ISSN Print: 2664-7591
ISSN Online: 2664-7605
Impact Factor: RJIF 5.2
IJAN 2024; 6(1): 25-28
www.pharmaceuticaljournal.in
Received: 20-11-2023
Accepted: 25-12-2023

Prangyasini Devi
Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal, India

Suranjana Sarkar
Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal, India

Subhasis Sarkar
Department of Microbiology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal, India

Semanti Ghosh
Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal, India

Bidisha Ghosh
Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal, India

Corresponding Author:
Bidisha Ghosh
Department of Biotechnology, School of Life Sciences, Swami Vivekananda University, Telinipara, Barasat-Barrackpore Rd, Bara Kanthalia, West Bengal, India

Computer aided drug design for breast cancer

Prangyasini Devi, Suranjana Sarkar, Subhasis Sarkar, Semanti Ghosh and Bidisha Ghosh

DOI: https://doi.org/10.33545/26647591.2024.v6.i1a.76

Abstract
Cancer remains a significant global health concern, affecting millions of women worldwide. It has been suggested through various scientific reports that if detected at an early stage, there can be an increase in the survival of the subject. Despite significant advances in conventional cancer therapies, treatment efficacy and patient outcomes continue to be limited by the complexity and heterogeneity of breast cancer subtypes. In recent years, the use of Computer-Aided Drug Development (CADD) has gained significant popularity. This study will encompass discussions about several successful examples of CADD tools like Autodock, Glide, Gold (Genetic Optimization factor Ligand Docking) and Autodock Vina in breast cancer research. The pharmacophore modelling study discovers the small-molecule inhibitors targeting specific oncogenic proteins like PARP (Poly (ADP-ribose) Polymerase), CDKS (Cyclin-Dependant Kinases), HER2 (Human Epidermal Growth Factor Receptor 2) and the optimization of drug candidates to enhance their potency and selectivity. Computer aided drug design has led to the discovery of various potential drugs for breast cancer like Palbociclib, Ribociclib, Abemaciclib, Lapatinib and Neratinib. Computer-aided drug design (CADD) has emerged as a powerful and innovative approach to expedite the discovery and development of novel targeted therapeutics for breast cancer.

Keywords: Breast cancer, computer aided drug design, HER2-targeted therapies, PARP inhibitors

Introduction
The second most deadly type of cancer among women in the United States, breast cancer is the most common non-cutaneous malignancy. It is also the most common cancer in women to be diagnosed, ranking second among causes of death from cancer in women. (Ellington *et al.* 2023) [1]. Literature evidence has demonstrated the significant impact that both past and present research has had in enhancing the clinical prognosis for breast cancer patients. The improvement made in the areas of screening, diagnosis, and treatment approaches for the management of breast cancer has been credited for this. Nonetheless, there are significant obstacles to controlling the disease at the moment, including the dismal prognosis of TNBC (Triple Negative Breast Cancer) and medication resistance. (Yadav *et al.* 2013 & Marra *et al.* 2020) [2, 3]. Computer-aided drug design has emerged as a significant ally in the search to discover effective treatments for breast cancer. Similarly, the rising rate of breast cancer incidence and mortality among the population of underdeveloped countries is a major topic of concern. Researchers can optimise the features of promising drug candidates, speed up the process of finding them, and raise the chance that preclinical and clinical trials will be successful by utilising computational simulations, predictive modelling, and data analysis. (Akash *et al.* 2023) [6]. This multidisciplinary strategy has the potential to advance personalised medicine significantly and enhance breast cancer patients' outcomes. Drug design involves the use of many programmes and tools, including as databases, visualisation tools, and computer modelling software. From target identification and lead optimisation to molecular docking and virtual screening, these technologies help researchers at different stages of the drug discovery process. The particular requirements and goals of the drug discovery project determine which technologies are best to use. An initial survey would point out the different software related to drug designing of breast cancer.

Schrödinger Software tools: Popular software for drug discovery and molecular modelling are mostly executed through Schrödinger. Their graphical user interface, Maestro, combines

a number of tools for virtual screening, structure-based drug discovery, and molecular dynamics simulation (Kumar *et al.* 2020) [7]. The different properties of adsorption, distribution, metabolism and excretion (ADME) related to drug properties can be assessed using Schrödinger analysis tools. Recent literature reviews have suggested aromatase inhibitors as promising drug candidates against breast cancer in which the ADME properties have been evaluated using the mentioned software (Sahu *et al.* 2023 & Edris *et al.* 2023) [4, 5].

