

QSAR Based Drug Repurposing: A New Paradigm in Breast Cancer Research

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ABSTRACT

Breast carcinoma is the world's most prevalent type of cancer. The building of predictive cytotoxicity breast cancer models assists permanent synthetic activities and give critical information about structure-activity of novel structure design through a quantitative Structure-Activity Relationship (QSAR) modelling application. Quantitative Structure-Activity Relationships (QSAR) present a model that links pharmacological and biological activities to chemical structures and molecular docking research reveals the medication's interaction with its targeted enzymes. This review is dedicated for the detailed study of models for designing highly effective breast anticancer MCF7 cells. The Per-ARNT-SIM transcription factor family includes the Aryl hydrocarbon Receptor (AhR), which is a member recognized as a viable novel aim for the cure of breast cancer. The development of a series of 2-phenylacrylonitriles that target AhR has showed enticing and discerning efficacy against malignancy cells while preserving healthy and non-cancerous cell lines. This study aims to use estimating techniques such molecular docking studies, Quantitative Structure-Activity Relationship (QSAR) and QSAR model parameters to more advanced design new effective molecules and analyse the pharmacokinetics "drug-likeness" assets of the new compounds before they could progress to pre-clinical trial. These investigations also showed that derivatives of 2-(4-fluorophenyl) imidazole-5-one were more potent anti-cancer therapeutic candidates against the MCF-7 cell line. This exemplifies a remarkable medical breakthrough in the fight against breast cancer (MCF-7 cell line).

Keywords: Breast carcinoma, MCF-7 cell line, 2-phenylacrylonitriles, QSAR, Model development, Drug design, Anti-cancer.

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Received: 06-01-2023;

Revised: 19-01-2024;

Accepted: 22-05-2024.

INTRODUCTION

As an essential area of chemo metrics, Quantitative Structure-Activity Relationship (QSAR) performs an essential role in the recognition of novel drugs. Theoretically the activities of freshly introduced chemical entities might be anticipated by the improved tooling of QSAR prior to their production beforehand. The prime focus of the QSAR studies with respect to novel series of chemicals is their specific biological activities and several physico-chemically measured and computed properties.¹ The study depends on molecular descriptors for the effective quantification of structural properties. QSAR presents a paradigm that links pharmacological biological actions to chemical structures, with molecular docking research revealing the interaction between the drug and its target enzyme.² Molecular docking is a method for determining the binding strength between the active site residue and the ligand in this method for creating

novel pharmaceuticals using a ligand-based approach. QSAR uses structural information from chemicals to predict biological activity like toxicity, inhibitory action and carcinogenicity.³ A schematic overview of the molecular screening has been depicted in (Figure 1). The pharmacological, toxicological and environmental activity of a group of substances can be linked to the molecular descriptors using stochastic approaches. Many qualities such as topological properties involving polar surface area, molar mass, geometric attributes and quantum chemistry including electronic properties can be better describe by these numerical descriptors. The QSAR model's physical interpretation has been providing distinct insights on the SAR, assisting in the identification of structural properties related to the compounds which convey activity and could have been used in structural design. The capacity to anticipate the activity of many potential candidates for planned synthesis, or virtual screening of many databases for potential leads, is also provided by such a model, as computer resources are sparse and virtual screening costs far less than physical screening.⁴ Basically, QSAR uses a variety of structural descriptors to link them to the specific activity of compounds, which in this case is inhibitory activity, through the establishment of a reliable relationship. Descriptors were



DOI: 10.5530/ijper.58.3.78

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calculated using Dragon and Chemo bio-office software. Dragon has the most calculated descriptors since it includes a wide range of descriptors such as topological, quantum, electrostatic and so on. It has been established that the number of independent variables in every QSAR model exceeds compound numbers.⁵

The occurrence of breast cancer is most prominent in women among the different types of cancers and it is the second in number culprit to take women lives. The bulk of deaths are caused by metastatic spread to distant locations. It has been observed the significant upsurge in cases related to breast carcinoma which is until now considered as the first line cause women fatality. In spite of the progress made in controlling breast cancer, the search for a cure is still ongoing because the tumor usually develops resistant to treatment after a short period of time.⁶

