH1 expression. These genes were involved in key pathways such as ubiquitin-mediated proteolysis, focal adhesion, mTOR signaling, and pyruvate metabolism. The study also found potential prognostic and diagnostic biomarkers, like TSPYL2 and MINK1, which could be linked to glioma progression and patient outcomes. These insights reveal metabolic vulnerabilities and suggest new therapeutic targets, paving the way for future clinical trials aimed at improving treatment for GBM patients [49].

Identifying drug-target interactions (DTI) is a pivotal step in anticancer drug design, significantly impacting drug development and lead compound discovery. Computational methods, including molecular docking simulations and machine learning-based approaches, aid in accurate DTI predictions (Figure 2) [50]. Choosing drug targets is equally crucial, and recent advancements, such as the KG4SL graph neural network model, address targeted drug synthesis challenges [51]. Integrating multiple data types through AI-powered methods like BANDIT, DDR, KG4SL, and Drugnome AI enhances predictive power [52]. The identification of therapeutic targets for anticancer drugs, screening for hit compounds is imperative. High-throughput screening methods, such as structure-based and ligand-based screening, play a key role [53]. Wang et al., 2022, explored the transformative impact of artificial intelligence on biomedical research, particularly in drug discovery, by developing a robust predictive tool for drug–target interactions (DTIs). Recognizing the high costs, lengthy timelines, and low success rates associated with traditional DTI methods, the study introduced MSPEDTI, a

deep-learning-based model that combines drug structure and protein evolutionary information. The model employs a convolutional neural network (CNN) to uncover hidden features and an extreme learning machine (ELM) to predict DTIs with high accuracy. In cross-validation experiments, MSPEDTI achieved prediction accuracies of 94.19% for enzymes, 90.95% for ion channels, 87.95% for G-protein-coupled receptors (GPCRs), and 86.11% for nuclear receptors. The model's effectiveness was further validated in ablation studies and comparisons with other methods. Additionally, 7 out of 10 potential DTIs predicted by MSPEDTI were confirmed by classical databases, demonstrating the model's reliability in identifying drug candidate targets and advancing drug repositioning and development [54]. Virtual screening, facilitated by deep learning models predicting docking scores, identifies molecules with strong binding affinity for target proteins. Fragment-based drug design, particularly with the POEM method, addresses rational fragment ligation in pockets, advancing drug discovery [55]. Recent years have seen the systematization of drug discovery through high-throughput screening and combinatorial chemistry (Table 1). Fragment-based drug design has gained prominence, and methods like POEM enable rational fragment ligation [56]. De novo drug design and virtual screening, leveraging variational auto-encoders, recurrent neural networks, generative adversarial networks, and deep reinforcement learning, contribute to generating and optimizing molecules [57]. Drug repositioning, a research focus, utilizes AI-based methods for predicting drug-target and drug-disease interactions, offering frameworks like GPSnet, DeepDRK, MTRD, SNF-NN, MBiRW, DR-HGNN, and GDRnet [52].

AI techniques extend to predicting drug reactions, encompassing aspects like Caco-2 permeability, carcinogenicity, blood-brain barrier permeability, and plasma protein binding. The development of anticancer drugs, such as REC-2282 and RLY-4008, through AI platforms underscores the transformative impact on drug discovery. BPM 31510, EXS-21546, and PHI-101 are examples of AI-designed drugs, showcasing their potential in optimizing the research paradigm [52,53, 55-58].

Convolutional Neural Networks (CNNs) are a class of neural networks widely utilized in the analysis of visual imagery. One prominent application of CNNs is in predicting drug-target interactions, where the DTI-CNN model, integrating Random Walk with Restart (RWR) and Denoising Autoencoder (DAE), plays a pivotal role [59,60]. This model constructs a heterogeneous network that combines various sources of drug and protein-related information. The DAE component aids in extracting low-dimensional representations of the complex features associated with drugs and proteins within the network [61].

DeepCPI, a tool based on an innovative framework, employs deep learning techniques and unsupervised representation learning to forecast drug-protein interactions. It utilizes methods such as latent semantic analysis and Word2Vec to learn compact feature representations of compounds and proteins [62,63]. Recent advancements in deep learning algorithms have shown remarkable progress in predicting Drug-Target Binding Affinity (DTBA) compared to traditional machine learning methods. These advanced algorithms leverage diverse input data, including SMILES, LMCS, ECFP, or combinations thereof, as features for drugs [64,65]. Leading the DTBA prediction methodologies is DeepDTA, utilizing SMILES for drug input data and employing a CNN with three 1D convolutional layers and max-pooling functions to discern latent features [66,67]. WideDTA, another CNN DL model, differs by representing ligand SMILES and protein sequences as sets of words rather than full-length sequences [68]. Deep Affinity, a deep learning (DL) model for predicting Drug-Target Binding Affinity (DTBA), utilizes the Simplified Molecular Input Line Entry System (SMILES) for drug representation. It employs a Recurrent Neural Network (RNN) model to encode structural

property sequence representations, resulting in superior accuracy compared to other machine learning (ML)-based methods [63]. In the field of drug discovery, DeepBAR, a DL-based tool for predicting binding affinity, represents a convergence of chemistry and machine learning. By employing the Bennett acceptance ratio method, DeepBAR accurately calculates binding free energy, thereby significantly enhancing the drug discovery process [69]. Reinforcement Learning for Structural Evolution (ReLeaSE) introduces a deep reinforcement learning (RL) approach to design chemical libraries with desired properties. This method consists of two Deep Neural Networks (DNNs): a generative model for producing chemically feasible novel molecules and a predictive model estimating the generative model's performance [70,71].

Deep Scaffold, a scaffold-based molecular generative model, as described by Nag et al., 2022, contributes significantly to addressing various drug design challenges. It assists in generating compounds with predefined scaffolds and facilitates de novo drug design for potential candidates. This AI-driven scaffold approach empowers medicinal chemists with large-scale diversification capabilities, accelerating drug design processes [67,69]. DeepVS, introduced by Pereira et al., 2016, leverages deep learning techniques to enhance docking-based virtual screening. By creating distributed vector representations of protein-ligand complexes using atom and amino acid embeddings, DeepVS improves screening accuracy and efficiency [72,73]. The AI-based virtual screening tool, SIEVE score, identified by Sarkar et al., 2023, surpasses conventional methods in terms of efficacy, offering enhanced performance for drug discovery initiatives [74]. Moreover, according to Jimenez-Carretero et al., 2018, Tox_(R)CNN utilizes deep learning algorithms to detect cytotoxicity from microscopic images, even without specific toxicity labeling, thereby proving invaluable for in vitro toxicity assessments [75]. Furthermore, Trials.ai, leverages Natural Language Processing (NLP) and other AI techniques to facilitate the design of clinical trial protocols, streamlining the trial process and enhancing efficiency. Lastly, AICURE, as highlighted by Miller et al., 2019, provides an AI-based platform for clinical trials, enabling participants to record medication videos. By analyzing facial expressions to monitor treatment responses, AICURE offers a novel approach to clinical trial monitoring, potentially revolutionizing patient care and trial outcomes [76]. Andreeva et al., 2021, addressed the challenges in diagnosing and treating non-melanoma skin cancer by exploring the use of fluorescence spectroscopy (FS) combined with deep learning (DL) algorithms. Traditional histological examination, the current gold standard, is invasive and time-consuming. In this study, 137 patients with various forms of basal cell carcinoma (BCC) were examined using a multispectral laser-based device equipped with a neural network (NN) called "DSL-1". The FS technique measured and compared the fluorescence spectra of suspected cancerous and normal skin tissues. These spectra were then analyzed using DL algorithms to classify the skin conditions as normal, pigmented normal, benign, or BCC. The AI-driven FS diagnostic method demonstrated an average sensitivity of 62% and specificity of 83% for predicting BCC lesions. This study suggests that the "DSL-1" diagnostic device could be a practical, real-time tool for diagnosing and guiding the resection of non-melanoma skin cancer, offering a less invasive and quicker alternative to traditional methods [77]. Further, Shukla et al., 2022, presented an advanced system for the automated detection and segmentation of liver tumors and hepatic lesions in magnetic resonance imaging (MRI) using innovative 3D affine invariant and shape parameterization approaches. This system addresses the variability in lesion characteristics across patients, imaging equipment, and lesion timing, which pose challenges in liver cancer staging. The proposed method uses geodesic active contour analysis to isolate the liver region, followed by segmentation using Cascaded Fully Convolutional Neural Networks (CFCNs). This approach minimizes error rates during training by leveraging segmented tumor areas. The system achieved an impressive accuracy of 94.21% in liver tumor analysis with a computation time of under 90 seconds per volume. Validation using the 3DIRCAD dataset confirmed a high

