REVIEW ARTICLE

Structure-Based Virtual Screening in Oncology: Repurposing FDA-Approved Drugs for Breast Cancer

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ABSTRACT

Structure-based virtual screening (SBVS) has been recently established as a significant and fruitful computational method in drug repurposing, where drugs already approved by the FDA are screened for their potential therapeutic effects against breast cancer. This review lays down the principles of SBVS while broaching important computational programs such as molecular docking software, molecular dynamic simulation, and AI-driven predictive models. Databases of drug repositioning such as DrugBank, PubChem, and ChEMBL provide comprehensive datasets mandatory for virtual screening. The past few years have seen SBVS emerge as a tool for drug repurposing with exciting new candidates. Some of these are metformin, statins, NSAIDs, beta-blockers, and antidepressants, with anti-cancer activities reported through a plethora of mechanisms. However, accuracy limits, experimental validation, and regulatory hurdles impede clinical translation. The way forward envisions approaches integrating AI, multi-target drug strategies, and personalized medicine to enhance SBVS's suitability and reliability in oncology. Utilizing computational methods and an inter-disciplinary dynamic, drug repurposing with SBVS is anticipated to get very far and create a viable toolkit for breast cancer therapeutic discovery.

Keywords: Structure-based virtual screening, drug repurposing, breast cancer, docking, AI in drug discovery, molecular dynamics simulation, repositioning databases, computationally assisted drug design, targeted therapies, personalized medicine.

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INTRODUCTION

Despite advances in early detection and treatment, breast cancer continues to challenge physicians due to its heterogeneous nature and variable response to therapy. The incidence of breast cancer has been on the rise in the past few decades, creating a demand for innovative strategies in management[1]. Breast cancer is among the most common malignancies to affect women globally; hence it accounts for a large share of cancer-related morbidity and mortality. Thus, it is seen that the breast has become an environmental socialized means of access to newer treatment modalities[2].

All the currently available treatment modalities for breast cancer, including chemotherapy, radiotherapy, and hormone therapy, have considerable limitations. There are significant side effects, treatment resistances, and financial constraints for the patients. Furthermore, breast cancers that have developed drug resistance are of little economic value for the available treatment options, thus creating the need for newer strategies that are both effective and economic[3].

Drug repurposing refers to the identification of new therapeutic uses for already-approved medicines. This method could rapidly advance into parts of therapeutics for breast cancer because it has the potential to bypass many of the obstacles blocking the de novo pathway for drug development. Repurposing accelerates drug discovery by applying the already-existing safety profiles of drugs, thereby markedly lowering the development costs. Computational methods such as structure-based virtual screening (SBVS) are gaining prominence for the identification of prospective drug candidates for the treatment of breast cancer. SBVS gives a scientifically grounded target for screening FDA-approved drugs against breast cancer targets that are well characterized, thus maximizing the chances of successful repurposing[4].

Drug Repurposing: A Paradigm Shift in Cancer Therapy

Drug repositioning, another name for drug repurposing, is defined as the process of discovering new therapeutic uses for existing drugs. Because of its ability to circumvent most of the developmental hurdles which beset drug discovery de novo, this strategy has drawn considerable attention in oncology. The use of drugs with known pharmacokinetics and safety profiles greatly shortens the timeline from discovery to clinical application.

Clearly, repurposing confers great advantages over outright drug development, which can take over a decade and cost billions. This is chiefly because such drugs have undergone at least preclinical tests and early-phase clinical trials, thus lessening the financial and regulatory burdens[5]. Furthermore, repurposed drugs will often have well-

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understood mechanisms of action, allowing for their rational integration into existing treatment regimens.

Several large classes of FDA-approved drugs have been successfully repurposed to treat cancers. Thalidomide was originally developed as a sedative, but it demonstrated anti-angiogenic activity and was restored for treatment of multiple myeloma. Metformin, a widely prescribed antidiabetic drug, was found to exert anticancer effects by modifying metabolic pathways. Nevertheless, intellectual property issues, regulatory barriers, and clinical validation must also be confronted if we are to maximize the potential of drug repurposing in cancer therapies[6].

Moreover, repurposed drugs often have multi-target potential, which is an advantage in treating cancer. While many anticancer drugs may have an unidimensional approach, resistance develops over time. Other diseases may be impinging upon multiple pathways, so those compounds may therefore be less likely to develop resistance. Long-term therapeutic efficacy on the management of breast cancer renders repurposing a very attractive route[7].

