A Review of Breast Cancer Treatment Advancement Using a Drug Designing Approach

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***Abstract*—** Despite these efforts, the cancer drug development research field continues to be incredibly difficult, and therapeutic advancements have not yet produced the desired clinical outcomes. Breast cancer (BC) continues to rank among all cancer types as one of the most dangerous diseases, accounting for a significant portion of cancer-related deaths among women globally, and the number of cases that are identified each year is rising. As a result, a new direction in research has emerged that sought to explain how drugs work, predict drug resistance, and identify biomarkers for numerous diseases. Drug design aims to locate a molecule with the right chemical and geometric properties to stick to a specific site on a protein target. It's difficult to discover new medicines. Structure-based and ligand-based drug design are the two main methods used in the pharmaceutical industry today. The key to developing drugs was understanding protein structure and function, for which contemporary methods based on combinatorial approaches like proteomics, genomics, and bioinformatics were applied. It's crucial to determine which cell or tissue the medicine will target in order to properly and profitably design a new drug. The main aim of this article is to impart a succinct introduction to computer-aided drug design, which is crucial to contemporary medical research and has a bright future in the development of novel treatments with less time and financial investment

Keywords: Therapeutic advancement, cancer, drug discovery, bioinformatics, Computational technology

INTRODUCTION

Breast cancer (BC) is among the most well-known diseases influencing women around the world. In 2016, there was a sum of 246,660 new instances of BC in the US, representing 14% of all deaths around the world [1]. Medication resistance and metastasis to other organs, like the lymph nodes, bone, lungs, and liver, are the leading causes of death from breast cancer. It is basically accepted that a protein belonging to the ATP-binding cassette takes part a vital role in therapy resistance in certain types of cancer. Breast cancer is difficult to diagnose and treat because of multidrug resistance (MDR), which is caused by the overexpression of proteins such as P-glycoprotein, ABCG2, and BCRP. Although progress in small molecules, proteins, and peptides for immunotherapy, controlled-release medicine administration and targeting are not yet feasible. The majority of deaths from breast cancer can be attributed to metastasis, as has already been shown [2,3]. Several mechanisms mediate breast cancer regulation and metastasis dissemination. Our understanding of the biological roles of ERs, PRs, and

HER-2 in the development of different breast cancer subtypes has increased [4-6]

DIFFERENT TYPES OF DRUG DELIVERY APPROACHES:

Drug delivery systemic approach

Nanocarrier-based chemotherapy works well on many cancer sites. Nanoparticles (NPs') versatile surface-modifying capacity leads cells to tumor vasculature. Nanoscale encapsulation of chemotherapeutic compounds is the greatest way to reduce side effects and increase breast cancer treatment absorption. In order to acquire a deeper and better understanding, the biodistribution and pharmacokinetics of EGFR-targeted polymer-blend nanoparticles packed with lonidamine and paclitaxel were studied. Certain nanoparticles excelled in drug solutions and nontargeted nanoparticles' pharmacokinetics, enabling new multidrug-resistant cancer treatments [7]. Organic and inorganic particles are the most prevalent and commonly used drug delivery methods.

Drug delivery using an Organic approach:

Polymeric micelles consist of a combination of surfactants, phospholipids, long-chain fatty acids, and water-soluble polymers. Micelles provide water-insoluble drugs. Paul Ehrlich proposed targeting diseased cells with them. Micelles improve retention, permeability, and medication half-life in tumors with restricted blood supply [8]. In MCF-7/doxorubicin-resistant cells, they increase intracellular drug concentration and cytotoxicity via inhibiting P-gp efflux and activating receptor-mediated endocytosis [9,10]. Breast adenocarcinomas have also been successfully treated using artificial immunological micelles loaded with antibodies. For HER-2-positive breast cancer, antibody-conjugated lysosomal P (LA-co-TMCC)-g-PEG furan micelles proved effective in combination with anti-HER-2 monoclonal antibody (mAb) [11-13].

Localized drug delivery approaches:

Recurrent breast cancer therapies include chemotherapy, radiotherapy, and surgery. Early-stage cancers benefit more from localized than systemic medication administration-stage cancers benefit more from localized than systemic medication administration. Natural (like hyaluronic acid and collagen polypeptides) as well as synthetic polymers are utilized for intratumor drug administration in malignant tissue. Continuous smart drug delivery therapy, nanofibers with adaptable shapes and strength, and intraductal injection of NPs or polymers via a microcatheter are all ways to boost performance [14].