overall accuracy rate of 93.85% across various volumes, demonstrating the efficacy and reliability of this automated method for liver cancer analysis [78].
In the fight against COVID-19, companies like Deargen and Benevolent AI utilize deep learning to identify potential drug leads. Deargen predicts interaction strength between drugs and target proteins, identifying Atazanavir as a promising candidate [79,80]. Benevolent AI accelerates research using biomedical data and ML, pinpointing six drugs with potential to impede SARS-CoV-2 viral replication [81]. In dermatology, the proliferation of skin cancer smartphone apps, utilizing AI, allows for immediate risk assessment and tailored recommendations for patients, aligning with the advancements in both medical science and AI technologies [82,83]. However, it is important to note that while AI greatly optimizes anticancer drug research, it comes with limitations, including high data dependence and limited explainability. Generative models like Variational Auto-Encoders (VAE), Recurrent Neural Networks (RNN), and Generative Adversarial Networks (GAN) play vital roles in generating molecules with specific properties [52,84]. Various drug generation models, including deep reinforcement learning, ReLeaSE, and MoleGuLAR, highlight the dynamic landscape of AI in drug discovery [85,86].

Table 1: *Anticancer drug target identification methods using artificial intelligence.*

S.no	Method	Model	Application	References
1	Deep Learning	Convolutional Neural Networks	Analyzing genomic data, predicting drug targets	[87]
2	Support Vector Machines	SVM	Classifying cancer subtypes based on gene expression	[88]
3	Random Forest	Ensemble of Decision Trees	Predicting drug responses, identifying biomarkers	[89]
4	Neural Networks	Multilayer Perceptron	Analyzing protein-protein interaction networks	[90,91]
5	Network-Based Approaches	Graph Neural Networks	Analyzing protein-protein interaction networks	[92,93]
6	Feature Selection Methods	Various (e.g., Relief, MIFS)	Identifying relevant biomarkers and features	[94,95]
7	Bayesian Networks	Probabilistic Graphical Models	Modeling probabilistic relationships in biological data	[96,97]
8	Transfer Learning	Pre-trained models (e.g., BERT)	Biomedical Literature	[97,98]
9	Evolutionary Algorithms	Genetic Algorithms	Analyzing drug Sensitivity Data	[99]

5. AI-Driven Molecular Design

AI-driven molecular design has sparked a revolutionary transformation in drug discovery and material design, empowering researchers to optimize molecular structures and properties and explore previously uncharted territories [89]. In contrast to traditional empirical trial-and-error methods, which were both time-consuming and resource-intensive, AI models have redefined molecular design by predicting properties, unravelling complex structure-activity relationships, and efficiently screening vast compound libraries [100].

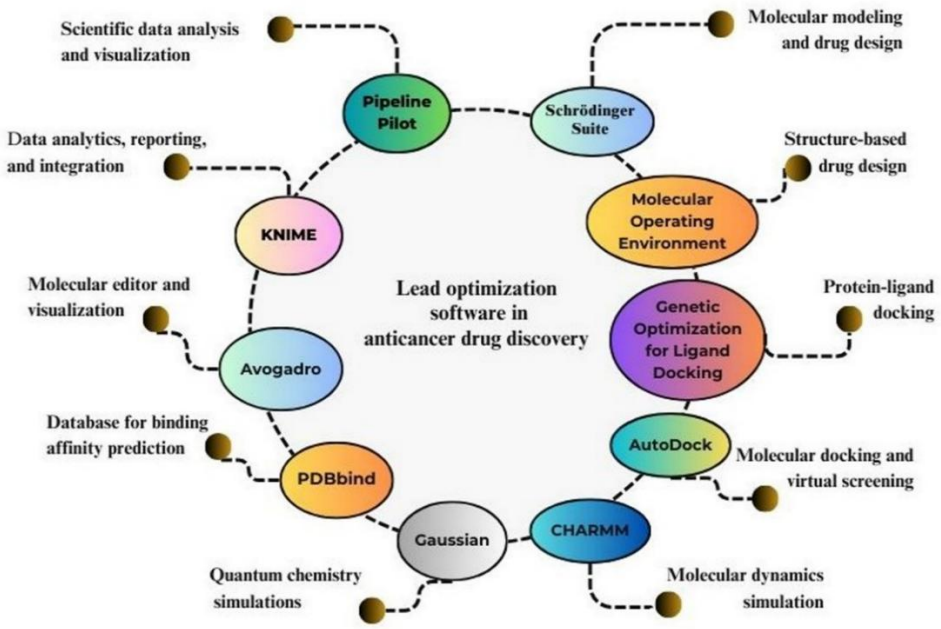

Figure 3: *Overview of lead optimization tools in drug discovery.*

Central to AI-driven molecular design is the adept representation and encoding of molecular structures. Graph-based neural networks, for instance, provide deeper insights into structure-activity relationships, enhancing predictive accuracy (Figure 3) [101]. Quantum mechanics-based models integrate the precision of quantum mechanics with the efficiency of AI to predict molecular energies, geometries, and spectra [102]. AI algorithms, surpassing traditional compound libraries, efficiently explore chemical space, often leading to the discovery of novel regions [103,104]. Latha et al., 2023, utilized Artificial Intelligence (AI) to enhance drug design and development in the pharmaceutical industry, specifically targeting the treatment of breast cancer. Their focus was on generating new inhibitors with high efficacy and minimal side effects compared to Tamoxifen, a commonly used Selective Estrogen Receptor Modulator (SERM) known for its adverse effects like bone pain, nausea, and hot flashes. Using an AI-based Virtual Screening (VS) method with a Generative Neural Network (GNN) model, they identified potential drug-like inhibitors. These inhibitors were evaluated for physicochemical properties, pharmacokinetics, and toxicity to confirm their drug-likeness. Molecular docking studies with DNA and protein were conducted to assess binding affinity and predict intermolecular interactions. The inhibitor M22 (methyl 2-[(2-benzoylphenyl) carbamoyl] benzoate) exhibited a significantly lower free energy of binding and inhibition constant compared to Tamoxifen, indicating higher efficacy. M22's structure, featuring three benzene rings, extended conjugation, and amide linkage, contributes to its potent inhibitory potential [105]. In another study, Molyneaux et al., 2023, investigated therapeutic strategies targeting PTPmu, a receptor protein tyrosine phosphatase involved in cell adhesion and signaling, which is downregulated in glioblastoma. Utilizing the AtomNet® platform, a deep learning neural network for drug discovery, they screened millions of compounds to identify 76 candidates likely to interact with PTPmu's critical extracellular domains. These candidates were tested in cell-based assays for PTPmu-mediated cell aggregation and glioma sphere growth. Four compounds inhibited cell aggregation, six inhibited glioma growth, and two were effective in both assays. The most potent compound inhibited glioma sphere formation at concentrations as low as 25 micromolar and directly interacted with PTPmu fragments. This study highlights a promising compound for further development as a PTPmu-targeting