Breast cancer claimed the lives of approximately 40,610 women in 2016, with an additional 252,710 diagnoses expected in 2017. Breast cancer accounts for around 24% of all cancer forms in women. Breast cancer patients are likely to share characteristics i.e. lack of prolonged breast feeding, progressing age, lack of activity, overdue age at first birth, weight gain and so on. Progesterone receptor (PR)\Estrogen receptor (ER) the positive form of breast cancer caused by estrogen receptor (ER) overexpression is a Luminal kind of breast cancer. About 70% of ER-positive (ER+) mammary tumor patients are included in this group. The endless stimulation of ER by estrogens causes cancer cells to multiply, MCF-7 cell line. High cytotoxicity and drug resistance are major difficulties in breast cancer treatment and no clinically effective compounds are known to target tumour cells specifically.⁷

Breast cancer is controlled by a number of mechanisms involving multiple enzymes. COX-2, an enzyme involved in the creation of prostaglandins linked to breast cancer formation, was discovered to be overexpressed in MCF-7 breast cancer cells. A highly effective treatment target for breast cancer is the Aryl hydrocarbon Receptor (AhR). The fundamental helix-loop-helix Per-ARNT-SIM family, which has long been associated with xenobiotic ligand metabolism, includes the transcription factor AhR. Exogenous and endogenous AhR ligands are either Halogenated Aromatic Hydrocarbons (HAH) or polyromantic hydrocarbons,

depending on whether they are agonistic or antagonistic (PAH). The kind of breast cancer, staging and technique of discovery all have an impact on the treatment plan and predicted outcome of breast cancer. Previously, the condition was mostly treated in clinics with surgery or chemo radiotherapy, but the results were disappointing. Targeted therapy is a type of treatment in which medications are utilized to act directly on tumour cells that have been identified.⁸ Targeted therapy has become very popular because to its precision, low toxicity and high efficiency. Targeted medications, on the other hand, have some flaws, including resistance produced by molecular target mutations, a long development cycle and a high drug development cost. The therapeutic potential of ER has been used in the cure of breast cancer. Fulvestrant is a drug that is used to treat postmenopausal women with ER positive breast cancer. However, due to its poor pharmaceutical properties, fulvestrant is only available as an intramuscular injection. Triple Negative Breast Cancers (TNBC) are highly aggressive breast tumors that lack the PR, ER and HER2 (Human epidermal growth factor receptor 2). Only 20% of TNBC responds favorably to traditional chemotherapy, which includes anthracycline-based (doxorubicin with cyclophosphamide) or paclitaxel treatment, among other options. As a result, improving treatment for metastatic TNBC is one of the top goals in modern breast cancer research. Several studies have been conducted to determine the sensitivity of metastatic TNBC cells to plant-based chemical scaffolds. TNBC prognosis research has recently focused on PARP1, mTOR, TGF- from Notch signaling, Wnt/catenin and Hedgehog pathways.⁹

The rate of breast cancer recurrences has risen and it has now become one of the world's most pressing worries. Regardless of the progress made in controlling breast cancer, the quest for a cure is still ongoing because the tumor usually develops resistant to treatment after a short period of time (Table 1). Despite the fact that a number of pivotal research and clinical trials have considerably improved treatment outcomes, the majority of practitioners are still unaware of many cancer instances and pathways. The anti-proliferative properties of various novel Parviflorons derivatives against the MCF-7 cell line were recently described in a study. To complement the other structural design

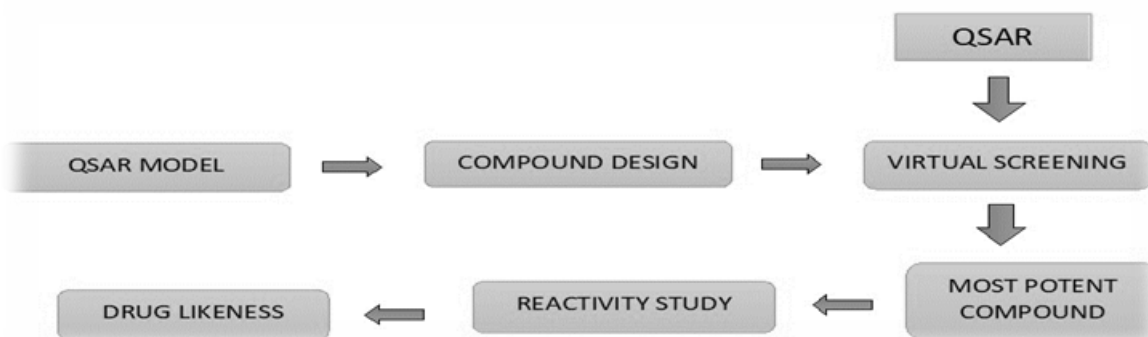


Figure 1: Overview activity of QSAR model for screening of drug molecule.

Table 1: A list of breast cancer treatments with clinical approval.

