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Harnessing Computational Drug Design for Innovative Breast Cancer Therapeutics

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ABSTRACT

Computational drug design has transformed pharmaceutical research by streamlining the discovery and development of innovative chemotherapy agents. In the context of breast cancer (BC), advanced computational techniques—such as molecular docking, virtual screening, and pharmacophore modeling—have significantly contributed to the identification of promising drug candidates. Both structure-based and ligand-based drug design strategies have enabled precise targeting of oncogenic proteins, including estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), BRCA1/BRCA2, and vascular endothelial growth factor (VEGF). The integration of artificial intelligence (AI) and machine learning (ML) has further enhanced predictive modeling, improving drug efficacy, optimizing lead compound selection, and reducing development timelines. AI-driven approaches, particularly deep learning and neural networks, have improved the prediction of binding affinities, selectivity, and potential off-target effects in ligand-based drug design. These methodologies have accelerated the discovery of novel therapeutic agents by efficiently analyzing extensive datasets and virtual screening outcomes. Numerous in silico-identified compounds with strong binding affinities have progressed to clinical evaluation. This review provides a comprehensive overview of computational strategies in BC drug discovery, highlighting key methodologies, emerging molecular targets, the impact of AI in drug design, and the translational challenges involved. By harnessing these computational tools, researchers can enhance precision, reduce costs, and accelerate the development of targeted therapies for breast cancer.

Keywords: *Computational drug design, breast cancer, molecular docking, pharmacophore modeling, virtual screening, machine learning, targeted therapy*

1. INTRODUCTION

A biggest reason for cancer-related death for females globally is still BC. Despite advancements in therapeutic strategies, the heterogeneity of BC and the emergence of drug resistance continue to pose significant challenges [1]. BC is classified into different molecular subtypes, including hormone receptor-positive (HR+), human epidermal growth factor receptor 2-positive (HER2+), and triple-negative breast cancer (TNBC), each exhibiting distinct biological characteristics and treatment responses [2]. Traditional drug discovery methods, reliant on extensive *in vitro* and *in vivo* experimentation, are often time-consuming, labor-intensive, and expensive. In response, computational drug design has emerged as a transformative approach, enabling the rapid identification and optimization of novel therapeutic agents, thereby expediting the drug development pipeline and increasing the likelihood of success in clinical trials [3]. Computational methodologies, particularly *in silico* approaches, play a pivotal role in accelerating the drug discovery process. Structure-based drug design (SBDD) and ligand-based drug design (LBDD) have been widely employed to target key oncogenic proteins such as estrogen receptor (ER), HER2, BRCA1/BRCA2, vascular endothelial growth factor (VEGF), and cyclin-dependent kinases (CDKs), all of which play crucial roles in BC pathogenesis [4,5]. Molecular docking, molecular dynamics (MD) simulations, quantum mechanics/molecular mechanics (QM/MM) hybrid modeling, and pharmacophore modeling provide valuable insights into

protein-ligand interactions, enabling the rational design of novel therapeutic agents with enhanced specificity and efficacy [6]. Furthermore, virtual screening techniques, including structure-based virtual screening (SBVS) and ligand-based virtual screening (LBVS), allow for the rapid assessment of chemical libraries, prioritizing promising candidates for further experimental validation [7]. The advent of AI and ML has revolutionized computational drug discovery by refining predictive models and improving the accuracy of drug-target interaction predictions. AI-driven techniques, such as deep learning-based QSAR modeling, generative adversarial networks (GANs), and reinforcement learning, enable the identification of novel lead compounds with optimal pharmacokinetic and pharmacodynamic properties [8]. These approaches facilitate the de novo design of small molecules with improved selectivity and bioavailability, addressing key challenges associated with drug resistance and toxicity [9]. AI-powered molecular docking algorithms, such as AutoDock Vina and Glide, further enhance the precision of binding affinity predictions, accelerating hit-to-lead optimization in BC drug discovery [10].

Beyond their efficiency, computational approaches provide an avenue for high-throughput screening of vast compound libraries, significantly reducing the time and costs associated with traditional experimental methods. The integration of cheminformatics, bioinformatics, and big data analytics has enabled researchers to predict the binding affinity, selectivity, toxicity, and off-target effects of potential drug candidates before their synthesis, improving the overall efficiency of the drug discovery pipeline [11]. Additionally, the incorporation of multi-omics data, including genomics, transcriptomics, proteomics, and metabolomics, has facilitated the identification of novel biomarkers and druggable targets, paving the way for personalized medicine in BC treatment [12]. Recent advancements in molecular simulations and AI-driven computational pipelines have also contributed to drug repurposing efforts, identifying clinically approved drugs that may be effective against BC subtypes. Drug repurposing strategies, coupled with network pharmacology and systems biology approaches, have led to the discovery of novel indications for existing drugs, accelerating their clinical translation [13]. Moreover, the application of quantum computing in molecular modeling holds great promise in overcoming current limitations in computational accuracy, offering unprecedented opportunities for precision drug design [14].

As computational methodologies continue to evolve, their integration with experimental validation strategies will be crucial in ensuring the successful translation of *in silico* predictions into clinically viable therapies. The synergy between computational and experimental approaches is expected to drive future innovations in BC treatment, ultimately improving patient outcomes and advancing the field of precision oncology [15]. This review explores the application of computational methodologies in BC drug discovery, emphasizing their role in identifying effective inhibitors and therapeutic targets. By integrating computational strategies, researchers can streamline drug development, reduce costs, and enhance the efficacy of targeted therapies for BC treatment.

Computational Approaches in Drug Discovery:

Computational methods have revolutionized pharmaceutical discovery, fundamentally changing how drugs are developed by offering essential tools throughout the entire process. These approaches significantly reduce costs and enhance the efficiency of identifying and manufacturing new medicines. Key computational techniques include docking, virtual high-throughput screening, and predicting protein structures. These methods facilitate the rapid assessment of large compound libraries and the identification of potential binding agents through advanced modeling, simulation, and visualization approaches [16]. Diverse approaches in computational drug discovery, including molecular docking, de novo design, pharmacophore modeling and mapping, sequence-driven virtual screening, and molecular similarity assessments, have been substantially enhanced over the past decades. As a result, the identification and formulation of potential drug candidates have achieved greater accuracy and efficiency. The incorporation of computational methodologies into drug design and discovery has become a fundamental aspect of this progress, allowing researchers to save considerable time and resources [17]. Moreover, various computational approaches, including the NMR structure-activity relationship, represent advanced adaptations of traditional techniques, demonstrating how technology can enhance and refine the drug development cycle [18]. As previously stated, advancements emphasize the crucial role of computational methods in modern pharmaceutical research, marking a significant shift in the framework of medications development and investigation.