cancer therapy, particularly for glioblastoma [106]. Further, Goswami and Sharma et al., 2023, explored the potential of deep learning-enabled computational design in identifying ligands targeting Estrogen Receptor Beta (ERβ) for breast cancer treatment. Their study underscores the role of ERβ in antagonizing ERα, thereby inhibiting the expression of growth-promoting genes like cyclin D1, cyclin A, and c-myc in breast tissues. Leveraging advanced technologies such as high-throughput screening (HTS), molecular simulations, and computer-aided drug design, the researchers utilized Biovia Discovery Studio and PyRx software for drug analysis. Using computerized pharmacophore modeling, they synthesized approximately 40 drug ligands. Through docking studies and deep learning algorithms in PyRx, they assessed ligand-protein interactions and binding affinities. The research demonstrated that deep learning algorithms, unlike traditional scoring functions, can predict complex associations, enhancing binding affinity predictions. Subsequent SwissADME, bio radar, Lipinski's rule, and Protox analyses confirmed the drug-likeness and efficacy of the synthesized ligands [107]. The integration of Deep Learning (DL) into small molecule design, renowned for its achievements in speech and image recognition, has addressed limitations in traditional techniques [108,109]. Notably, the Chemistry42 platform developed by in-silico Medicine stands as a prime example of DL's application in driving drug discovery. This platform seamlessly combines advanced generative AI algorithms with expertise in medicinal and computational chemistry, following industry best practices [110]. Chemistry42 enables the user-friendly creation of generative experiments tailored to ligand or structure-based drug design workflows. Leveraging a suite of proprietary generative models such as autoencoders, Generative Adversarial Networks (GANs), flow-based approaches, evolutionary algorithms, and language models, Chemistry42 operates across diverse molecular representations, encompassing string-based, graph-based, and 3D-based structures. Moreover, the platform dynamically evaluates generated structures using reward and scoring modules, integrating multiple scores and in-house Medicinal Chemistry Filters (MCFs) to ensure the quality and relevance of the candidates. Synthetic accessibility is assessed through the Retrosynthesis Related Synthetic Accessibility (ReRSA) score, while structural diversity is monitored using a custom similarity function, thereby facilitating comprehensive and efficient small molecule design processes [111].

Moreover, Chemistry42 integrates modules such as ConfGen for conformational ensembles, 3D-Descriptors for evaluating 3D similarity, Pharmacophore for assessing matches with specified hypotheses, and Shape Similarity for evaluating 3D-shape similarity. The platform's effectiveness is highlighted by the success of the GENTRL model in generating experimentally validated potent DDR1 kinase inhibitors [112,113]. Beyond small molecules, AI has also impacted protein structure prediction. AlphaFold2 generated 3D protein structures have been utilized in a Structure-Based Drug Design (SBDD) case study, demonstrating successful design and optimization of Cyclin-Dependent Kinase 20 (CDK20) inhibitors [114].

6. Optimizing Lead Compounds: Predicting Bioavailability and Toxicity

In the realm of optimizing lead compounds, the utilization of chemical and pharmacological resources has become indispensable for efficient drug discovery. Only a small fraction of the vast array of medicinal chemistry-accessible compounds has been synthesized and tested, necessitating the reliance on major databases such as ChEMBL and PubChem [115]. These repositories house chemical data on small molecules and experimentally determined bioactivities, including information on absorption, distribution, metabolism, excretion, and toxicity [116]. For a comprehensive understanding of molecular structures, the Protein Data

Bank (PDB) serves as a vital resource, providing a repository of 3D structures of proteins and small molecules [117]. The wealth of data contained in ChEMBL, PubChem, and PDB supports researchers in elucidating the role of mutations in diseases and informs structure-based drug design (Figure 2) [118]. Generative AI models play a pivotal role in creating novel compounds by learning from extensive datasets. Leveraging techniques like variational autoencoders and generative adversarial networks, these models seamlessly integrate into existing molecular design pipelines [119]. Through AI-driven simulations and algorithms, structure-based design can be employed to craft molecules with enhanced properties, augmenting the creative process in drug discovery [120]. In a study, Kurniawan et al., 2023, investigated the potential of indenopyrazole derivatives as anti-cancer drugs using advanced computational methods. The study involved 93 indenopyrazole derivative compounds, each with 1876 descriptors. To identify the most relevant features, the Pearson Correlation Coefficient (PCC) was initially used to reduce the descriptors, followed by the Ant Colony Optimization (ACO) algorithm, which narrowed them down to ten key descriptors. An Artificial Neural Network (ANN) prediction model was then developed with three different architectures varying in the number of hidden layers. The model with three hidden layers demonstrated the best performance, achieving R^2 values of 0.8822 for the test set, 0.8495 for the training set, and a Q^2 train value of 0.8472. This study highlights the efficacy of combining ACO and ANN for predicting the anti-cancer potential of indenopyrazole derivatives, paving the way for more targeted and efficient drug development [121]. Czub et al., 2023, developed an AI-based system to improve the prediction of drug permeability, which is crucial for the absorption of oral medications. Focusing on APIs with serotonergic activity, the study addressed the complexities and data limitations of predicting intestinal absorption. By combining classification and regression models, the researchers created a hierarchical system that accurately identifies highly permeable molecules. The system achieved high prediction accuracy, correctly selecting 38% of highly permeable molecules without any false positives [122].

AI models extend their utility to predicting molecular interactions, elucidating binding mechanisms, and unravelling complex molecular processes. This predictive capability empowers researchers to design molecules with tailored properties, accelerating the understanding of intricate structure-property relationships [123]. The development of interpretable AI models, feature importance analysis, and model visualization tools becomes imperative to foster trust and facilitate seamless integration into molecular optimization workflows.

As AI-driven molecular optimization progresses, considerations about safety, unintended consequences, and long-term effects become paramount. Striking a balance between innovation and responsible stewardship is crucial to ensure ethical and sustainable progress in this field [124]. AI-powered innovation has not only contributed to the discovery of new materials with enhanced properties but has also optimized catalyst structures, showcasing its versatility across domains (Figure 3). AI-guided synthesis planning and property prediction have the potential to design molecules with desirable properties, reducing experimental waste and expediting the development of eco-friendly materials and drugs [125].

Quantitative Structure-Activity Relationship (QSAR) modelling, employing machine learning algorithms, emerges as a valuable tool to predict various properties, guiding researchers toward the most promising compounds early in the optimization process [126]. This transformative impact of AI algorithms in drug discovery and material design is underscored by their ability to make informed decisions, leveraging diverse data sources, including experimental data, molecular simulations, and chemical databases. Such an interdisciplinary approach enriches the quality of predictions and facilitates a comprehensive exploration of

molecular optimization strategies [127]. Hou et al., 2018, have identified Matrix metalloproteinase-9 (MMP-9) as a promising target for cancer therapy. Their study involved constructing and validating a 3D QSAR pharmacophore model for MMP-9 inhibitors. This model includes four essential chemical features: two hydrogen bond acceptors (HBA), one hydrophobic (HY), and one ring aromatic (RA). The model's reliability was thoroughly validated, highlighting the significance of HY and RA features for their influence on the interaction with the S1′ pocket of MMP-9, which is crucial for inhibitor selectivity. By integrating the pharmacophore model with molecular docking, the researchers conducted virtual screening to identify selective MMP-9 inhibitors from natural products. This approach led to the discovery of four potential selective MMP-9 inhibitors. Bioassay experiments with one of these inhibitors demonstrated strong inhibitory activity, with an IC50 value of 26.94 μM. Further validation using quantum mechanics/molecular mechanics (QM/MM) calculations and molecular dynamics simulations confirmed the predicted binding modes. Additionally, an assessment of ADMET properties for the four natural product inhibitors indicated their promise as candidates for future structural modifications and optimizations [128,129]. ADMET, which stands for Absorption, Distribution, Metabolism, Excretion, and Toxicity, plays a pivotal role in the early phases of anticancer drug discovery [130]. As an integral component of drug development, the study of ADMET properties encompasses an array of critical evaluations, each bearing profound implications for the success and safety of potential anticancer agents [131].The assessment of a drug's absorption properties delves into how efficiently it can enter the bloodstream, which is essential for achieving therapeutic concentrations at the target site [132]. The distribution stage investigates the drug's journey throughout the body, including its ability to access tumor sites. Understanding the drug's metabolism is crucial as it can influence both its efficacy and potential for adverse effects. Excretion studies shed light on the removal of the drug and its metabolites from the body, impacting drug duration and dosage [133]. Perhaps most crucially, toxicity assessments unveil the potential adverse effects a compound might induce, an aspect that necessitates careful scrutiny to ensure the well-being of patients. Collectively, an in-depth exploration of ADMET properties significantly enhances the efficiency and safety of the drug discovery process, thereby offering promise for the development of effective and well-tolerated anticancer therapies [134].