Drug delivery using an inorganic approach:

Chemotherapy with gold nanoparticles (GNPs) is used to treat different cancers. They are capable of freely moving between tumor cells thanks to their tiny size (about 130 nm) and high selectivity. Biomarkers for cancer diagnosis and antibiotic development both benefit from GNP coatings' usage as probes in transmission electron microscopy. The Brust-Schiffrin method as well as the citrate reduction of gold in water are the two most prevalent approaches to producing GNP. Cellular absorption of GNP-attached transferrin molecules was shown to be higher than that of transferrin molecules without GNPs in an experiment using breast cancer cells [15, 16].

Receptor-based drug delivery approaches:

A network of receptors controls the growth of breast cancer, and each of these receptors could be a target for treatment. Clinical trials based on receptor-targeting research are now recruiting patients with advanced breast cancer. Despite advancements in cytotoxic medications such as gemcitabine, doxorubicin, and vinorelbine, overall survival rates remain dismal. Breast cancer cells have been shown

to target several different receptors, including HER-2, EGFR and VEGFR. The studies showed that tyrosine kinases regulate IGF-IR, while VEGFR stimulates angiogenesis. In triple-negative breast cancer, the EGFR family member HER-2 is poorly differentiated [17].

Anti-Cancer drug target prediction:

Over 30,000 genes in the human genome 6 to 8 thousand have been determined to be potentially useful for medicine. Thus far, only about 400 encoded proteins have been found to be useful in creating new treatments [18]. In contrast to numerous other human diseases, cancer today offers a rich variety of molecular targets on which to focus the creation of new therapies [19]. Even if drug and protein interactions are possible, the "one molecule, one target, one disease" approach is still commonly adopted in traditional drug development. Yet, the importance of various target proteins in relation to several different types of complex disorders has been underestimated [20, 21]. Off-target drug effects are undesirable and hard to regulate, and the "poly-pharmacological" properties of some treatments can have unintended consequences. These effects are notably noticeable in anti-cancer medications.

Structure-based drug discovery:

In a “structure-based method," structural knowledge is used to figure out how bioactive compounds interact with the receptors that recognize them [22]. The development of biomolecular spectroscopic tools like Crystallography using X-rays and NMR has helped us learn a lot more about the structure of the therapeutic target. Both of these tools have made a big difference in the amazing progress that has been made in this field. The three-dimensional protein structure can be used to create novel ligands with therapeutic benefits. So, structure-based design (SBD), which is the process of finding and improving early lead compounds, could give us important information about how to design and make new medicines [23, 24]. To get the pharmacological and therapeutic effects that are wanted, the high-affinity ligand must first selectively change the activities of cells that are known to be drug targets [25]. Captopril, the first ACE inhibitor produced in the 1980s, is often cited as an early and successful example of utilising structural knowledge to optimise the design of medication [26]. Since the publication of this study, structure-based drug development has developed into a cutting-edge and powerful algorithm as well as a strategy that supports quicker, less expensive, and more efficient drug development. An escalating number of effective applications have played key roles in cutting-edge medical research over the past 10 years, thanks in large part to the enormous efforts that have been made to advance the SBD strategy [27-31].

Molecular Docking

In rational drug design, docking is a common structure-based approach. This strategy entails investigating the biomolecule binding preferences and interaction strengths of the ligand and the receptor, and then formulating predictions based on those findings. [32] Docking can be broken down into two categories, rigid and flexible docking, according to the level to which the ligands that are employed in the computational approach are flexible [33, 34]. The rigid docking method is a type of binding model that does not take into consideration flexibility or the induced-fit theory [35]. Instead, it places emphasis on how well the ligand and the target proteins match up physically, chemically, and geometrically. For high-throughput virtual screening using a plethora of datasets for very small molecules, rigid docking is commonly used because of its speed and efficiency. This is done in order to be time-efficient, as rigid docking is both quick and very effective. The flexible docking strategy, on the other hand, takes into account data that is more exact and accurate. The rapid increase in computer power and efficiency led to a broadening of the availability of flexible docking approaches. These techniques have continued to make strides forward. Docking software is available in a wide variety of

types, including Glide, FlexX, DOCK and AutoDock amongst others.