Computational approaches have evolved into essential complements to traditional experimental methods in cancer drug discovery, significantly enhancing efficiency while reducing the costs involved in developing new treatments [16]. The rapid advancement of computational methods in drug discovery, especially those focused on anticancer treatments, has profoundly impacted the development of such drugs. These approaches have generated valuable insights into cancer therapy, opening new avenues for identifying and investigating novel pharmaceutical contenders [19].

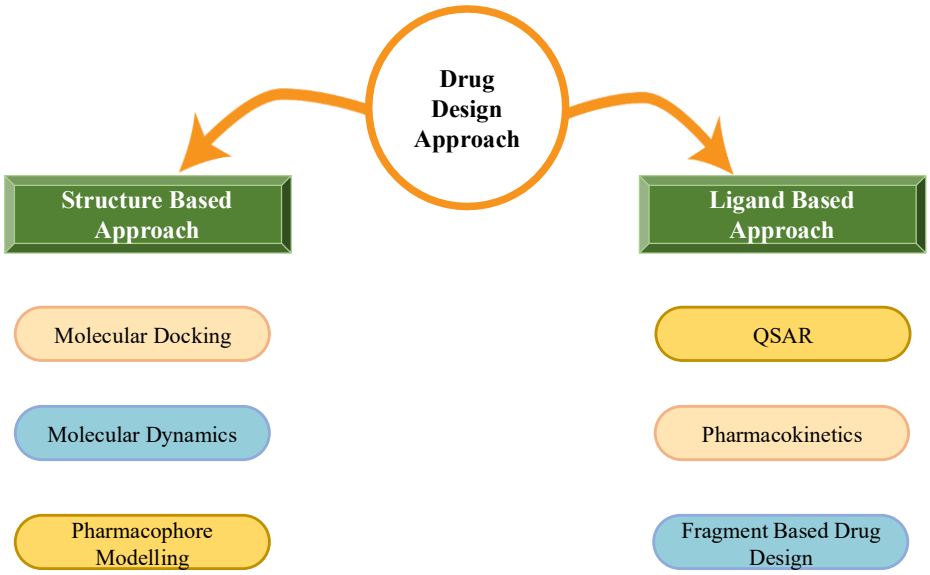

Figure 1. Approaches for CADD in Anticancer Therapy

The past couple of decades have seen significant advances in computational methods carried out using *in silico* methodologies, particularly in the simulation of biological pathways intended to identify novel targets linked to illnesses. Machine learning and deep learning techniques have been essential to these advancements, helping to identify hitherto unknown drug-phenotype and interactions between drugs and their targets [20]. The application of computer-based methods in the creation of potential anticancer drugs has led to substantial progress in cancer therapy over time [21]. The advancement of omics data over the past ten years has facilitated computational forecasting of anti-cancer treatments, thereby improving the effectiveness of pharmaceutical research. For example, integrating large-scale transcriptomic datasets with drug response information has been widely applied in the identification of biomarkers and the prediction of therapeutic agents [22].

In the past several years, algorithmic search for drugs has advanced significantly. Researchers may now represent molecular frameworks, ascertain three-dimensional frameworks, improve and build new chemical compounds, and study atomic-level interactions in medicines and naturally occurring chemicals thanks to CADD. The efficiency of therapeutic development has been significantly increased by the advent of sophisticated approaches, which have resulted in the recognition of numerous products for clinical evaluation, some of which the FDA are authorised (see Tables 1 & 2). Many methods for preventing tumour growth are currently accessible in the realm of chemotherapy drugs, and they may broadly separate as 02 main tactics: structure-based along with ligand-based design of medications [23].

Table 1. Antineoplastic agents identified through CADD currently in clinical evaluation.

Treatment	Healing domain	Target	Phase	Reference
Resveratrol	Mammary, dermal, pulmonary, and colorectal carcinoma	EGFR, VEGFR or FGFR inhibitor	I	[24]
DZD9008	Non–small cell lung cancer (NSCLC).	EGFR tyrosine kinase inhibitor	II	[25]

Epigallocatechin Gallate	Mammary carcinoma, pulmonary neuroendocrine carcinoma, and various solid neoplasms.	Bcl-2 inhibitors	I	[26]
AZD5991	Several marrow-derived malignancies together with acute leukemia.	Mcl-1 inhibitor	Suspended	[27]
TAK− 659	Persistent lymphocytic leukemia, systemic T-cell lymphoma, sudden myeloid leukemia, and widespread large B-cell lymphoma.	SYK inhibitor	I	[28]
Quercetin	Bowel malignancy, mammary carcinoma, pulmonary neoplasm, liver carcinoma, hematologic malignancy, and plasma cell neoplasm.	Wnt/β-catenin inhibitor	I	[29]
SHR-3162	Ovarian carcinoma.	PARP inhibitor	I	[30]

Table 2. Cancer-fighting substances identified through CADD and authorized by the FDA.

Drug	**FDA Approval Year**	**Target**	**Healing domain**	**References**
Erlotinib	2004	EGFR kinase inhibitors	NSCLC, Pancreatic carcinoma.	[31]
Crizotinib	2011	HGFR, ALK and cMET inhibitor	Lung carcinoma, esophageal malignancy, and lymphoma.	[32]
Imatinib	2003	Tyrosine kinase inhibitors	Persistent myeloid leukemia.	[33]
Axitinib	2012	VEGFR inhibitor	Kidney cancer.	[34]
Abiraterone	2011	Inhibitor of androgen synthesis	Castration-resistant metastatic prostate	[35]

			cancer.	
gefitinib	2015	EGFR inhibitor	Progressed or advanced metastatic NSCLC.	[36]
Lapatinib	2007	ERBB2)/ EGFR inhibitor	Mammary carcinoma.	[37]

Structure-based drug design (SBDD):

SBDD necessitates the analysis of the three-dimensional structure of biological molecules. Spectroscopic methods such as NMR and X-ray crystallography have greatly improved the understanding of the structure of therapeutic targets, leading to significant progress in this field. This approach leverages structural knowledge of the target to predict whether a new chemical compound will bind strongly to the site where it alters protein function, producing a therapeutic outcome. The target serves as a template to simulate interactions with various small compounds from a compound library, and the optimal match is selected. These methods are used to increase the impact of previously identified ligands with little chemical change by utilising molecular evidence regarding ligand-receptor relationships [38]. Structure-based pharmacophore modelling, molecular docking and dynamics are employed to investigate interaction pathways, target adaptability, and ligand attachment to target proteins.