Chemical name	Commercial name	Category	Type of breast cancer	Molecular mechanism
Ado-transtuzumab-Emstansine	Kadcyla	Targeted therapy.	HER2+, early stage.	Reduces cell growth.
Abemaciclib	Verzenio	CDK4/6 inhibitor.	ER+, PR+, HER2-, advanced and metastatic.	Controls cell division.
Atezolizumab	Tecentriq	Immune checkpoint inhibitor.	TNBC, PD-1+, Advanced stage.	Elevates anti-tumour immuno response.
Anastrozole	Arimidex	Aromatase inhibitor.	ER+, PR+	---
Bevacizumab	Avastin	Targeted therapy.	HER2-	Anti-angiogenic
Carboplatin	Paraplatin	Platinum based.	Advanced stage	Damages genetic material
Darbepoetin alfa	Aranesp	Erythropoiesis stimulating agent.	To treat anemia caused by chemotherapy	-----
Docetaxel	Taxotere	Taxane	Early and advanced stages.	Interferes with cell division.
Eribulin	Halaven	Microtubule inhibitor	Advanced stages.	Disrupt cell division.
Fluorouracil	Adrucil	Antimetabolite	Early and advanced stages.	False nucleotide incorporation.
Leucovorin	Folinic acid, Wellcovorin, Citrovorum factor.	Folic acid (B9 Vitamin).	Combination	Protects healthy cells
Paclitaxel	Taxol	Taxane	Early and advanced stages	Interferes with cell division
Tamoxifen	Nolvadex, Tamofen, Tamone, Soltamox	SERM	ER+, PR+, Advanced stage.	Binds to estrogen receptor.
Zoledronic acid	Zometa	Bisphosphonate	Combination	Limits osteoclast activity.

and data analysis methodologies utilized previously, we opted to integrate a different modelling feature in this work. Developments of QSAR approaches are basically due to the inherent properties of modelling methods and phenotypical attributes of a biological activity. The QSAR model's physical interpretation can offer a fresh viewpoint on the SAR, assisting in the identification of structural properties of chemical entities that activity and can be used to build structures. A model like this can also anticipate the activities of a large number of candidates' quickly.¹⁰

QSAR-based approaches

Molecular docking

Molecular docking is a technique for forecasting the chemical compounds' likely receptor-binding conformations. The goal of this research was to determine interactions between the compounds under study and the active site residues of the selected protein, as well as to compare their affinities and select the best conformer based on lowest docked energy. Molecular docking studies are usually carried out in one of three modes: automated, ligand, or residual. In the Automatic mode, docking

is normally done in the protein's biggest binding cavity. The ligand-based approach was chosen for this study, in which an active co-crystallized ligand of mTOR protein (4JT6) was isolated and a protocol was produced, which served as a binding pocket.¹¹

QSAR Modelling

When there are many descriptors in a QSAR model, a useful method called the Genetic Algorithm (GA) can be used to remove irrelevant descriptors. As a technological method, GA treats various descriptors as genes and uses natural evolution to filter various variables. The best descriptors for all categories were produced using this feature selection method and QSAR models were built using MLR and LS-SVM. To determine the best-validated model, it is required to examine the models and have specific criteria. Leave-one-out cross validation was introduced as a strong validation method. The number of independent variables in the QSAR model is more than the number of compound numbers; there may be correlations between distinct descriptors. These correlations can cause QSAR models to have a lot of mistakes. To discover the appropriate descriptors to create the model, it is vital to remove unneeded and useless descriptors.

Some descriptors had the same value or were too near together to be useful, thus they were eliminated. Descriptors having a strong correlation with one another were separated and those with a high correlation with inhibitory activity were acceptable to keep as helpful descriptors.¹²

QSAR-Based Approaches for Breast Cancer

Recent research has demonstrated that new imidazole compounds coupled to the chalon moiety have potent anti-breast cancer effects against the MCF-7 cell line. In natural and manmade compounds, Imidazole and its derivatives play an important role. The unique molecules have a lot of electrons, which allows them to attach to a lot of different enzymes and receptors, giving them a lot of anti-proliferative activity. Compounds containing the imidazole moiety have been explicitly reported as having anticancer, antibacterial, angiotensin II receptor antagonistic action and cardio-activity. Chemotherapy is still one of the most effective and swift clinical therapies, but it is frequently constrained by side effects such as nausea, weight loss, weariness and anorexia, making it crucial to develop more effective medication options with reduced toxicity. The computer-aided drug design method, which also saves time, will result in a pharmaceutical candidate that is more effective. This research will be concentrated on the discovery of novel imidazole derivatives through the development of a mathematical model (QSAR) that forecasts anti-proliferative properties from its chemical entity and the use of the plk1 receptor with the associated derivatives to comprehend their interactions through molecular docking studies toward the development of anti-breast cancer drugs, with a focus on less toxicity and more effectiveness.¹³