Structure-Based Pharmacophore (SBP) Mapping

Target-ligand complex-based approaches and target-binding server (without ligand) approaches can be distinguished based on the ease with which their respective ligand structures can be accessed [36]. The target-ligand complex-based method makes locating the protein's ligand-binding pocket easy and evaluates the primary ligand-protein interactions. As an illustration, consider the apps Ligand Scout, Pocket v.2, and GBPM [37]. Notably, they are inapplicable as settings when the identities of the ligands are unknown. Discovery Studio is a good illustration of a program that takes a macromolecule-based approach rather than relying on ligands or receptor-ligand interactions [38].

Standard of Care and Emerging Therapies for Breast Cancer Subtypes

Emerging Therapies like Metastatic HR+ BC may develop resistance to conventional hormone therapy if the ER's genetic makeup is altered or if other signalling pathways are upregulated. New medications have been developed in an effort to counteract the body's natural resistance to hormone treatment [39, 40]. As time passes, advancement in the field of medical science and the pharmaceutical sector new molecules are identified and are currently in different phases of trial as shown in the table1.

Table: New medications for breast cancer's many molecular subtypes (BC) with the most recent Stage of Clinical Development of Various

I. For treating HR+ BC		
Palbociclib Phase III **Ribociclib** Phase III (ongoing) **Abemaciclib** Phase III (ongoing) **Buparlisb** Phase III	**Pictilisib** Phase II (will not be further pursued) **Pilaralisib** Phase I/II (will not be further pursued) **Voxtalisib** Phase I/II (will not be further pursued) **Alpeisib** Phase III (ongoing)	**Taselisib** Phase II (ongoing) **Entinostat** Phase III (ongoing) **Vorinostat** Phase II

II. For treating HER2+ BC	**III. For treating triple-negative breast cancer**
Buparlisb Phase II **Pilaralisib** Phase I/II **MK-2206** Phase I	**Olaparib** Phase III **Talazoparib** Phase III (ongoing) **Veliparib** Phase III (ongoing) **Niraparib** Phase III (ongoing) **Rucaparib** Phase II (ongoing) **Glembatumumab**

	Phase II (ongoing) **Bicalutamide** Phase II **Pembrolizumab** Phase II (ongoing)

Numerous promising novel drugs and combination techniques are currently being tested in clinical trials, and if they prove beneficial, they will offer a glimmer of hope for improving the treatment of BC [41]. Furthermore, a specific treatment approach based on the biological and molecular characterization of individual patients can further revolutionize BC therapy by allowing for the optimization of dose and regimen. Using gene profiling results to find genetic biomarkers, effective treatment options can be developed. Yet, the complexity of regulatory permissions and data integrity presents the greatest obstacle to the successful healthcare translation of this technique.

Conclusion

The use of computational approaches in biological research has become essential. Building new, effective methods to create new pharmaceuticals has been made possible by the use of bioinformatics and knowledge from the domains of genomes and proteomics. The body of information in these areas aids in understanding the genetics of disease, predicting protein structure, and annotating DNA and genomes. There has been a shift in pharmaceutical research towards demonstrating how drugs work, foreseeing the development of drug resistance, and discovering biomarkers for a wide range of illnesses. Drug development is a labour-intensive, expensive, and complex process. In many aspects, bioinformatics is a significant help in overcoming cost and time constraints. Numerous drug-related databases and pieces of software are made available by bioinformatics, and they can be applied in a variety of ways to the process of designing and developing new drugs. Rational drug design has been considered ideal because many factors, including bioavailability, toxicity, and metabolism, can impact a drug's effectiveness. Rational drug design has become possible thanks to recent important technological advances in computer science, molecular biology, and the structural characterization of biomacromolecules.

Abbreviation

ER = estrogen receptor,
Her2 = human epidermal growth factor receptor 2,
PR = progesterone receptor

Conflict of interest

Nil

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REFERENCES

1. Siegel RL, Miller KD, Jemal A. *Cancer statistics, 2016*. CA Cancer J Clin. 2016;66(1):7–30.
2. Carty NJ, Foggitt A, Hamilton CR, Royle GT, Taylor I. *Patterns of clinical metastasis in breast cancer: an analysis of 100 patients*. Eur J Surg Oncol. 1995;21(6):607–608.
3. Grobmyer SR, Zhou G, Gutwein LG, Iwakuma N, Sharma P, Hochwald SN. *Nanoparticle delivery for metastatic breast cancer.* Nanomedicine. 2012;8 Suppl 1: S21–S30.
4. Davies E, Hiscox S. *New therapeutic approaches in breast cancer*. Maturitas. 2011;68(2):121–128.
5. Eroles P, Bosch A, Pérez-Fidalgo JA, Lluch A. *Molecular biology in breast cancer: intrinsic*

subtypes and signalling pathways. Cancer Treat Rev. 2012;38(6):698–707.