Molecular docking:

It is a computational technique employed to study the interactions between a ligand and a target. The procedure entails utilizing docking algorithms to place small molecules into the active site of the target, aiming to identify the optimal conformations and orientations. These algorithms examine the conformational space for potential docking arrangements and apply a scoring function to estimate the ligand's binding affinity in each configuration [39]. This allows for the recognition of lead compounds that exhibit strong binding affinities and specificity for a target protein or other biomolecular structures essential in cancer biology. This facilitates the acceleration of the anticancer drug development process by minimizing the number of compounds requiring synthesis and testing *in vitro* and *in vivo*. Various computational software tools exist for molecular docking studies in anticancer drug discovery. Glide is a widely used molecular docking algorithm in drug discovery [40]. It employs specialized domain expertise to narrow the search area and offers additional precision, standard precision, and high throughput virtual screening options. These approaches enhance the accuracy of ligand binding predictions to target proteins, facilitating the identification of therapeutic candidates. Another widely used drug discovery docking tool, GOLD, forecasts ligand binding mechanisms and affinity for target proteins. It utilizes a genetic algorithm and incorporates advanced capabilities such as a graphical interface, scoring functions, protein flexibility, solvation effects, and metal-containing active sites [41]. Morris and colleagues created the molecular docking software AutoDock in 2009. It performs global optimization using a Lamarckian genetic algorithm and local optimization through a local search method. AutoDock is distinguished by its capability to model protein-ligand interactions accurately, particularly in handling flexible ligands and receptor positions. For virtual screening of small molecule databases, tools such as Fred, LeDOCK and AutoDock Vina are also employed [42]. These computational software techniques can identify new lead compounds that exhibit strong binding affinities and specificity for cancer-associated target proteins, thereby expediting drug discovery and contributing to the development of novel and effective cancer treatments. Every program has its advantages and disadvantages; thus, the selection depends on the research goals and available resources [43].

Molecular dynamics (MD):

MD simulation enables the evaluation of drug-target interactions at the atomic level. It assists in exploring drug resistance, prediction, and discovery by analyzing structural changes caused by genetic mutations. MD simulation employs a comprehensive model of interatomic forces to forecast the movement of each atom in a protein or other molecular structures over time with femtosecond precision. It allows the study of conformational shifts, ligand binding, and protein folding. Notably, MD simulations can predict how biomolecules respond at the atomic scale to mutations, phosphorylation, protonation, and the addition or removal of ligands. To enhance precision, X-ray crystallography and NMR techniques are commonly integrated with MD simulations [44]. NAMD, AMBER and GROMACS, are widely recognized software packages for molecular dynamics simulations. More recently, DESMOND has emerged as a vital tool for examining molecular dynamics and interactions. Its simulation capabilities are particularly valuable for studying interactions such as protein-ligand, protein-protein, and protein-DNA. This knowledge aids in the design of novel drugs and the enhancement of existing pharmaceuticals in terms of specificity, efficacy, and safety. DESMOND uses integrator algorithms to solve the system dynamics equations, with the Verlet and velocity Verlet methods being the most commonly employed to model large and complex systems. Atom interactions in DESMOND are modeled using force fields, which calculate the potential energy

between atoms based on their positions. DESMOND supports several force fields, including AMBER, GROMACS and CHARMM. Its intuitive interface, outstanding performance, flexibility, compatibility with other software, robustness, and incorporation of cutting-edge computational chemistry and molecular dynamics techniques make it superior to other tools. A notable success in using MD simulations for anticancer drug development is the creation of imatinib (Gleevec), a treatment for chronic myeloid leukemia [45]. The interactions between Imatinib and BCR-ABL were examined through MD simulations, revealing the crucial structural and dynamic features of the binding site. This insight was applied to design imatinib derivatives with enhanced binding affinity and specificity for BCR-ABL, leading to the development of an effective and targeted treatment for CML [46]. The creation of vemurafenib, a medication utilized for melanoma treatment, represents yet another example of utilizing MD simulations. This substance forms consistent hydrogen bonds with the protein and engages with essential amino acids in the binding region [47].

Structure-based pharmacophore (SBP) modelling:

SBP modeling is a crucial method utilized to improve the effectiveness of existing anticancer therapies and discover new treatments. By integrating the three-dimensional structure of a protein and the chemical properties of its interacting ligands, this method creates pharmacophore models. These models offer valuable insights into the essential molecular traits necessary for binding, which can be applied to refine drug development and enhance binding effectiveness. The importance of SBP is growing as a key tool in drug discovery and development. It facilitates large-scale structural chemogenomics studies to identify novel ligands for specific proteins or new targets for particular ligands. SBPs are less dependent on known ligand chemotypes, enabling the identification of innovative scaffolds. In addition to supporting the formation of hypotheses regarding protein-ligand binding within the structural framework of the protein, SBPs are also useful for optimizing ligands based on their structure. Furthermore, SBPs help pinpoint ligand-binding sites, which can be used to design ligands for orphan receptors or explore similarities in ligand-binding sites across proteins for cross-pharmacology and the discovery of new therapeutic targets. SBPs have been extensively utilized in lead optimization, virtual screening, de novo drug design, and multi-target drug development [48]. The development of anticancer medications targeting the Bcl-2 protein illustrates the application of structure-based pharmacophore modeling in drug discovery. Bcl-2 plays a vital role in regulating cell death and survival, and its levels are often increased in cancerous cells. Inhibiting Bcl-2 has been recognized as a promising approach for cancer treatment. Through structure-based pharmacophore modeling, novel compounds that bind to Bcl-2 and trigger apoptosis in cancer cells have been developed [49].

Ligand-based drug design (LBDD):

Pharmacophore modeling and QSAR have emerged as significant techniques in drug discovery to address the challenge of insufficient 3D structural data for potential drug targets. These approaches help identify interactions between targets and ligands, facilitating the discovery and optimization of lead compounds through predictive models. In the pharmaceutical sector, ligand-based drug discovery methods are employed to screen new ligands exhibiting promising biological activities and to enhance drug pharmacokinetic properties such as ADMET. These methods leverage the structure of known ligands to predict similar chemical compounds, under the assumption that molecules with comparable structures often produce similar biological effects. They examine the 2D or 3D structures of ligands that bind to the target molecule. The primary aim is to capture the essential physicochemical properties required for successful interactions while eliminating irrelevant data.

Ligand-based pharmacophore modelling:

It represents an alternative approach to computational drug design, pinpointing ligands that interact with a protein while exhibiting comparable structural and physicochemical characteristics. This technique constructs a three-dimensional representation of a ligand's biologically relevant features, including hydrophobic domains, aromatic rings, and hydrogen-bonding sites. The development of a ligand-based pharmacophore involves superimposing multiple active compounds to achieve geometric alignment. In more refined applications, molecular flexibility plays a role in determining the overlapping regions. By precomputing the conformational space of each ligand and generating a generalized model or dynamically adjusting molecular positions based on the alignment algorithm, conformational adaptability can be integrated [50].