Another important point surrounding drug repurposing is the allowance for the personalization of medicine. Breast cancer is a very heterogeneous disease, with different subtypes responding differently to different treatments. These repurposed drugs can be assigned for subtype-specific molecular targets, thereby ensuring a more focused and effective treatment approach. Such an individualized approach can enhance the outcome for patients and reduce their exposure to unwanted drugs that may not be effective[8].

Structure-Based Virtual Screening (SBVS) in Drug Repurposing

Virtual screening is a computational technique designed to search for potential drug candidates by establishing how they interact with biological targets. Of all the virtual screening approaches, SBVS capitalizes the most on structural information about the target protein. By molecular docking algorithms, SBVS enables investigators to predict the anticipated binding affinity and interaction pattern of small molecules with cancer-related proteins.

The provision of high-resolution structural data for the drug targets is one of the major components of SBVS. Using X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy, many structures have been studied for cancer-related proteins such as estrogen receptor (ER), HER2, BRCA, and CDK4/6. These structural implements provide accurate docking studies for drug-target interaction predictions[9].

The usual SBVS flow constitutes several important steps. Target identification and validation assure that selected proteins are putatively relevant with respect to pathophysiological implications in breast cancer. Protein structure preparation means refinement and optimization of molecular builds for reliable docking results. Ligand preparation is about selecting a diverse library of FDA-approved drugs for-use screening. Thereafter docking studies, molecular dynamics simulation is conducted to assess the complex's stability and conformational behavior of the drug-target pair. Finally, an in-silico ADMET (absorption-distribution-metabolism-excretion-toxicity) profile is undertaken and analyzed regarding drug-likeness and potential side effects profile[10].

In addition, hybrid computational methods have reinforced SBVS much more. By combining molecular docking techniques with pharmacophore modeling and machine-learning algorithms, scholars have the potential of perfecting virtual screening processes through improvement in the overall accuracy and efficiency of the hybrid methods[11].

Another addition to SBVS has been the infusion of deep learning techniques. Deep-learning models driven by AI analyze huge datasets and figure out intricate molecular interaction patterns that standard algorithms usually miss. This means it may also help find potential pharmacants, which can otherwise be excluded from historical main-computational profiles. Thus, expanding the scope of SBVS uses in breast cancer therapy[12].

Main Targets for Drug Repurposing in Breast Cancer

Breast cancer institute's the high heterogeneity which would depict temp-heights of multiple clinical molecular subtypes, every one of which bears distinct therapeutic vulnerabilities. Two major hormones- estrogen, and progesterone receptors demonstrated importance in regard to their roles in the hormone-positive breast cancer, as such they become the most potential targets for drug repurposing. The drugs which predominantly modulate these pathways, such as selective estrogen receptor modulators (SERMs), have displayed promising response to ER-positive breast cases such as breast cancer[13].

HER2-positive breast cancer does least favorably when compared to other types of invasive breast cancer- it is characterized by overexpression of the HER2 receptor. Their introduction and availability on an FDA-approved list have significantly changed the outlook for patient outcomes through remedies, such as trastuzumab; however, their resistance proves challenging. Existing HER2-targeting kinase inhibitors may have new applications in the treatment of cases that do not respond to these popular therapies[14].

Another area of interest is the CDK4 and CDK6 signaling pathway, which controls cell cycle progression. Drugs that inhibit this pathway have already shown good activity in metastatic breast cancer. The new vista in targeted therapy was opened by drugs affecting DNA repair pathways such as PARP inhibitors, which are used for BRCA-mutated breast cancer. The widening of new repurposing indications for breast cancer has become possible because of immune checkpoint inhibitors and epigenetic regulators[15].

Emergent targets have been developed especially into tumor metabolism regulators most recently introduced into breast cancer research. A hallmark of cancer is metabolic reprogramming. Drugs such as targeting molecular pathology glycolysis and oxidative phosphorylation can be used for therapeutic improvement. Some agents like metformin: they alter metabolic states and have yielded promising anticancer effects; thus, they can be termed potential drugs for repurposing[16].