Discovery Studio: Discovery Studio is a suite of molecular modelling, simulation, and visualisation tools. It is frequently utilised in applications such as breast cancer treatment and medication development. (Kumar *et al.* 2020 & Saha *et al.* 2022) [7, 8]. Reports hint at the evaluation of several drugs that were analysed through Discover Studio which gave an idea about the two dimensional or three dimensional image of the drugs (Raghav *et al.* 2023) [9].

AutoDock / Vina: AutoDock and AutoDock: Software tools for molecular docking research are widely used, such as Vina. They facilitate the identification of lead compounds by helping researchers estimate how putative drug candidates would interact to their target proteins. The ligands ZINC04670539, ZINC05607079, and ZINC04344028 have been suggested as effective initial candidates for inhibiting LMTK3, which is seen as a breast cancer target (Anbarasu *et al.* 2017) [10].

PyRx: PyRx is an open-source molecular docking and virtual screening software platform. It is easy to use and has the capability to carry out docking experiments automatically. (Abdulrahman *et al.* 2021) [11]. Through the use of this software the binding affinities of the drug targets as well as of the potential drug molecules can be analysed. Examples can be cited that of different phytochemicals who's initial *in silico* properties were assessed through PyRx (Akash *et al.* 2023) [6].

MOE (Molecular Operating Environment): MOE is the comprehensive software package for molecular modelling, simulations, and structure-based drug creation as provides resources for protein-ligand docking and molecular dynamics simulations, among other things. (Patel *et al.* 2022) [13]. MOE enable the creation of highly customised user interfaces for integrating both internal and external tools (Muegge *et al.* (2017) [14].

Computational Approaches in Targeted Drug Discovery for Breast Cancer

Simulations through CADD has been a roadmap to the researchers that can help in the tuning a drug's chemical properties, increasing its biocompatibility with additional aiding factors like stability. For the identification and validation of the genetic basis and the underlying myriad causes of breast cancer, CADD provides the doorway to pick different targets for drug invention. In the context of breast cancer research, CADD provides an overview of the molecular and genetic basis of breast cancer, emphasizing the importance of identifying specific targets for therapeutic intervention. (Opeyemi *et al.* 2023) [15]. The principles and methodologies of CADD, including molecular docking (Mukherjee *et al.* 2009) [16] virtual screening (Yousuf *et al.* 2017) [17], pharmacophore modelling (Ramgopu *et al.* 2019) [18] and quantitative structure-activity relationship (QSAR), demonstrate its potential impact on improving breast cancer treatment and patient outcomes (Yadav *et al.* 2017) [19]. As computational tools and algorithms continue to advance, CADD holds promise in shaping the future of personalized and targeted breast cancer therapy (Akash, 2023) [6]. There were several target cells for breast cancer that have been identified for drug design. There might be more recent developments. The different drug targets using various software are been listed in Table 1.

Table 1: Drugs & their target site with their plausible functions using commonly used softwares

Target cell	Drug molecules	Function	Software	References
HER2 (Human Epidermal Growth Factor Receptor 2)	Trastuzumab (Herceptin)	Treatment of HER2-positive breast cancers.	Autodock	(Elseginy *et al.* 2020) [20]
Estrogen Receptor (ER)	Tamoxifen and aromatase inhibitors	Reduction of estrogen production that halt tumor growth	PyRx	(Jain *et al.* 2020) [21]
CDK4/6 (Cyclin-dependent kinases 4 and 6)	Palbociclib, Ribociclib	For ER-positive, HER2-negative breast cancers.	Autodock	(Shan *et al.* 2021 & Zaman *et al.* 2023) [22, 23]
PD-1/PD-L1 (Programmed cell death protein 1/Programmed cell death-ligand 1)	Pembrolizumab and atezolizumab	Treatment of triple-negative breast cancers.	PyRx	(Konieczny *et al.* 2020 & Pourzardosht *et al.* 2022 [24, 26]
Aurora Kinases	Thiazole compounds	Treatment of Breast Cancer	AutoDock	(Bathula *et al.* 2023) [25]

Multifaceted use of CADD for breast cancer

As discussed in the earlier section, Computer-Aided Drug Design (CADD) used in the drug development process to find possible drug candidates and forecast how they will interact with biological targets. For breast cancer drug discovery, a series of steps are followed.

Define the target: Specific protein should be identified which can be seen has close connection in causing breast cancer (Yu *et al.* 2017) [27]. XRD and other structural information about the target protein is collected (Sheridan *et al.* 1987) [28], along with NMR data (Arroyo *et al.* 2013) [29] or a common homology modelling.

Preparation of a compound library: Build a library of tiny molecules or compounds and test them for the ability to attach to the intended target. To carry out docking simulations and get binding affinity ratings for every chemical, use molecular docking tools such as Autodock Vina or Schrödinger Suite.