In the realm of predicting toxicity, AI-based approaches such as LimTox, pkCSM, admetSAR, and Toxtree are instrumental. As well, SEA, eToxPred, TargeTox, and PrOCTOR are employed for safety target prediction. The Tox_(R) CNN model evaluates the cytotoxicity of drugs exposed to DAPI-stained cells. These tools contribute to the prediction of potential toxic effects, enhancing the safety assessment of drug molecules during the optimization process [75].

7. Repurposing Existing Drugs

Drug repurposing, a strategic approach to identify new therapeutic purposes for approved drugs beyond their original use, presents significant advantages, particularly in expediting the discovery process [135]. Advanced translational bioinformatics technologies, such as artificial intelligence (AI) and technology-based approaches, offer promising avenues for enhanced cancer management through the discovery and efficacious use of repurposed drugs [136]. Machine learning algorithms, categorized into supervised, unsupervised, and reinforcement learning techniques, play a crucial role in predicting trends and correlations from user-generated data. These algorithms eliminate the need for explicit programming, providing a versatile tool for various applications, including drug repurposing [137].

AI-based algorithms excel in predicting and generating molecular surface contact fingerprinting, shedding light on repurposed drug-protein interactions. Furthermore, these models contribute to patient-centric drug repurposing strategies [58]. Network medicine, integrating systems biology and disease gene networks, emerges as a potent computational tool for identifying and ranking drug candidates suitable for repurposing in cancer therapy [138].

In recent years, computational approaches, including machine learning and artificial intelligence algorithms, along with deep learning models, have been developed to systematize the drug repurposing process. Noteworthy examples include Axitinib, an endothelial growth factor receptor inhibitor initially approved for renal cell carcinoma, demonstrating unexpected activity in chronic myeloid leukaemia and acute lymphoblastic leukaemia cells. However, challenges arise when additional compound mutations emerge, affecting Axitinib's potency in BCR-ABL1 [139]. Rao et al., 2023, addressed the high failure rate in drug discovery by developing a computational framework to repurpose existing drugs. This framework combines AI/machine learning and chemical similarity-based methods with cross-species transcriptomics to predict drug–target interactions. Analyzing 2766 FDA-approved drugs, the study identified 27,371 off-target interactions involving 2013 protein targets, averaging around 10 interactions per drug. Notably, 63% of these predicted interactions were confirmed in vitro, with many showing strong binding affinities. This approach highlights the potential for repurposing existing drugs for new therapeutic applications, offering a promising strategy to enhance the efficiency and success rate of drug discovery [140].

Publicly available drug-target activity resources play a pivotal role in training supervised machine learning models for *in-silico* off-target predictions and drug repurposing. These resources, categorized by the type of activity data they contain, contribute to the computational exploration of drug repurposing possibilities [141]. Pathways, elucidating cellular responses to drugs, prove valuable in drug repurposing efforts. Various databases representing biological pathways may yield diverse results in statistical target pathway enrichment analysis, emphasizing the need for careful consideration in these analyses [142]. To expedite the identification of drug-target interactions (DTIs), computational approaches, such as orthogonal drug-target space deconvolution, crowd-sourcing-based AI and ML methods, and pairwise multi-kernel learning, have been developed. Methods like convolutional network models, deep neural network models, and multi-label learning frameworks enhance the prediction of DTIs, offering novel leads for drug repurposing [118,143].

Molecular docking, a widely used *in-silico* method, meets challenges when target protein 3D structures are unresolved. AI emerges as an accurate approach for predicting protein 3D structures from amino-acid sequences [144].

After predicting the target activity potential of a drug, its efficacy in a relevant cell context must be investigated. Cancer cell line models and patient-derived primary cells serve as valuable tools for predictive purposes [145]. Various prediction algorithms have been developed to match cancer cell omics features to cell-based drug efficacies. Noteworthy methods such as similarity-regularized matrix factorization (SRMF) and pairwise multi-kernel learning (pairwiseMKL) exhibit superior performance in drug response prediction across diverse cancer cell lines [146]. Despite progress, challenges persist in accurately predicting drug efficacy, particularly in identifying predictive multi-omics features and determining tissue-specific drug efficacy. Addressing these challenges requires a meticulous understanding of patient response data, experimental noise, and the intricate dynamics of

cancer patients. The pursuit of accurate tissue-specific drug efficacy predictions remains an ongoing area of refinement in drug repurposing efforts [147,148].

8. AI in Cancer Imaging

Artificial intelligence (AI) has emerged as a transformative force in optimizing and streamlining clinical workflows, significantly impacting cancer imaging. Within this realm, AI plays a pivotal role in the detection, characterization, and monitoring of tumours. Detection tools based on AI reduce observational oversights, acting as an initial screen against errors of omission [149].

Lung cancer, a global leading cause of cancer-related mortality, faces challenges in late-stage diagnosis. Current screening methods exhibit limitations, including false positives and over diagnosis [150]. AI holds promise in addressing these challenges by reducing false positives, accurately distinguishing between benign and cancerous nodules, and enhancing the prediction of lung cancer risk. Moreover, AI in medical imaging aids in quantifying intra-tumor characteristics, such as intratumor heterogeneity, providing real-time 3D phenotypes of entire tumors [151,152]. In the context of lung cancer imaging, Artificial Intelligence (AI) algorithms have emerged as pivotal tools, tasked with a diverse array of responsibilities ranging from enhancing screening programs to detecting, characterizing, and predicting therapy response and prognosis [149].

A cornerstone of this approach is radiomics, which leverages sophisticated AI algorithms to extract and analyze extensive quantitative metrics from medical images, thereby furnishing clinicians with invaluable insights for clinical decision-making [153]. At the heart of radiomics lies machine learning (ML), which employs models and algorithms within a theoretical framework to automate pattern detection in data, catalyzing advancements in lung cancer diagnostics [154].

Recent studies, as highlighted by Cellina et al., 2022, underscore the effectiveness of AI models in predicting long-term lung cancer incidence and improving diagnosis accuracy, surpassing traditional risk models. Particularly, computer-aided detection (CAD) systems, a significant AI contribution to lung cancer screening, depend on training with high-quality datasets to achieve optimal performance. Deep learning-based tools for pulmonary nodule detection, exemplified by 3D convolutional neural networks (CNNs), demonstrate promising sensitivity and specificity, offering enhanced capabilities for early detection and characterization of lung nodules [155–157].

AI's application extends beyond lung cancer to breast cancer imaging. AI-assisted breast imaging diagnosis relies on computer-aided detection/diagnosis (CADe/CADx) systems, integrating mathematics, statistics, and image processing [158]. Challenges include high false-positive rates and the need for manual annotation, which impacts repeatability [159]. Mammography, ultrasound, and breast MRI are key modalities in breast cancer detection. AI models, including convolutional neural networks (CNNs) like VGG16, demonstrate high accuracy in detecting breast cancer in mammograms [160].