Moreover, the tumor microenvironment (TME) plays an important role in breast cancer progression and resistance to therapy, and the medications directed towards the TME,

Table 1: Case Studies in Structure-Based Drug Repurposing for Breast Cancer[20-22]

Repurposed Drug	Original Use	Mechanism of Action in Breast Cancer	Computational and Experimental Evidence	Clinical Implications	Ref.
Metformin	Antidiabetic	Targets AMP-activated protein kinase (AMPK), disrupts mitochondrial respiration, inhibits cancer cell proliferation	In silico studies confirm strong binding affinity to metabolic regulators in breast cancer cells	Potential anticancer effects; ongoing clinical trials	[20]
Statins	Cholesterol management	Modulates cholesterol biosynthesis, disrupts cancer cell membrane integrity, induces apoptosis, inhibits metastasis	Computational studies indicate binding to oncogenic proteins involved in breast cancer progression	Promising clinical trial results support repurposing	[21]
NSAIDs (Aspirin, Celecoxib)	Anti-inflammatory	Inhibits cyclooxygenase-2 (COX-2), reduces inflammation-driven tumor growth, modulates apoptotic pathways	Structure-based virtual screening identifies interactions with key cancer-associated proteins	Requires further experimental validation for optimal dosing and safety	[22]

that is, angiogenesis inhibitors and immunomodulators, might also be excellent repurposed treatments. With these, modifications can be made to tumor-stroma interactions, drug-delivery improvement by alteration of interaction conditions, and enhancement of any existing treatment in combination strategies[17].

Computational Tools and Databases for Virtual Screening in Drug Repurposing

Integrating heterogeneous computational tools revolutionized drug repurposing by enabling rapid screening and validation of future candidates. Molecular docking software under p, such as Schrödinger Glide and GOLD, that possesses high advanced scoring functions are employed for the assessment of binding affinities and prediction toward the safest ligand-target interactives. These will allow one to run through initial stages of virtual screening and select researchers with compounds, potentially and maximally effective.

Molecular dynamics simulation is the other major refinement for docking results in judging the conformation stability and flexibility of drug-protein complexes at physiological conditions. Simulation platforms like AMBER and CHARMM provide the data regarding the dynamic molecular behavior and hydrogen bonding interactions and binding free energies, thus certifying the candidate drugs are stabilized when interacting with the breast cancer targets[18]. This boosts the selection's accuracy while minimizing false positives in virtual screening.[19]

Recent Advances and Case Studies in Structure-Based Drug Repurposing for Breast Cancer

Recent breakthroughs in drug repurposing have demonstrated the effectiveness of existing FDA-approved drugs in targeting breast cancer-specific pathways as provided in table 1.

Challenges and Future Outlook of Structure-Based Drug Repurposing for Breast Cancer

Though advantageous, SBVS must contend with inherent challenges that must be resolved if clinical translatability is to occur. One prime obstacle is computational prediction accuracy and reliability. Although docking studies and molecular dynamics offer insight into predicted target interactions, these need to be counter-validated through some experimental systems *in vitro* and *in vivo*. Many promising hits obtained through virtual screening ultimately failed to show any meaningful biological activities that could support their proposed use, which necessitates further experimental evaluation before any serious consideration of moving forward in the clinic[23].

There are some significant hurdles posed by regulations to drug repurposing. Even though the repurposed drugs have an established safety profile, the regulatory approval of new indications would involve extensive preclinical and clinical studies. The high cost of these trials, particularly in view of the limitations of extending intellectual property rights, discourages pharmaceutical companies from entering into repurposing initiatives in the first place. Policy changes and a collaborative effort from academic, industry, and regulatory paradigms could help ease the approval pathway and promote innovations in this area[24].

In the future, the practical orientation of SBVS-driven drug repurposing will be in merging multi-targeting and personalized medicine concepts. AI-driven predictive models can be used to identify drugs that simultaneously target multiple oncogenic pathways, thus increasing therapeutic efficacy from this other perspective. In addition, genomic and proteomic profiling will enable the design of patient-specific drug repurposing strategies resulting in precise and effective treatment regimens. Interdisciplinary cooperation, such as cross-field research, will undergird the actual research to overcoming the challenges present and conversion of computational findings into clinically applicable therapies[25].

CONCLUSION

SBVS techniques in drug repurposing bring forth a much-needed paradigm shift in breast cancer therapy, presenting a cost-effective and time-saving alternative to conventional drug development. Using computational tools, researchers can rapidly screen FDA-approved drugs that may have anticancer activity, thereby speeding the development of innovative therapy strategies. Nevertheless, SBVS holds promise but faces a number of challenges, including limited experimental validation, regulatory hurdles, and intellectual property issues. Solving these barriers needs a

multidisciplinary effort combining computational modeling with laboratory experimentation and clinical trials. Collaborative engagement among researchers, clinicians, and policymakers would foster innovation and speed up the drug repurposing process.

Looking ahead, the integration of AI, machine learning, and personalized medicine will improve the efficiency and accuracy of drug repurposing by SBVS. As technology continues to advance methods for predictive modeling and data analysis, the road for repurpose drugs within the breast cancer domain appears bright. If sustained, SBVS can catalyze a change in oncology for the identification of viable and affordable treatments for patients around the globe.

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