Extensive database-driven virtual drug screening employs pharmacophore modeling. The primary ligand-based pharmacophore generation tools include DISCO, GASP, and Catalyst. These software applications utilize molecular alignment, conformational flexibility, and feature extraction techniques. In recent years, ligand-based pharmacophore modeling has gained significant attention in anticancer drug discovery. Employing the Catalyst HypoGen module, Al-Sha'er and Taha [51] developed a pharmacophore model based on 83 Hsp90 inhibitors. This compound engages with various oncogenic proteins, establishing it as a potential target for anticancer therapy [52]. Pharmacophore modeling based on ligand analysis has recognized key characteristics responsible for EGFR inhibition. Altering the chemical frameworks of EGFR inhibitors has uncovered shared pharmacophoric elements, including hydrogen-bond acceptors, hydrogen-bond donors, and hydrophobic domains. These attributes have been utilized to develop a three-dimensional pharmacophore model that encapsulates the crucial molecular features necessary for binding to the EGFR protein and suppressing its function. Consequently, this approach has facilitated the development of novel EGFR inhibitors with enhanced efficacy and specificity.

Ragno [53] employed ligand-oriented pharmacophore modeling to develop hydroxamic acid derivatives capable of inhibiting HDAC. Relative to the original analog, multiple synthesized derivatives demonstrated enhanced selectivity and potency, with notable anticancer efficacy observed both *in vitro* and *in vivo*. Beyond EGFR and HDAC inhibitors, ligand-based pharmacophore modeling has facilitated the identification of potential drug candidates targeting kinases, proteases, and nuclear receptors.

Quantitative structure-activity relationship (QSAR) modelling:

Computational QSAR techniques strive to establish a quantitative correlation between molecular descriptors and biological activity. This approach operates on the premise that structurally analogous compounds exhibit comparable biological effects. QSAR modeling is widely applied in drug discovery, toxicology, environmental science, and materials science. These models are developed through statistical evaluations of the physicochemical and structural attributes of molecules. Additionally, QSAR can predict the activity of new molecular analogs, refine lead compounds, and identify novel structural frameworks in pharmaceutical research. Traditional 2D-QSAR relies on steric, electronic, and hydrophobic properties of pharmaceutical compounds to anticipate biological activity, representing these interactions through mathematical expressions. More sophisticated 3D-QSAR techniques, which incorporate force field calculations, include methods such as comparative molecular field analysis and molecular similarity indices for comparative assessments [54]. Thus, the developed models are represented using 3D contour maps to facilitate visualization and interpretation. Frequently employed computational tools for QSAR modeling include OpenBabel, and Accelrys Discovery Studio, Schrodinger Suite, which are used for generating and modifying the three-dimensional structures of molecules. Additionally, various software applications are utilized for descriptor calculation, machine learning algorithms, and data mining processes. Descriptor calculation software computes the molecular descriptors necessary for QSAR modeling, which characterize the physicochemical and structural properties of molecules. Commonly used software for this purpose includes ChemAxon, PaDEL-Descriptor, and Dragon. Machine learning algorithms are employed to construct predictive models based on QSAR data, with Random Forest, Artificial Neural Networks and Support Vector Machines being the most widely used approaches. Furthermore, large datasets are analyzed using data mining tools to extract relevant insights for QSAR modeling. The most commonly utilized data mining tools include KNIME, Weka and Orange.

Numerous studies have employed QSAR modeling to forecast the anticancer potential of various compounds. Through QSAR modeling, a novel category of phenylpyrimidine compounds was identified as strong c-Met inhibitors [55]. Gupta and colleagues forecasted the inhibitory potential of novel quinazoline analogues against breast carcinomas through the application of QSAR models [56]. This proves that QSAR is an effective computation technique for identifying cancer fighting medications, resulting in the creation of new chemical scaffolds with enhanced medicinal value and fewer adverse effects.

Pharmacokinetic (PK) and pharmacodynamic (PD) modelling:

Simple but insightful compartmental frameworks have been created as a result of new developments in modelling the developmental dynamics of lung tumours. These models are used to describe the PK and PD of antitumor medications in the individual physique. These models go beyond conventional structure-based simulations by taking into account the intricate dynamics of drug ADME in particular organs and tissues (Fig. 2) [57].

Population-based pharmacokinetic/pharmacodynamic (popPK/PD) models are designed to evaluate variability in drug responses among patients receiving clinically relevant doses of a specific medication. These models have proven effective in predicting docetaxel-induced neutropenia in Japanese patients with non-small cell lung cancer. Utilizing a 3-compartment pharmacokinetic model in conjunction with a modified semi-mechanistic myelosuppression model, popPK/PD analyses have identified serum albumin and α1-acid glycoprotein as significant covariates influencing neutropenia development, providing valuable insights for optimizing therapeutic approaches [58]. Furthermore, population pharmacokinetic (popPK) models have effectively described the pharmacokinetic profile of lucitanib, facilitating dose adjustment to maximize clinical efficacy, with no detected influence from demographic factors or tumor classification [59].