Virtual Screening Assessment: Arranging the compounds in order of binding affinities and rank them subsequently choosing the compounds with the highest scores as possible possibilities.

Hit Validation: Utilise additional computational techniques or experimental tests to perform additional analysis and validation of the compounds that scored highest.

Optimization of the lead: Improve the binding affinity, selectivity, and drug-like qualities of these compounds by further optimisation if validated hits are discovered.

Validation of the Experimental data: Synthesise and assess the most promising drugs of potent use in the lab employing several *in vitro* experiments along data retrieved through experiments using proper animal models to validate their safety and efficacy.

Clinical Trials: A candidate may proceed to human subject clinical trials if preclinical research shows promising outcomes. If the experiment works out, the medication can be submitted for approval to the governing bodies.

Conclusion

In recent times using computational techniques along with molecular modelling coupled with bioinformatics, computer-aided drug design (CADD) has been observed as a potent tool for finding effective treatments for breast cancer that speeds up the discovery process. By offering customised medication candidates for increased efficacy, selectivity, and safety, CADD aids researchers in their understanding of the molecular pathways underlying the onset and progression of breast cancer. Newer drugs with less resistance thus can be formulated with the effective use of computer aided drug designing technique.

Conflict of Interest

The authors have no potential conflict of interest.

References

1. Ellington TD, Henley SJ, Wilson RJ, Miller JW, Wu M, Richardson LC, *et al*. Trends in breast cancer mortality by race/ethnicity, age, and US census region, United States. 1999-2020. Cancer. 2023;129(1):32-38.
2. Yadav S, Sehrawat A, Eroglu Z, Somlo G, Hickey R, Yadav S, *et al*. Role of SMC1 in overcoming drug resistance in triple negative breast cancer. PloS one. 2013;8(5):e64338.
3. Marra A, Trapani D, Viale G, Criscitiello C, Curigliano G. Practical classification of triple-negative breast cancer: intratumoral heterogeneity, mechanisms of drug resistance, and novel therapies. NPJ breast cancer. 2020;6(1):54.
4. Sahu A, Ahmad S, Imtiyaz K, Kizhakkeppurath Kumaran A, Islam M, Raza K, *et al*. In-silico and *in-vitro* study reveals Ziprasidone as a potential aromatase inhibitor against breast carcinoma. Scientific Reports. 2023;13(1):16545.
5. Edris A, Abdelrahman M, Osman W, Sherif AE, Ashour A, Garelnabi EA, *et al*. Design of Novel Letrozole Analogues Targeting Aromatase for Breast Cancer: Molecular Docking, Molecular Dynamics, and Theoretical Studies on Gold Nanoparticles. Metabolites. 2023;13(5):583.
6. Akash S, Aovi FI, Azad MA, Kumer A, Chakma U, Islam MR, *et al*. A drug design strategy based on molecular docking and molecular dynamics simulations applied to development of inhibitor against triple-negative breast cancer by Scutellarein derivatives. Plos one. 2023;18(10):e0283271.
7. Kumar R, Saha P, Kumar Y, Sahana S, Dubey A, Prakash O, *et al*. A Review on Diabetes Mellitus: Type1 & Type 2. World Journal of Pharmacy and Pharmaceutical Sciences. 2020;9(10):838-850.
8. Saha P, Nyarko RO, Lokare P, Kahwa I, Boateng PO, Asum C, *et al*. Effect of Covid-19in Management of Lung Cancer Disease: A Review. Asian Journal of Pharmaceutical Research and Development. 2022;10(3):58-64.
9. Raghav M, Singh M, Kumari A, Singh A, Bansal P, Katiyar D, *et al*. In-silico molecular prediction of de-novo pteridophytes ligands targeting fungal Sec-14p: A CADD based analysis. Materials Today: Proceedings; c2023.
10. Anbarasu K, Jayanthi S. Designing and optimization of novel human LMTK3 inhibitors against breast cancer–a computational approach. Journal of Receptors and Signal Transduction. 2017;37(1):51-59.
11. Abdulrahman HL, Uzairu A, Uba S. QSAR, ligand based design and pharmacokinetic studies of *Parviflorus* derivatives as anti-breast cancer drug compounds against MCF-7 cell line. Chemistry Africa. 2021;4:175-187.
12. Akash S, Bibi S, Biswas P, Mukerjee N, Khan DA, Hasan MN, *et al*. Revolutionizing anti-cancer drug discovery against breast cancer and lung cancer by modification of natural genistein: An advanced computational and drug design approach. Frontiers in Oncology; c2023. p. 13.
13. Patel JR, Joshi HV, Shah UA, Patel JK. A review on computational software tools for drug design and discovery. Indo Global Journal of Pharmaceutical Sciences. 2022;12:53-81.
14. Muegge I, Bergner A, Kriegl JM. Computer-aided drug design at Boehringer Ingelheim. Journal of computer-aided molecular design. 2017;31(3):275-285.
15. Opeyemi I, Paul O, Olawale F, Olorunfemi B, Elekofehinti OO, Kikiowo B, *et al*. Computer-aided drug design in anti-cancer drug discovery: What have we learnt and what is the way forward? Informatics in Medicine Unlocked; c2023. p. 101332.
16. Mukherjee S, Majumder D. Computational molecular docking assessment of hormone receptor adjuvant drugs: breast cancer as an example. Pathophysiology. 2009;16(1):19-29.
17. Yousuf Z, Iman K, Iftikhar N, Mirza MU. Structure-based virtual screening and molecular docking for the identification of potential multi-targeted inhibitors against breast cancer. Breast Cancer: Targets and Therapy; c2017. p. 447-459.
18. Rampogu S, Parate S, Parameswaran S, Park C, Baek A, Son M, *et al*. Natural compounds as potential Hsp90 inhibitors for breast cancer-Pharmacophore guided molecular modelling studies. Computational Biology and Chemistry. 2019;83:107113.
19. Yadav DK, Kumar S, Saloni, Singh H, Kim MH, Sharma P, *et al*. Molecular docking, QSAR and ADMET studies of withanolide analogs against breast cancer. Drug Design, Development and Therapy; c2017. p. 1859-1870.
20. Elseginy SA, Hamdy R, Menon V, Almehdi AM, El-Awady R, Soliman SS, *et al*. Design, synthesis, and