AI's impact on breast cancer extends to ultrasound, overcoming operator-dependent limitations. Elastography improves ultrasound accuracy, and AI recognizes the challenges of subjective bias [161]. Breast MRI, the most sensitive imaging method, benefits from DL technology integration into the clinical workflow. Nuclear medicine techniques, like 18F-FDG

PET/CT, play roles in diagnosis, staging, and treatment response assessment [162,163]. Radio genomics, correlating medical imaging features with gene expression pathways, offers insights into the molecular basis of lesions [164].

Despite the advancements, challenges persist, including FP rates, the interpretability of AI decisions, liability concerns, and limited data on cost-effectiveness. Future developments may involve AI algorithms predicting patient outcomes and guiding diagnostic decisions based on prior cases. As AI continues to evolve, integrating it with established systems like PACS is likely to have a substantial impact on reinforcing its role in radiological diagnosis and patient outcome prediction [165,166].

9. ML Approaches Biomarker Discovery

Machine learning (ML) approaches play a crucial role in biomarker discovery, aiming to enhance clinical trial performance, drug differentiation, and understanding drug mechanisms [167]. However, the conventional process of biomarker discovery in the later stages of clinical trials is both time-consuming and costly [168]. To address this challenge, it is imperative to implement, construct, and validate predictive models during the early stages of clinical trials. ML algorithms can be effectively utilized to predict translational biomarkers in preclinical data, enabling validation and proposing medications for patient indications [169].

MicroRNAs (miRNAs) are small, non-coding RNA molecules consisting of 21-25 nucleotides that play a crucial role in post-transcriptional gene regulation, influencing several signaling pathways, including Notch, Wnt/beta-catenin, PI3K-Akt, and the epithelial-mesenchymal transition (EMT) pathway [170]. The EMT pathway is linked to various malignant behaviours such as proliferation, invasion, and metastasis, with miRNAs playing a crucial role in controlling the EMT phenotype. Understanding the relationship between EMT-associated miRNAs and cancer chemoresistance is essential for both basic and clinical research, particularly in cervical cancer (CC), where miRNAs have been associated with chemoresistance. Utilizing miRNA-based treatments could be a potential method to overcome chemoresistance. One notable advantage of miRNAs is their stability in body fluids like blood, urine, and tissue, making them effective biomarkers for human cancers. However, translating miRNA-based biomarkers from the laboratory to practical applications remains a challenge, despite their potential as biomarkers for pre-cancer diagnosis in humans [171].

Non-coding RNAs, particularly long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), serve as master regulators in the regulation of tumorigenesis. Among them, lncRNA NEAT1 has gained significant attention due to its dysregulation in various cancers, where it can function as either an oncogene or a tumor suppressor. Evidence indicates that NEAT1 is involved in several carcinogenic processes, including proliferation, invasion, survival, drug resistance, and metastasis. As such, NEAT1 is considered a biomarker and a novel therapeutic target for the diagnosis and prognosis of different cancer types. The critical role of NEAT1 in cancer is primarily mediated through its interactions with miRNAs. These NEAT1-miRNA regulatory networks are pivotal in tumorigenesis and have garnered considerable interest from researchers worldwide [172].

Hamidi et al., 2021, addressed the challenge of classifying high-dimensional and small-sample gene expression data, particularly focusing on miRNAs, which are small non-coding RNAs that play significant roles in gene regulation and cancer. The study utilized LASSO and Elastic Net feature selection techniques to identify 10 miRNAs differentially regulated in ovarian

serum cancer samples compared to non-cancer samples from the publicly available dataset GSE106817. The identified miRNAs include hsa-miR-5100, hsa-miR-6800-5p, hsa-miR-1233-5p, hsa-miR-4532, hsa-miR-4783-3p, hsa-miR-4787-3p, hsa-miR-1228-5p, hsa-miR-1290, hsa-miR-3184-5p, and hsa-miR-320b. The researchers then implemented advanced machine learning classifiers, such as logistic regression, random forest, artificial neural network, XGBoost, and decision trees, to construct clinical prediction models. The diagnostic performance of these models was evaluated using ROC analysis on both the internal dataset (GSE106817) and an external validation dataset (GSE113486). Remarkably, the first four prediction models consistently achieved an AUC of 100%, demonstrating their high diagnostic accuracy [173].

In preclinical stages, predictive models and biomarkers are identified, yet only a limited number are translated into clinical trials. One of the primary challenges lies in the assessment of ML approaches that often focus on community efforts to develop regression and classification models. For instance, the US FDA-led MAQC II project evaluated ML algorithms in predicting gene expression data during the final stages of clinical trials [174]. Cox regression models have been employed to predict patient risk factors based on gene expression signatures in diseases like multiple myeloma [175].

Various initiatives, such as the NCI challenge, aim to construct drug predictive models using diverse data profiles and regression models, highlighting the role of ML in advancing drug development and discovery [136]. RNA sequencing for single-cell innovation has become pivotal in advanced biomarker discoveries and gene clustering [176]. Probabilistic generative structures and variational autoencoders have been introduced to reduce high-dimensional gene expression data, aiding in the identification of subpopulations within hidden tumors [177]. Despite the success of ML approaches in biomarker discovery, there are persistent challenges. These include the need for interpretable classifiers for clinical adoption and the validation of multi-institutional, multi-site datasets to ensure generalizability.

IntelliGenes represents a pioneering Machine Learning (ML) pipeline designed to integrate multi-genomics, clinical, and demographic data for the precise prediction of complex traits. Central to this innovative approach is the introduction of the Intelligent Gene Score (I-Gene Score), a novel metric crafted to evaluate the significance of individual biomarkers in disease prediction scenarios. Calculated through the application of Shapley Additive exPlanations (SHAP) and Herfindahl-Hirschman Indexes (HHI), the I-Gene Score leverages the direction of gene expression within the context of a disease, thereby providing valuable insights into the contribution of specific genes to the overall predictive model. Notably, this pipeline boasts user-friendly attributes, offering portability and cross-platform compatibility. Accessible through repositories such as GitHub and Code Ocean, IntelliGenes ensures broad accessibility and usability across diverse research environments [178]. To leverage its capabilities optimally, users are advised to utilize Python versions 3.6 to 3.11. Furthermore, machine learning methodologies have elucidated the genetic variances underlying traits such as height and body mass index, leveraging data from Single Nucleotide Polymorphism (SNP) arrays. Additionally, the application of multi-omic profiling has facilitated the measurement of clinical remission, marking a significant advancement in disease monitoring and management strategies [179].

10. AI in Clinical Trial Optimization

Artificial intelligence (AI) is positioned to transform pharmaceutical development, impacting the entire drug discovery process and clinical research landscape. Utilizing advanced data analysis techniques, AI systems effectively navigate different repositories, including electronic health records, molecular databases, academic literature, and clinical trial data, to identify critical trends, correlations, and potential therapeutic targets [180]. AI-driven insights enable tailored clinical trial designs and precise patient selection criteria, thereby enhancing trial success rates and advancing personalized medicine [181]. Moreover, AI facilitates continuous post-marketing surveillance by meticulously monitoring real-world data for adverse events or drug interactions, ensuring the ongoing safety of licensed medications [182]. In the field of clinical trials, AI emerges as a catalyst for accelerating medical breakthroughs by revolutionizing data collection, bio-simulation, and disease diagnosis. By automating data generation, management, and interpretation throughout the trial lifecycle, AI enhances the efficiency of drug development research, patient recruitment, safety monitoring, and drug discovery endeavors [183]. Although struggling with challenges such as unstructured data from manual approaches and associated high costs, AI integration into clinical trials promises substantial enhancements in trial design, patient recruitment, and protocol development, ultimately bolstering success rates and improving patient outcomes [180].