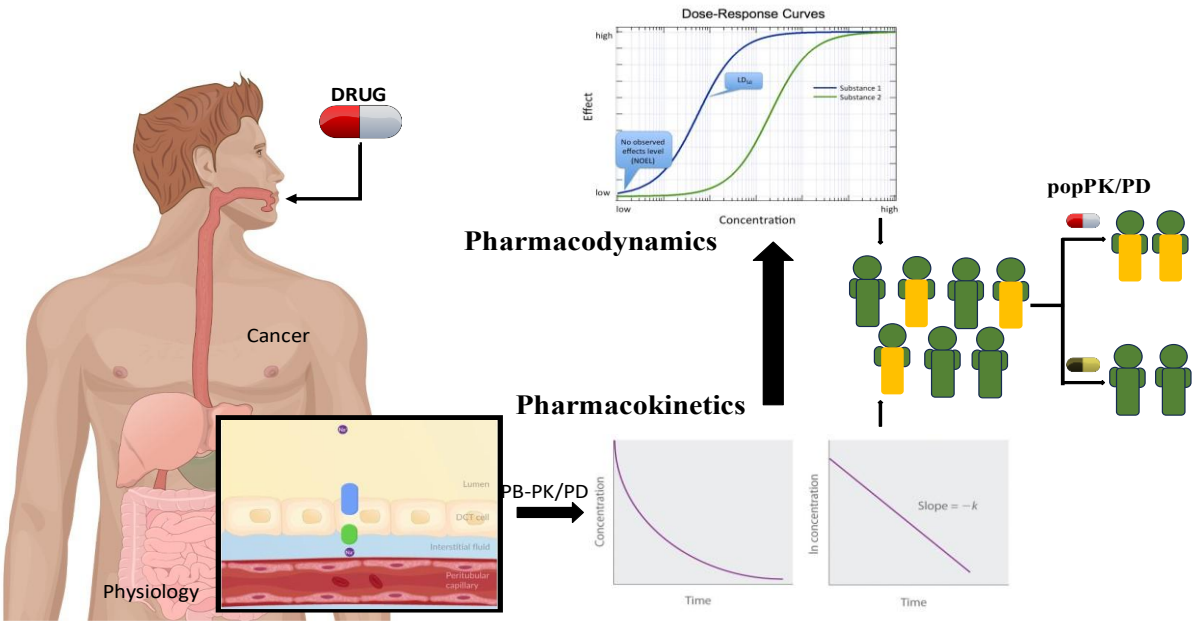

Figure 2. Utilization of pharmacokinetic/pharmacodynamic (PK/PD) modeling in oncology, in which oral drug delivery is defined by biological variables to construct time-concentration and dose-response graphs using mathematical formulations, offering understanding of medication effects (ED50) and dispersion. This methodology can be additionally applied to the patient cohort administered therapeutically significant drug dosages (popPK/PD).

Identification of breast cancer suppressors and therapeutic targets:

BC is a multifaceted condition. Identifying effective therapeutic targets and inhibitors proves challenging due to its intricate nature [60]. The discovery of novel targets and the optimization of drug development have been hindered by several critical obstacles, including the heterogeneity of BC, the absence of appropriate animal models for preclinical research, and a limited understanding of the molecular mechanisms underlying its initiation and progression [61]. Furthermore, numerous genetic variants of BC are present, each characterized by unique biological and clinical attributes [62]. Identifying effective inhibitors and therapeutic targets across all BC subtypes is difficult due to this diversity. Additional challenges arise from resistance to inhibitors and our limited understanding of the molecular mechanisms driving BC onset and progression.

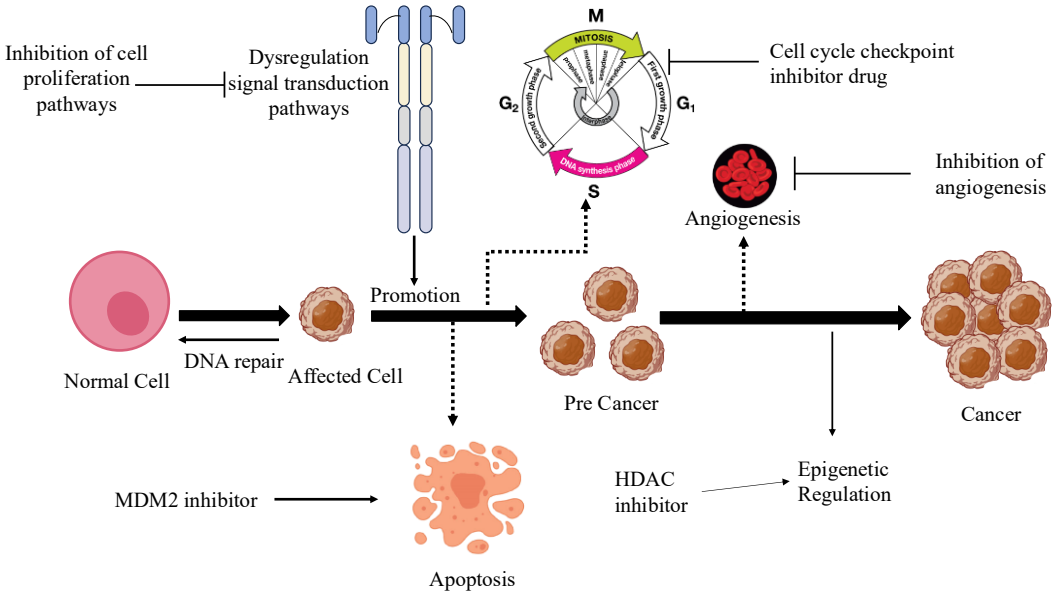

Figure 3. Significant oncology drug targets investigated using CADD.

To restate, identifying effective antagonists and targets for BC treatment at the computational and molecular docking stages is a complex task that requires accurate models and a comprehensive understanding of the disease's molecular mechanisms. Due to the diversity in the origins of cancer proteins, multiple options exist for selecting a target or targets for anti-BC therapy, as nearly all essential proteins have been thoroughly studied. Furthermore, combined approaches have been developed to detect binding sites/active residues and discover BC inhibitors using molecular dynamics, docking, and virtual screening methods. These techniques have also been employed to assess molecular interactions after initial experimental analysis [63].

ER-

Function in BC:

BC is predominantly affected by estrogen throughout both its initial and later phases. It operates by engaging with receptors on BC cells, promoting cell division, survival, and expansion [64]. A complex series of signaling events is triggered when estrogen attaches to its receptors, involving various proteins and enzymes, such as PI3K and AKT [65]. The growth, suppression of programmed cell death, and formation of new blood vessels are induced by the activation of these proteins [66]. Estrogen raises the likelihood of BC by encouraging the formation of DNA adducts and oxidative stress, both of which can harm DNA [67]. Oestrogen eventually causes BC through a complicated process that involves a number of physiological processes and activities [68]. Since it plays a major role in the development and propagation of this illness, focussing on and investigating its processes is still an essential treatment strategy.

Utilising computational modelling to find ER blockers:

A transcription factor called oestrogen receptor regulates the transcription of nuclear genetic DNA, which is in charge of breast development. Using an amalgamation of *in silico* research and the MTT test, it has been demonstrated that newly developed variants of benzophenone and depsidone that were derived from the tree bark of *Garcinia porrecta* exhibit antineoplastic properties in the MCF-7 human BC line. According to this investigation, the benzophenone analogue interacts with the ER more strongly and has inhibitory effects on the MCF-7 cell line [69]. To find new ER inhibitors in 2016, scientists combined molecular docking simulations with simulated screening. After screening more than a million molecules, they found a number of lead compounds with a high affinity for adhering to ER. Compound 2, one of the main molecules, demonstrated strong ER inhibitory action both *in vitro* and *in vivo* [70]. In 2017, a separate team of scientists employed a blend of molecular docking, molecular dynamics simulations, and free energy assessments to discover potential inhibitors of the estrogen receptor (ER). They examined more than 600,000 compounds and identified several promising candidates that exhibited significant activity against ER-positive breast cancer (BC) cells in laboratory settings. One of the primary compounds, referred to as compound 6, demonstrated strong inhibitory effects on ER and also displayed favorable pharmacokinetic characteristics [71].