6. Kreike B, van Kouwenhove M, Horlings H, et al. *Gene expression profiling and histopathological characterization of triple-negative/ basal-like breast carcinomas*. Breast Cancer Res. 2007;9(5): R65.
7. Milane L, Duan ZF, Amiji M. *Pharmacokinetics and biodistribution of lonidamine/paclitaxel loaded, EGFR-targeted nanoparticles in an orthotopic animal model of multi-drug resistant breast cancer*. Nanomedicine. 2011;7(4):435–444.
8. Zhang Y, Huang Y, Li S. Polymeric micelles: *nanocarriers for cancer targeted drug delivery.* AAPS PharmSciTech. 2014;15(4):862–871.
9. Mohajer G, Lee ES, Bae YH. *Enhanced intercellular retention activity of novel pH-sensitive polymeric micelles in wild and multidrug-resistant MCF-7 cells*. Pharm Res. 2007;24(9):1618–1627.
10. Yuan Y, Cai T, Xia X, Zhang R, Chiba P, Cai Y. *Nanoparticle delivery of anticancer drugs overcomes multidrug resistance in breast cancer*. Drug Deliv. 2016;23(9):3350–3357.
11. Sadat SM, Saeidnia S, Nazarali AJ, Haddadi A. *Nano-pharmaceutical formulations for targeted drug delivery against HER2 in breast cancer*. Curr Cancer Drug Targets. 2015;15(1):71–86.
12. Lee AL, Wang Y, Cheng HY, Pervaiz S, Yang YY. *The co-delivery of paclitaxel and Herceptin using cationic micellar nanoparticles*. Biomaterials. 2009;30(5):919–927.
13. Lee KS, Chung HC, Im SA, et al. *Multicenter phase II trial of Genexol-PM, a Cremophor-free, polymeric micelle formulation of paclitaxel, in patients with metastatic breast cancer*. Breast Cancer Res Treat. 2008; 108(2):241–250.
14. Wolinsky JB, Colson YL, Grinstaff MW. *Local drug delivery strategies for cancer treatment: gels, nanoparticles, polymeric films, rods, and wafers*. J Control Release. 2012;159(1):14–26.
15. Jain S, Hirst DG, O'Sullivan JM. *Gold nanoparticles as novel agents for cancer therapy*. Br J Radiol. 2012;85(1010):101–113.
16. Li JL, Wang L, Liu XY, et al. *In vitro cancer cell imaging and therapy using transferrin-conjugated gold nanoparticles*. Cancer Lett. 2009;274(2):319–326.
17. Lu RM, Chen MS, Chang DK, et al. *Targeted drug delivery systems mediated by a novel peptide in breast cancer therapy and imaging*. PLoS One. 2013;8(6):e66128.
18. Drews, J. Drug discovery: a historical perspective. Sci. (New York N.Y.) 2000; 287, 1960–1964.
19. Lazo, J. S., and Sharlow, E. R. *Drugging Undruggable Molecular Cancer Targets.* Annu. Rev. Phar. Toxicol. 2016;56, 23–40.
20. Hopkins, A. L. *Network pharmacology: the next paradigm in drug discovery*. Nat. Chem. Biol. 2008;4, 682–690.
21. Chen, X., Liu, M.-X., and Yan, G.-Y. *Drug-target interaction prediction by random walk on the heterogeneous network*. Mol. Biosyst. 2012; 8, 1970–1978.
22. Wang, J. L., Liu, D., Zhang, Z. J., Shan, S., Han, X., Srinivasula, S. M., et al. *Structure-based discovery of an organic compound that binds Bcl-2 protein and induces apoptosis of tumor cells.* Proc. Natl. Acad. Sci. United States America 2000; 97, 7124–7129.
23. Prada-Gracia, D., Huerta-Yepez, S., and Moreno-Vargas, L. M. *Application of computational methods for anticancer drug discovery, design, and optimization*. Boletin Med. Del Hosp. Infantil. Mexico 2016;73, 411–423.
24. Lu, P., Bevan, D. R., Leber, A., Hontecillas, R., Tubau-Juni, N., and BassaganyaRiera, J. *"Computer-aided drug discovery,"* in Accelerated Path to Cures (Springer),2018a; 7–24.
25. Urwyler, S. *Allosteric Modulation of Family C G-Protein-Coupled Receptors: from Molecular Insights to Therapeutic Perspectives*. Pharmacol. Rev. 2011;63, 59–126.
26. Anthony, C. S., Masuyer, G., Sturrock, E. D., and Acharya, K. R. *Structure Based Drug Design of Angiotensin-I Converting Enzyme Inhibitors*. Curr. Med. Chem. (2012);19, 845–855.