The transformative impact of AI extends beyond conventional boundaries, development personalized medicine, enabling more efficacious therapies, realizing cost efficiencies, and augmenting overall efficiency in medical research and patient care [184]. By leveraging AI-driven solutions, hospitals and Contract Research Organizations (CROs) streamline data management, automate data collection, monitor data quality, and analyze vast datasets, thereby expediting and refining the clinical trial process. The utilization of personalized AI technology empowers precision in patient recruitment, enrollment, monitoring, and adherence, leading to a paradigm shift towards optimized healthcare delivery [185]. In a recent study, Panchal et al., 2023, proposed an AI and blockchain-enabled secure data exchange framework for the Medical Internet of Things (IoT). This framework utilizes machine learning classifiers to distinguish between normal and attack data, with K-Nearest Neighbor achieving the highest accuracy. The data is securely stored in an IPFS-based blockchain network, ensuring transparency and privacy [186]. Furthermore, AI-based cybersecurity solutions for medical IoT devices have been shown to enhance data security and protection against cyber threats. By incorporating AI and machine learning, these solutions can improve anomaly detection, threat intelligence, compliance, encryption, and data protection in medical IoT environments [187].

In traditional clinical trials, challenges related to patient cohort selection and recruitment pose significant obstacles. However, AI-driven approaches offer promising solutions to address these issues. By leveraging AI algorithms, eligibility criteria can be effectively informed, patient diversity can be enhanced, sample sizes can be reduced, and patient matching and recruitment processes can be improved [188]. Tools like Trial Pathfinder utilize electronic health record (EHR) data to simulate various inclusion criteria, thereby enhancing the efficiency of patient selection and increasing overall survival rates [189].

Moreover, AI-based clinical trial matching systems, powered by natural language processing tools and machine learning algorithms, can streamline the patient screening process by extracting crucial information from patient real-world data (RWD) and trial protocols [68].

These AI-driven systems have demonstrated high accuracy and efficiency in identifying suitable candidates for specific trials, particularly in the field of cancer research [190].
Despite the promising potential of AI in transforming clinical trials, several challenges must be addressed to ensure successful integration into the clinical trial ecosystem. One critical aspect is the necessity of high-quality data to build robust AI models. This requires standardized construction of biomedical databases and the inclusion of diverse data sources such as clinical records, medical images, omics data, wearables, and social media data [191].

11. Future Implementation and Impact of AI in Anticancer Drug Discovery

11.1. Clinical translation

The AI-CDSS (Artificial Intelligence Clinical Decision Support System) is a powerful tool designed to assist healthcare professionals in making informed, evidence-based decisions in patient care. By leveraging artificial intelligence algorithms and data analysis techniques, the AI-CDSS provides personalized recommendations and insights [192]. It offers a range of features and benefits, including patient data analysis, diagnostic and treatment recommendations, drug interaction and adverse event detection, predictive analytics, real-time monitoring and alerts, and continuous learning and improvement. The system's applications are vast, spanning areas such as cancer diagnosis and treatment, chronic disease management, medication optimization, surgical decision support, infectious disease outbreak management, radiology and medical imaging analysis, mental health support, and clinical trials and research [193]. Chebanov et al., 2023, developed an advanced algorithm integrated into a software platform to design novel anti-tumor drugs, specifically targeting lung cancer. Utilizing deep learning (DL) techniques, the team assessed genes associated with poor clinical outcomes in lung cancer patients. By employing generative adversarial networks (GAN), they expanded their patient data pool. The results were systematically organized, highlighting genes with a significant impact on prognosis, identified through intersections with overall survival (OS) and progression-free interval (PFI) data. To refine their findings, another DL model distinguished between normal and tumor tissues, pinpointing targetable genes. A subsequent module predicted interactions between inhibitors and proteins, leveraging vector representations of protein sequences and chemical compounds for virtual screening in the PubChem database. This screening produced a dataset of 118,379 drug-protein interaction pairs, which were further analyzed using DL, achieving a ROC-AUC of 0.86. They identified 160,000 pairs with an interaction probability above 0.99 and 2,921 pairs with a probability of 1.0. Ultimately, five small molecules were identified as potential candidates for further validation. This study underscores AI-driven methods in automating drug discovery, validated through rigorous cross-validation using public data sources [194]. Geaney et al., 2023, have highlighted the transformative impact of digital pathology (DP) and artificial intelligence (AI) in oncology research and cancer diagnostics. By digitizing pathology images and applying machine learning (ML) techniques such as Deep Learning Convolutional Neural Networks and Multiple Instance Learning, the study has enhanced morphological interpretation, biomarker quantitation, and the introduction of novel diagnostic concepts like spatial cellular distribution. These advancements have led to improved detection and grading of tumors, precise biomarker quantification, and better treatment prediction and prognostic purposes, thereby revolutionizing clinical trials. However, the integration of DP/AI into clinical practice brings new regulatory and design challenges for manufacturers, emphasizing the need for updated accreditation processes for diagnostic tools [195]. In a research study,

Tran et al., 2023, utilized artificial intelligence (AI) to enhance drug repurposing and target identification for cancer treatment. Through an AI-driven screening strategy, the team identified N-(1-propyl-1H-1,3-benzodiazol-2-yl)-3-(pyrrolidine-1-sulfonyl) benzamide (Z29077885) as a promising new anticancer drug. This compound was initially discovered using deep learning methods and was subsequently validated through various in vitro and in vivo experiments. Z29077885 demonstrated significant anticancer efficacy by inhibiting Serine/threonine kinase 33 (STK33) and inducing apoptosis via S-phase cell cycle arrest in lung (A549) and breast (MDA-MB 231) cancer cells. The compound's anti-tumour efficacy was further confirmed in an A549 xenograft model in BALB/c nude mice [196].

11.2. Patient-centric approach

The implementation of a patient-centric approach in AI diagnostics is vital to uphold transparency and empower patients in making informed healthcare decisions. Ploug and Holm, 2020, discuss this approach through the lens of "effective contestability," which ensures patients have the necessary information to understand and challenge AI-driven diagnoses. This concept encompasses four essential dimensions: the data dimension, the bias dimension, the performance dimension, and the division of labor dimension. The data dimension focuses on providing patients with clear insights into how their data is used by the AI system, ensuring they are aware of the sources and types of data involved. The bias dimension addresses potential biases in AI algorithms, requiring transparency about the training data and any inherent biases that could affect diagnostic outcomes. The performance dimension emphasizes the need for patients to understand the accuracy, limitations, and reliability of AI systems, allowing them to critically assess the diagnostic recommendations provided. Lastly, the division of labor dimension clarifies the respective roles of AI systems and healthcare professionals in the diagnostic process, ensuring patients know who is responsible for different aspects of their care. By adhering to these dimensions, the framework aligns with ethical and legal standards, promoting an explainable AI that respects patient autonomy and fosters trust in AI-driven medical interventions [197].

11.3. Interdisciplinary collaboration

Interdisciplinary collaboration between computational scientists, biologists, clinicians, and data analysts is essential to advance the development and validation of AI models in healthcare. Computational scientists bring expertise in algorithm development and data processing, which is crucial for creating sophisticated AI models [198]. Biologists provide deep insights into biological processes and molecular mechanisms, ensuring that the models are biologically relevant and accurate. Clinicians contribute their understanding of patient care and clinical workflows, helping to tailor AI applications to real-world medical settings. Data analysts play a key role in managing and interpreting large datasets, ensuring the integrity and usability of the data used to train and validate AI models [199].

Artificial Intelligence (AI) language models, leveraging natural language processing and pretrained algorithms, excel in tasks such as text generation and comprehension. In Fetal Medicine, these models can support healthcare professionals by providing detailed and precise information, enhancing decision-making, and improving communication between doctors and patients. However, integrating AI language models in this field presents challenges, including ethical issues, privacy concerns, and potential algorithmic biases. Ensuring transparency and interpretability of AI systems is crucial for building trust. Rigorous validation studies are necessary to assess their performance [200]. Lee et al., 2023,

conducted a study on the use of an AI-powered PD-L1 CPS analyzer to evaluate PD-L1 expression, a predictive marker for immune checkpoint inhibitor (ICI) treatment, across six cancer types: biliary tract, colorectum, liver, pancreas, prostate, and gastric cancers. The AI tool, Lunit SCOPE PD-L1 CPS, was developed using over 1.51 million tumor cells and 873,000 immune cells from 2,372 PD-L1 stained whole-slide images (WSI) and tissue microarray cores. This algorithm employed tissue area segmentation and cell detection models to calculate the combined positive score (CPS), which correlates with immunotherapeutic responses. Validation was performed on 135 PD-L1 stained WSIs reviewed by three pathologists. Discrepancies between the pathologists and the AI model led to re-evaluations, resulting in increased unanimous agreement to 92.6% and an improved OPA of 91.9%, with a range from 82.6% (liver) to 100.0% (pancreas) [201].