HER2-

Function in BC:

HER2 plays a role in the development and aggressiveness of BC [72]. HER2 is highly expressed in twenty percent of mammary tumours and is linked to better tumour development, spread, and aversion to therapy [73]. Its function involves the initiation of signaling pathways that promote cell survival, growth, and movement. It is a receptor tyrosine kinase located across the cell membrane. Upon overexpression of HER2, it interacts with other HER family members, such as HER3, EGFR, and HER4, forming various dimer types. This dimer formation triggers the activation of the PI3K/AKT and MAPK/ERK pathways, which enhance cell growth and survival (Fig. 9) [74].

The increased expression of HER2 in BC cells has been demonstrated to activate the NF-κB pathway, which facilitates immune evasion and inflammatory reactions [75]. In individuals with HER2-positive BC, therapies aimed at blocking HER2 activity have produced favorable results.

Utilising computational modelling to find HER2 blockers:

Research carried out by Moradipoodeh and his team in 2019 reveals that Amygdalin, a powerful nitriloside, exhibits anticancer properties and can promote apoptosis in the SK-BR-3 breast cancer cell line. This was confirmed through a computational investigation that included the MTT assay and molecular docking, which led to a decrease in the pro-apoptotic Bax protein and an increase in the expression of the anti-apoptotic Bcl-2 proteins. Significant interactions with the amino acid residues at the active site of HER2 were also noted [76]. Finding a possible plant-based blocker for HER2-positive BC was the goal of a subsequent investigation [77]. The investigators examined a collection of 11,247 natural substances and pinpointed one (ZINC15122021) that demonstrated promising inhibitory effects on HER2. They conducted computational docking analyses to study how the compound interacts with HER2 and determined that ZINC15122021 may hinder HER2 function by binding to the ATP-binding region of the kinase domain. To further explore the top compound, an in vitro assay was carried out using HER2-overexpressing SKBR3 and BT474 cell lines to evaluate ZINC15122021's ability to inhibit cell

growth. The researchers found that ZINC15122021 exhibited a strong affinity for HER2 and showed favorable ADMET properties. Moreover, ZINC15122021 effectively inhibited cell proliferation in both SKBR3 and BT474 cell lines and exhibited notable kinase inhibition against HER2 [77]. The research conducted by Balogun et al. discovered several possible HER2 inhibitors from *Mangifera indica* and assessed their stability in HER2-ligand complexes through molecular dynamics simulations. The study found that the compounds rutin, mangiferin, and epicatechin formed stable HER2-ligand complexes. The molecular dynamics simulations revealed that these complexes, maintained stability throughout the simulation, with a low root-mean-square deviation, suggesting that they stayed close to their initial structure. Additionally, the study indicated that the compounds exhibited strong binding affinity to the HER2 receptor, outperforming the reference drug neratinib in binding free energy calculations. The findings suggested that, with further investigation, rutin, epicatechin and mangiferin, could potentially serve as HER2 inhibitors for treating HER2-positive BC [78].

BRCA-

Function in BC:

To preserve genomic strength, the tumour inhibitor alleles BRCA1 and BRCA2 should effectively restore harm to DNA. A higher risk of carcinomas of the breast and ova has been linked to alterations that affect these genes. Females with BRCA1 or BRCA2 abnormalities are at a greater risk of developing BC [79]. A key function of BRCA in breast cancer involves its role in DNA repair. The BRCA1 and BRCA2 proteins assist in repairing double-strand DNA breaks via the homologous recombination process [80]. As a result of mutations in these genes, DNA repair becomes impaired, leading to the accumulation of DNA damage and genomic instability. BRCA1 and BRCA2 have been found to be involved in several other cellular functions, such as chromatin remodeling, transcription regulation, and cell cycle control [81]. BC may begin and progress as a result of these systems being disrupted by BRCA abnormalities. The lack of DNA repair in BRCA1 and BRCA2 variant BC cells has led to the development of targeted therapies, which involve PARP blockers [82].

Utilising computational modelling to find BRCA blockers:

To find biologically active substances which attack the BRCA receptor, the researchers used virtual screening in an earlier investigation. Important details about the possible drug candidates were provided by the dock score, drug-likeness simulation rating and ADMET description. Since it showed strong action towards both BRCA1 and BRCA2, taxodione was the main chemical in this study [83]. In a separate study, the researchers employed a blend of virtual screening and molecular docking techniques to identify active phytochemicals as inhibitors of BRCA2. They subsequently applied molecular dynamics simulations to assess the binding affinity and stability of the most promising compounds. The optimal drug candidate was determined based on the dock score, ADMET description, and drug-likeness simulation rating [84].

VEGF-

Function in BC:

A vital molecule known as vascular endothelial growth factor (VEGF) controls angiogenesis, the formation of new blood vessels, and lymphangiogenesis, the development of new lymphatic vessels, in various physiological and pathological events, such as cancer [85]. In BC, the activity of hypoxia-inducible factor-1 is elevated, leading to the activation of several pro-angiogenic genes, including VEGF [86]. By encouraging endothelial cell movement, growth, and maturation and raising permeability to blood vessels, VEGF contributes to the development and metastasis of tumours [87]. VEGF impairs the immune system by encouraging the growth of T cells, limiting the development of dendritic cells, and decreasing the activity of natural killer cells [88]. Blocking VEGF signaling has thus been identified as a possible therapeutic strategy for BC. Among the various VEGF inhibitors developed and evaluated in clinical studies, with differing levels of effectiveness, bevacizumab stands out [89].

Utilising computational modelling to find VEGF blockers:

Methods of computational modeling, including virtual screening and molecular simulation, have been employed to identify potential VEGF inhibitors for BC therapy [90]. In this investigation, the investigators employed a blend of virtual screening and molecular docking to pinpoint possible VEGF inhibitors. Subsequently, molecular dynamics simulations were performed to assess the binding strength and stability of the top candidates. The primary compound in the study, a small molecule recognized as 5-(5- (4- (1H- 1,2,3- triazol- 1- yl) phenyl) -1,3,4-oxadiazol -2 -yl) isoxazole, demonstrated significant anti-VEGF efficacy in both *in vitro* and *in vivo* experiments [91]. In another investigation, Jaceidin, a flavonoid derived from *Chiladenus montanus*, was found to exhibit cytotoxic effects in the MCF-7 human breast cancer cell line through *in vitro* analysis. This effect was linked to its interaction with the VEGF receptor, facilitated by binding mechanisms such as hydrogen bonds and both hydrophilic and hydrophobic interactions, as revealed by molecular docking studies [92].