computational validation of novel compounds selectively targeting HER2-expressing breast cancer. Bioorganic & Medicinal Chemistry Letters. 2020;30(24):127658.
21. Jain S, Das A. Virtual screening of natural compounds as combinatorial agents from Indian medicinal plants against estrogen positive breast cancer. International Journal on Integrated Education. 2020;3(10):266-275.
22. Shan H, Ma X, Yan G, Luo M, Zhong X, Lan S, *et al*. Discovery of a novel covalent CDK4/6 inhibitor based on palbociclib scaffold. European Journal of Medicinal Chemistry. 2021;219:113432.
23. Zaman N, Yousaf R, Akhtar Z, Azam SS. Modulating structural dynamics of dual drugs for CDK4 complex addressing prostate cancer. Journal of Molecular Liquids. 2023;376:121454.
24. Konieczny M, Musielak B, Kocik J, Skalniak L, Sala D, Czub M, *et al*. Di-bromo-based small-molecule inhibitors of the PD-1/PD-L1 immune checkpoint. Journal of Medicinal Chemistry. 2020;63(19):11271-11285.
25. Bathula S, Sankaranarayanan M, Malgija B, Kaliappan I, Bhandare RR, Shaik AB, *et al*. 2-Amino Thiazole Derivatives as Prospective Aurora Kinase Inhibitors against Breast Cancer: QSAR, ADMET Prediction, Molecular Docking, and Molecular Dynamic Simulation Studies. ACS omega. 2023;8(46):44287-44311.
26. Pourzardosht N, Hashemi ZS, Mard-Soltani M, Jahangiri A, Rahbar MR, Zakeri A, *et al*. Liothyronine could block the programmed death-ligand 1 (PDL1) activity: An e-Pharmacophore modeling and virtual screening study. Journal of Receptors and Signal Transduction. 2022;42(1):34-42.
27. Yu W, MacKerell AD. Computer-aided drug design methods. Antibiotics: Methods and protocols; c2017. p. 85-106.
28. Sheridan RP, Venkataraghavan R. New methods in computer-aided drug design. Accounts of Chemical Research. 1987;20(9):322-329.
29. Arroyo X, Goldflam M, Feliz M, Belda I, Giralt E. Computer-aided design of fragment mixtures for NMR-based screening. PLoS One. 2013;8(3):e58571.
30. Kumar R, Saha P, Lokare P, Datta K, Selvakumar P, Chourasia A, *et al*. A Systemic Review of *Ocimum sanctum* (Tulsi): Morphological Characteristics, Phytoconstituents and Therapeutic Applications. International Journal for Research in Applied Sciences and Biotechnology. 2022;9(2):221-226.
31. Saha P, Kumar R, Nyarko RO, Kahwa I, Owusu P. Herbal Secondary Metabolite for Gastro-Protective Ulcer Activity with API Structures; c2021.