11.4. Long-term sustainability

There has been significant research on the advantages, disadvantages, and future perspectives of AI, highlighting its transformative impact on various societal areas. In healthcare, AI's remarkable potential is evident in pharmaceutical and biomedical studies, which are crucial for the socioeconomic development of the population. AI applications aim to tackle diseases such as cancer and neurodegenerative disorders. The lengthy drug development process can also be expedited with AI, accelerating research and improving medical care [202].

Early-stage drug discovery heavily relies on evaluating drug targets, understanding disease progression, and identifying patient characteristics, all while exploring chemical libraries of potential drug candidates. Artificial intelligence (AI) has become a credible approach to managing the diversity and volume of data in modern drug development. Many pharmaceutical sponsors prefer to keep their data within closed solutions due to intellectual property concerns. However, newer platforms offer outsourced solutions that combine sponsor data with external open-source data to make predictions using proprietary algorithms [203]. Digital research environments (DREs) provide mechanisms to ingest, curate, integrate, and manage diverse data types relevant to drug discovery. They also offer workspace services for target sharing and collaboration, allowing sponsors to control the platform, data, and predictive algorithms. Regulatory engagement will be crucial for operationalizing these solutions, as current regulations may not adequately address the quality and usability of drug discovery data in the future. More sophisticated AI/ML algorithms are expected, leveraging diverse data types such as imaging and genomic data. This supports the need for a dynamic, DRE-enabled environment to enhance drug discovery [204]. A major challenge in TCR-T therapy is accurately predicting the pairing between TCRs and peptide-human leukocyte antigens (pHLAs). Modern computational immunology, leveraging AI-based platforms, addresses this challenge by optimizing TCR screening and discovery. Bujak et al., 2023, proposed an observational clinical trial to collect patient samples and generate a database of pHLA:TCR sequences to support AI-driven TCR selection. The multicenter study enrolled 100 patients with stage II-IV colorectal cancer. Primary tumor tissue and peripheral blood samples were collected, with peripheral blood mononuclear cells isolated and cryopreserved. Nucleic acid extraction was completed in 86 cases, and 57 samples underwent whole exome and RNA sequencing [205].

12. Comparing AI with Traditional Drug Discovery Methods

Artificial Intelligence (AI) is revolutionizing pharmaceutical research. Traditional drug discovery is often lengthy and costly, with many drugs failing to gain regulatory approval

due to their unsuitability. Virtual screening (VS) offers a new method to streamline the research and development process by reducing the initial effort needed to identify potential drug components. Deep Learning (DL) algorithms are crucial in VS, as they can detect patterns within existing datasets [206]. In drug discovery, DL algorithms analyze patterns of chemical compounds related to diseases. AI's capabilities are expanding, with platforms like DeepChem enabling the creation of AI models to identify potential drug components for various diseases. This research paper explores Tyrosine-protein kinase in cancer, using the VS process to identify potential drug components. The results show that the AI-enabled VS method can predict potential drugs with 85% accuracy on a small cancer dataset [207].

Recent advancements in AI-driven technologies, particularly in protein structure prediction, are significantly reshaping the landscape of drug discovery and development. By enhancing the precision and speed of drug target identification and the design and optimization of drug candidates, these technologies streamline the entire drug development process (Table 2). AlphaFold2, for example, has been instrumental in cancer drug development, offering insights into its efficacy, limitations, and potential challenges. Comparing AlphaFold2 with other algorithms like ESMFold reveals diverse methodologies in this field and their practical implications for specific applications. Traditionally, the three-dimensional structures of proteins were deciphered using labor-intensive and costly experimental methods such as X-ray crystallography, nuclear magnetic resonance (NMR), and cryogenic electron microscopy (cryo-EM). While invaluable, these techniques are limited by speed, cost, and applicability to certain protein structures [208]. In contrast, AI advancements in protein structure prediction, exemplified by AlphaFold2, have dramatically expanded our capabilities, complementing and occasionally surpassing experimental approaches. Following AlphaFold2's success, other AI tools like RoseTTAfold, ESMFold, and OpenFold, as well as novel protein design tools like ProGen, ProteinMPNN, EvoDiff, and RFdiffusion, have emerged. Additionally, DiffDock enhances molecular docking capabilities. These rapidly developing tools employ novel algorithms and AI architectures, each with unique strengths and weaknesses, further revolutionizing drug discovery [209].

In a recent development, AlphaMissense, a computational tool created by Google DeepMind, has been shown to accurately assess the pathogenic potential of missense variants. Utilizing structural insights from AlphaFold, AlphaMissense evaluates the effects of mutations on protein functionality. This tool holds significant promise in cancer drug discovery by aiding researchers in efficiently selecting genetic mutations for in-depth study, expediting the identification of novel drug targets. AlphaMissense also has the potential to enhance our understanding of less-explored segments of the genetic code, particularly genes crucial to human health whose functions are not yet fully understood [210].

Docking, a computational strategy used to predict the formation of stable complexes between two molecules, is typically divided into ligand docking and protein-protein docking. AI significantly enhances the speed and precision of this process. Deep Docking (DD), an AI-enabled method for virtual screening of ultra-large chemical libraries, accelerates structure-based virtual screening. DD iteratively docks subsets of a chemical library, synchronizing with ligand-based predictions to improve virtual hit enrichment without significantly losing potential drug candidates [211]. AI revolutionizes drug discovery by enhancing the speed and precision of identifying and optimizing drug candidates, often surpassing traditional methods. Understanding the strengths and limitations of both AI and traditional approaches is essential for developing effective and safe treatments.

Table 2: *Comparative Analysis of Tools and Techniques in Traditional and Modern Anticancer Drug Discovery Approaches.*

Category	Traditional Approaches	Modern Approaches	References
High-Throughput Screening	Natural product screening	Target-based screening, High-content screening, Virtual screening	[212]
Cell-Based Assays	Simple cell lines, primary cultures	3D cell cultures, patient-derived models	[213]
Animal Models	Mouse xenograft models, syngeneic models	Genetically engineered mice, Patient-derived xenografts (PDX)	[214]
Molecular Biology	Limited genetic insights	Genomic sequencing, Next-generation sequencing (NGS), CRISPR-Cas9	[215]
Bioinformatics & Computational Tools	Basic data analysis, manual processing	Advanced bioinformatics, Machine learning, Molecular modeling	[216]

13. Ethical Considerations and Validation of AI Models in Anticancer Drug Discovery

13.1. Ethical considerations

The potential for highly personalized oncology care using artificial intelligence (AI) has been anticipated since AI's inception. Advances in machine learning and deep learning algorithms, coupled with the growth of comprehensive multiomics databases and the reduced cost of computational power, are bringing this promise closer to reality [217]. AI's successful clinical applications span the cancer continuum, particularly in multidisciplinary practices. Notable examples include computer vision-assisted image analysis with several FDA-approved applications, whole blood multicancer detection through deep sequencing, virtual biopsies, natural language processing to derive health trajectories from medical notes, and advanced clinical decision support systems integrating genomics and clinical data [218].