Elmaaty and collaborators [93] conducted both *in silico* and *in vitro* investigations to explore the potential application of benzimidazole anthelmintics (a class of medications frequently used to treat parasitic worm infections) as inhibitors of VEGFR-2 (vascular endothelial growth factor receptor 2) for cancer treatment. A set of 13 benzimidazole anthelmintics was

subjected to molecular docking in order to identify VEGFR-2 inhibitors. Additionally, a 200 ns molecular dynamics simulation was performed to analyze their stability, thermodynamic, and dynamic characteristics. The study particularly focused on mebendazole, a benzimidazole anthelmintic, and developed innovative mebendazole-loaded mixed micelles (a type of drug delivery system) that exhibited improved dissolution and anticancer effects. The researchers tested the impact of the mebendazole-loaded mixed micelles on MCF7 cell lines. The results indicated that mebendazole could potentially be repurposed as an anticancer agent due to its ability to inhibit VEGFR-2, and the developed mixed micelles may offer a promising approach for delivering mebendazole [93].

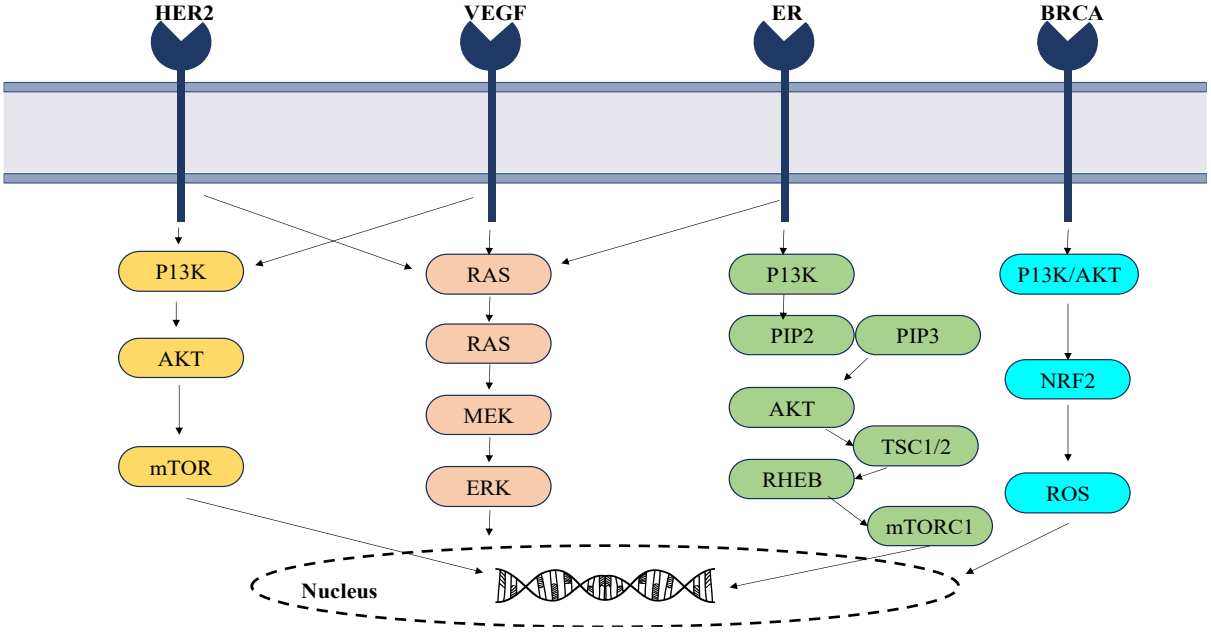

Figure 4. Illustrative depiction of ER, HER2, BRCA and VEGF's roles in activating the PI3K/AKT/mTOR and RAS/RAF/MEK pathways. These are crucial elements in tumor development, playing a role in the initiation, spread, and advancement of cancer cells. As a result, these proteins and their receptor-driven signaling pathways have emerged as central targets in cancer treatment strategies.

Artificial Intelligence in LBDD for BC:

LBDD plays a crucial role in identifying potential drug candidates by leveraging information from known bioactive molecules to design and optimize new compounds. The integration of Artificial Intelligence (AI) into LBDD has revolutionized the drug discovery process by accelerating hit identification, lead optimization, and pharmacokinetic profiling while reducing the time and cost associated with traditional drug development methods [94]. AI-driven methodologies, including machine learning (ML), deep learning (DL), and advanced cheminformatics, have significantly improved the prediction of drug-target interactions, molecular properties, and toxicity profiles, ultimately enhancing the precision and efficacy of novel breast cancer therapeutics [95]. AI-powered approaches have significantly improved the efficiency of ligand-based drug design by utilizing machine learning models for QSAR modeling. Traditional QSAR methods relied on statistical regression techniques to predict the activity of a molecule based on its structure. However, modern machine learning-based QSAR models employ support vector machines (SVM), random forests (RF), k-nearest neighbors (k-NN), and deep neural networks (DNN) to enhance predictive accuracy. These models analyze large datasets of molecular descriptors to establish strong correlations between chemical structures and biological activity [96]. In breast cancer drug discovery, AI-driven QSAR models have successfully identified inhibitors targeting key molecular markers such as estrogen receptor (ER), human epidermal growth factor receptor 2 (HER2), and cyclin-dependent kinases (CDKs). Furthermore, AI-based QSAR models integrate physiochemical, steric, and electronic properties to refine drug-likeness predictions, ensuring optimal bioavailability and minimal toxicity risks [97].

Another major breakthrough in AI-driven ligand-based drug design is the application of deep generative models for de novo drug design [98]. Advanced deep learning architectures, such as variational autoencoders (VAEs), generative adversarial networks (GANs), and reinforcement learning-based molecular generators, enable the automated creation of novel drug-like molecules with desired pharmacological properties. VAEs learn the underlying distribution of known bioactive compounds and generate structurally diverse and pharmacologically relevant molecules, while GANs optimize molecular structures through iterative refinement based on similarity to known active ligands. Reinforcement learning-based molecular design

further optimizes lead compounds by prioritizing binding affinity, solubility, and synthetic accessibility. These AI-driven generative approaches have led to the discovery of HER2 inhibitors with improved selectivity and metabolic stability, demonstrating the potential of AI in the rational design of next-generation breast cancer therapeutics [99]. AI-powered virtual screening has also become a fundamental tool in ligand-based drug design, allowing for the rapid identification of active compounds from extensive chemical libraries. Traditional similarity-based virtual screening methods have been significantly improved through the use of deep learning models, including graph neural networks (GNNs), convolutional neural networks (CNNs), and transformer-based architectures. Graph-based deep learning models, such as Graph Attention Networks (GATs) and Message Passing Neural Networks, represent molecular structures as graphs, where atoms serve as nodes and bonds as edges, extracting high-dimensional molecular features to improve screening accuracy [100]. Transfer learning techniques further enhance virtual screening by leveraging pre-trained deep learning models trained on large compound datasets to predict ligand activity for novel breast cancer targets with limited data availability. Once active hits are identified, AI-driven multi-objective optimization techniques refine ligand properties by improving binding affinity, optimizing ADME (absorption, distribution, metabolism, and excretion) parameters, and minimizing toxicity risks through approaches like Bayesian optimization, genetic algorithms, and Monte Carlo tree search (MCTS) [101].