27. Debnath, S., Kanakaraju, M., Islam, M., Yeeravalli, R., Sen, D., and Das, A. *In silico design, synthesis and activity of potential drug-like chrysin scaffoldderived selective EGFR inhibitors as anticancer agents.* Comput. Biol. Chem. 2019; 83.
28. Hong, J. Y., Price, I. R., Bai, J. J., and Lie, H. *A Glycoconjugated SIRT2 Inhibitor with Aqueous Solubility Allows Structure-Based Design of SIRT2 Inhibitors.* ACS Chem. Biol. 2019;14, 1802–1810.
29. Mendoza, J. L., Escalante, N. K., Jude, K. M., Bellon, J. S., Su, L., Horton, T. M., et al. *Structure of the IFN gamma receptor complex guides design of biased agonists.* Nature 2019;567, 56–59
30. Itoh, Y. *Drug Discovery Researches on Modulators of Lysine-Modifying Enzymes Based on Strategic Chemistry Approaches.* Chem. Pharmaceut. Bull. 2020; 68, 34–45.
31. Tondo, A. R., Caputo, L., Mangiatordi, G. F., Monaci, L., Lentini, G., Logrieco, A. F., et al. (2020). *Structure-Based Identification and Design of Angiotensin Converting Enzyme-Inhibitory Peptides from Whey Proteins*. J. Agric. Food Chem. 2020; 68, 541–548.
32. Ferreira, L. G., Dos Santos, R. N., Oliva, G., and Andricopulo, A. D. (2015). *Molecular Docking and Structure-Based Drug Design Strategies*. Molecules 2015; 20, 13384–13421.
33. Halperin, I., Ma, B., Wolfson, H., and Nussinov, R. *Principles of docking: An overview of search algorithms and a guide to scoring functions*. Proteins 2002; 47, 409–443.
34. Dias, R., and De Azevedo, W. F.Jr. *Molecular Docking Algorithms*. Curr. Drug Targets 2008; 9, 1040–1047.
35. Salmaso V, Moro S. *Bridging molecular docking to molecular dynamics in exploring ligand-protein recognition process: An overview*. Frontiers in pharmacology. 2018 Aug 22;9:923.
36. Pirhadi S, Shiri F, Ghasemi JB. *Methods and applications of structure-based pharmacophores in drug discovery.* Current topics in medicinal chemistry. 2013 May 1;13(9):1036-47.
37. Wolber G, Dornhofer AA, Langer T. *Efficient overlay of small organic molecules using 3D pharmacophores.* Journal of computer-aided molecular design. 2006 Dec;20(12):773-88.
38. Chen J, Lai L. Pocket v. *further developments on receptor-based pharmacophore modelling*. Journal of chemical information and modelling. 2006 Nov 27;46(6):2684-91.
39. Ortuso F, Langer T, Alcaro S. *GBPM: GRID-based pharmacophore model: concept and application studies to protein–protein recognition.* Bioinformatics. 2006 Jun 15;22(12):1449-55.
40. Lu X, Yang H, Chen Y, Li Q, He SY, Jiang X, Feng F, Qu W, Sun H. *The development of pharmacophore modelling: Generation and recent applications in drug discovery*. Current pharmaceutical design. 2018 Aug 1;24(29):3424-39.
41. Tong CW, Wu M, Cho WC, To KK. *Recent advances in the treatment of breast cancer*. Frontiers in oncology. 2018 Jun 14; 8:227.