However, broad adoption of AI in oncology faces significant challenges. Issues such as data transparency and the interpretability of AI's "black box" mechanisms hinder trust, while biases against underrepresented populations limit the reproducibility of AI models and exacerbate healthcare disparities. In the midterm, AI's evolution is expected to involve increasingly complex models using multimodal data to better simulate biological systems. Looking further ahead, the concept of "living databases" that continuously integrate all aspects of a person's health into comprehensive data sets could drive sophisticated modeling for highly tailored treatments, dose determinations, and surveillance strategies [219].

The integration of AI in anticancer drug discovery presents significant ethical considerations that must be addressed to ensure responsible development and deployment. Ethical concerns primarily revolve around data privacy, bias, transparency, and the validation of AI models [220]. Firstly, ensuring the privacy and security of patient data used to train AI models is paramount. Given the sensitive nature of health data, robust measures must be implemented to protect against unauthorized access and breaches, safeguarding patient confidentiality [221]. Bias in AI models is another critical issue. AI systems trained on unrepresentative datasets may perpetuate existing biases, leading to unequal healthcare outcomes. It is essential to use diverse and comprehensive datasets to train AI models, thus ensuring equitable treatment across different patient demographics. This approach helps in mitigating health disparities and promoting fairness in AI-driven healthcare solutions [222]. Transparency in AI decision-making processes is crucial for building trust among healthcare providers and

patients. AI models must be designed to provide clear and understandable explanations for their predictions and recommendations. This transparency allows clinicians to make informed decisions and fosters confidence in AI-assisted diagnostics and treatments [223].

In their 2023 study, Durur-Subasi and Özçelik highlight the transformative impact of artificial intelligence (AI) in breast imaging, driven by the global rise in breast cancer cases. Utilizing deep learning techniques, AI promises to refine diagnostic processes significantly, though its adoption varies globally. AI's capability to handle extensive datasets and process multidimensional information is pivotal for advancing precision medicine in breast cancer research. However, its integration faces several challenges, including data-related obstacles and the need for transparency and trust in decision-making [224]. Remote monitoring technologies are digital health tools that use patient reporting and wearable sensors to track health data such as vital signs, physical activity, sleep patterns, PROs and PRD. Depending on the system, humans or human-assisted AI algorithms analyze these data, promising to provide personalized insights and early detection of health issues such as poor tolerance of oral chemotherapy. These are more automated than virtual consultations, but they often require clinical expertise, such as from oncology nurse navigators, to interpret results and guide patients [225,226].

A cancer diagnosis carries significant social stigma, making the preservation of human dignity paramount. Despite its sophistication, AI lacks the empathy, compassion, and cultural understanding that human caregivers provide. Overreliance on AI could lead to impersonal care and reduced human interaction, potentially eroding patient dignity and weakening therapeutic relationships. As AI advances towards greater algorithmic autonomy, the risk to human dignity increases. To mitigate these threats, it is crucial to involve humans in AI interpretation and maintain human contact points. Avoiding humanoid interfaces can also help remind patients that AI is not human, thereby helping to preserve their dignity [227].

Artificial Intelligence (AI) has become a prevalent force in diverse medical domains, including image diagnostics, pathological categorization, treatment plan selection, and prognosis analysis. The collaboration between human and computer interactions has notably matured in the context of image-assisted cancer diagnosis. However, the ethical considerations associated with the incorporation of AI into clinical decision-making processes remain inadequately addressed. Consequently, the AI-driven Clinical Decision-making System has not fully embraced interactions between humans and computers [228].

The validation of AI models is a crucial step to ensure their efficacy and safety in clinical settings. AI models must be rigorously tested using diverse datasets to confirm their generalizability across various populations. The validation process should include clinical trials conforming to established reporting standards, such as the Consolidated Standards of Reporting Trials–Artificial Intelligence (CONSORT-AI) and the Standard Protocol Items: Recommendations for Interventional Trials–Artificial Intelligence (SPIRIT-AI). Providing detailed performance metrics, such as the area under the receiver-operating characteristic curve (AUC-ROC) and false-positive/false-negative rates, is essential for transparency. These metrics should be clearly communicated to clinicians and end-users to ensure that the AI models are applied correctly and effectively [229]. Huwaimel and Alobaida 2022, explored the use of supercritical CO2 (SC-CO2) as an alternative to traditional solvents in the pharmaceutical industry, focusing on predicting and validating drug solubility with AI. They evaluated tamoxifen solubility in SC-CO2 using machine learning (ML) techniques, employing Adaboost-enhanced models: K-nearest Neighbor (KNN), Theil-Sen Regression (TSR), and Gaussian Process (GPR). The study analyzed pressure and temperature as inputs

to predict solubility, with ADA-KNN, ADA-GPR, and ADA-TSR showing R^2 values of 0.996, 0.967, and 0.883, respectively. ADA-KNN was the best model, achieving optimal solubility predictions. This research demonstrates AI's potential to enhance drug development by improving solubility predictions and optimizing pharmaceutical processes [230].

13.2. Challenges and Considerations in AI-Driven Drug Discovery

Machine learning (ML) models have demonstrated success in predicting drug combinations, but challenges persist with higher-order combinations. Striking a balance between toxicity and effectiveness necessitates careful examination, requiring the evaluation of patient data to assess the predictions accurately [231]. Deep learning (DL) techniques show promise in detecting drug responses; however, the development of more advanced algorithms is imperative to enhance their efficacy. The implementation of explainable artificial intelligence (XAI) techniques is crucial to interpret black-box models and ensure fairness in model outcomes [232].

The advancement of AI research in oncology demands access to high-quality, large datasets. Collaborative efforts across multiple institutions are essential to acquire diverse datasets, including data from large-scale clinical trials. Researchers should collectively work toward creating comprehensive datasets to drive impactful AI research [233].

The effectiveness of AI research is contingent on the quality of input imaging data, prompting efforts to develop scoring and assessment methods for image quality. Once AI solutions show promise in addressing oncological challenges, validation in real clinical settings becomes imperative to establish their clinical utility [234].

Legal and ethical considerations pose potential barriers to the research and implementation of AI in oncological imaging. Establishing clear legal and ethical frameworks, involving input from all stakeholders, is essential to navigate these challenges effectively [235].

Translating AI research results into clinical practice requires extensive collaboration among researchers, radiologists, surgeons, radiation oncologists, oncologists, and other healthcare practitioners [236]. Seamless integration of AI technology into existing clinical picture archiving and communication systems (PACS) and clinical workflows is crucial for successful implementation and adoption in oncological imaging. The interdisciplinary collaboration ensures a holistic approach to enhancing patient care through the synergistic application of AI technologies in the field of oncology [237].

14. Conclusion and Future Prospects

This review underscores the significant role of Artificial Intelligence (AI) in revolutionizing anticancer drug discovery, offering a glimpse into a future where drug development is both precise and efficient. AI's capability to process vast datasets has markedly accelerated the identification of therapeutic targets and the design of novel drug molecules, paving the way for personalized cancer treatments. Despite these advancements, the path forward is not without challenges. Key among these are ensuring the quality and diversity of data, improving the interpretability of AI models, and effectively integrating AI insights into clinical practice to yield tangible patient benefits.

Moving forward, it is imperative that collaborative efforts between computational scientists, biologists, and clinical practitioners intensify to address these challenges. Such collaborations

will be crucial in refining AI algorithms and ensuring that the insights derived from AI models are clinically relevant and lead to improved patient outcomes. Additionally, the field must embrace advancements in explainable AI to enhance transparency and trust in AI-driven decisions.

In conclusion, while AI has already begun to transform the landscape of anticancer drug discovery, its full potential is yet to be realized. The continued evolution of AI technologies, coupled with robust interdisciplinary collaborations, promises to further break down the barriers in drug discovery and lead to the development of more effective anticancer therapies. As we navigate this evolving landscape, vigilance, collaboration, and innovation will be essential to harness the full potential of AI in the fight against cancer.

Acknowledgement

The authors are highly obliged for the kind and needful support of DBT funded Bioinformatics Centre, and DST-FIST program under Banasthali Vidyapith, for providing the necessary facility to conduct this study.

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