Molecular docking is another essential component of ligand-based drug design that has benefited from AI advancements. Traditional docking methods, such as GOLD, AutoDock, and Glide rely on scoring functions to predict ligand binding affinity, but they often fail to account for protein flexibility and solvation effects. AI-powered docking approaches incorporate deep learning-based scoring functions, such as DeepDock and DeepBind, which integrate experimental binding assay data to improve docking accuracy. Furthermore, AI-enhanced flexible docking simulations, including AlphaFold-MD and DeepFlex, predict protein conformational changes upon ligand binding, providing a more realistic representation of molecular interactions [102]. AI-driven end-to-end docking frameworks, such as DeepDocking and AtomNet, predict docking poses with higher accuracy by leveraging DL-based energy minimization techniques. For breast cancer drug discovery, these AI-enhanced docking strategies have been instrumental in identifying high-affinity ligands for HER2 tyrosine kinase inhibitors and estrogen receptor antagonists, facilitating the development of targeted therapies [103].

Pharmacophore modeling, a key step in LBDD, has also been enhanced by AI-powered feature selection techniques. Pharmacophore models identify essential molecular features required for ligand binding, such as hydrogen bond donors, acceptors, and hydrophobic regions. AI-based pharmacophore generation tools employ deep reinforcement learning, natural language processing (NLP) models, and unsupervised clustering techniques to extract pharmacophoric elements from known active compounds. For instance, AI-assisted pharmacophore models have successfully predicted novel selective estrogen receptor modulators (SERMs) by identifying critical binding motifs necessary for estrogen receptor interaction. Additionally, AI-driven feature selection techniques, such as SHAP (SHapley Additive exPlanations) and LIME (Local Interpretable Model-agnostic Explanations), enhance the interpretability of AI models by highlighting the most influential molecular descriptors in ligand activity predictions [102].

The integration of AI with multi-omics data has further strengthened ligand-based drug design by aligning drug discovery with precision medicine approaches. Breast cancer is a highly heterogeneous disease, characterized by distinct genetic and molecular alterations. AI-driven drug design benefits from the integration of multi-omics datasets, including genomics, proteomics, and metabolomics, to identify novel drug targets and predict personalized therapeutic responses. AI models, such as multi-omics deep learning networks and graph-based transcriptomics predictors, analyze complex biological datasets to uncover patient-specific drug targets, leading to the development of precision therapies tailored to breast cancer subtypes. By leveraging AI for multi-omics data integration, researchers can identify biomarkers for drug resistance, predict patient response to therapy, and design drugs with improved efficacy and safety profiles. Despite its tremendous potential, AI-driven ligand-based drug design faces several challenges. One of the primary limitations is data scarcity and bias, as high-quality experimental datasets are often limited, leading to biased predictions and reduced model generalizability [103]. Additionally, the interpretability of deep learning models remains a challenge, as many AI-driven predictions lack mechanistic explanations. The computational cost associated with training and deploying deep learning models also poses a barrier to widespread adoption. Addressing these challenges through explainable AI (XAI), self-supervised learning, and quantum computing-assisted drug design will further enhance the reliability and applicability of AI in drug discovery. Integrating AI with high-throughput experimental validation techniques, such as organoid-based drug screening and microfluidics, will bridge the gap between computational predictions and real-world drug efficacy [104].

AI-driven ligand-based drug design has transformed breast cancer therapeutics by enabling rapid hit identification, precise molecular optimization, and enhanced target specificity. AI methodologies, including machine learning, deep learning, and generative models, have significantly improved the efficiency and accuracy of drug discovery, facilitating the development of novel inhibitors for key breast cancer targets. The integration of AI with multi-omics data has further personalized drug design, paving the way for precision medicine approaches in breast cancer treatment. As AI technologies continue to evolve, they will play a crucial role in accelerating drug discovery, reducing development costs, and improving clinical outcomes for breast cancer patients [105].

2. CONCLUSION

Computational drug design has significantly advanced the field of BC therapeutics, offering innovative solutions to overcome the challenges of drug discovery and development. The application of molecular docking, pharmacophore modeling, and machine learning has enabled the identification of promising drug candidates, many of which have demonstrated efficacy in preclinical and clinical evaluations. In particular, the targeting of key oncogenic pathways, including, HER2, VEGF, BRCA1/BRCA2, and ER has paved the way for the development of precision medicine approaches in BC treatment. Additionally, advancements in artificial intelligence and machine learning have refined predictive models, enabling the identification of novel compounds with optimal pharmacokinetic and pharmacodynamic properties. These computational strategies have accelerated the discovery of therapeutics for various BC subtypes, including hormone receptor-positive, HER2-positive, and triple-negative breast cancer.

Despite these advancements, several challenges persist, including the need for improved predictive accuracy, validation through experimental studies, and the optimization of drug candidates for clinical translation. The integration of high-throughput screening, artificial intelligence, and big data analytics holds promise in addressing these limitations, further enhancing the efficiency and success rates of computational drug discovery. Moreover, the continual evolution of computational methodologies, such as quantum computing and systems biology, will drive future innovations in drug design, offering novel solutions to address complex biological networks in BC treatment. Furthermore, the ongoing integration of omics data and multi-omics approaches is refining drug-target identification and biomarker discovery, allowing for more precise therapeutic interventions. As computational tools continue to evolve, they will enable the development of more targeted, effective, and personalized BC therapies. Future research should focus on refining computational algorithms, expanding drug libraries, and developing multi-targeted therapeutics to combat drug resistance, one of the significant hurdles in current BC treatment regimens. The combination of computational approaches with experimental validation will not only accelerate drug discovery but also improve treatment specificity and reduce adverse effects.

Collaborations between computational biologists, medicinal chemists, and clinical researchers will be critical in bridging the gap between theoretical predictions and practical drug development. By leveraging computational methodologies alongside experimental validation, the pharmaceutical industry can expedite the discovery of novel BC therapies, ultimately improving patient outcomes and advancing the field of precision oncology. The future of computational drug design in BC treatment is promising, offering potential breakthroughs in targeted and personalized therapies that will benefit patients worldwide, providing hope for more effective and tailored therapeutic solutions

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