Depending on the type of cancer, treatment may include surgery to remove the tumor, radiation and chemotherapy, either alone or in combination. Chemotherapy anticancer medicines function systemically and have anti-proliferative properties, destroying cells as they divide. Ant metabolic agents, alkylating agent, mitotic inhibitors, hormones and DNA complexing agents are all ant metabolic agents that interfere with cell repair, cell division,

DNA replication and translation. Anticancer medicines' lack of selectivity causes considerable damage in growing non-cancer cells. This toxicity and the resistant traits that tumors exhibit are the fundamental challenges in chemotherapy. In recent studies, it was identified that several compounds that produced erroneous cytotoxicity results in the conventional MTT experiment. By identifying substances with abnormal biological behaviour, the model reported in this study not only predicts compound activity in the MCF-7 breast cancer cell line but also identifies structures that caused false positive MTT assay results. By permitting the *in vitro* design of future breast cancer cytotoxic activity and enabling the avoidance of the synthesis of compounds that are anticipated to exhibit unsatisfactory cytotoxic behaviour, this work considerably improves the design of such compounds. When there are many descriptors in QSAR modelling, a useful method called Genetic Algorithm (GA) can be used to reduce superfluous descriptors. As a technological method, GA treats various descriptors as genes and uses natural evolution to filter various variables. The best descriptors for all categories were produced using this feature selection method and QSAR models were built using MLR and LS-SVM. To determine the best-validated model, it is required to examine the models and have specific criteria. Leave-one-out cross validation was introduced as a strong validation method (Figure 2).¹⁴

Overview of Metabolic Programming in Breast carcinoma

Breast carcinoma is the most abundant malignant tumour in females and stand second in causing death due to cancer worldwide. Although breast carcinoma is no longer the most common primary tumour, it is the sole cause for nearly 90% of cancer-related deaths. In a SEER-based investigation, it was discovered that among with metastatic breast cancer patient's metastasis is found, 21-32% in the lung, 30-60% in the bone, 4-10% in the brain and 15-32% in the liver. Additionally, it appears that the pathological subtypes of primary breast tumours influence the targeted metastatic web sites.¹⁵

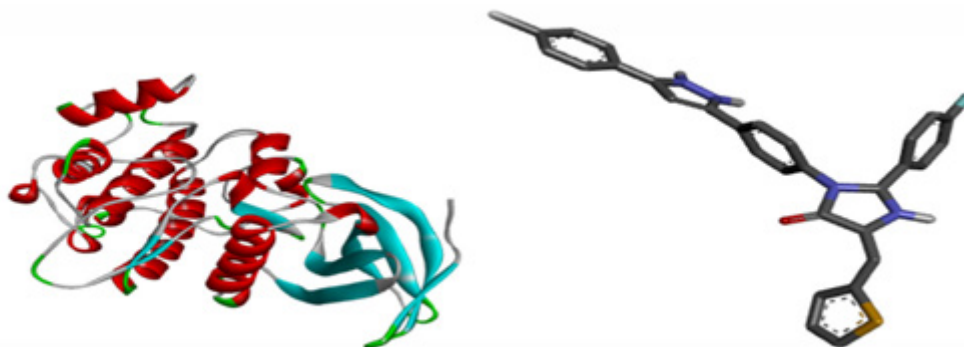


Figure 2: 3D diagram of prepared ligand and receptor.

Amino Acid Metabolism

Glutamate and its metabolic intermediaries, which include the antioxidants Glutathione (GSH), Nicotinamide Dinucleotide (NADH) and adenine assist cells in coping with oxidative stress and maintain cancer cell proliferation and development. Some cancer cells need exogenous glutamine to survive because they have a "glutamine addiction." More importantly, glutamine metabolic activity can be increased in cancer cells via the stimulation of glutamine transporters like enzymes and Alanine-Serine-Cysteine Transporter 2 (ASCT2) that convert glutamine to glutamate, including Glutamines (GLS)-1. For instance, in the presence of lactic acid, c-MYC stimulates the production of GLS-1 and, ASCT2 boosting glutamine absorption and breakdown in cancer cells. Specifically in Oestrogen Receptor (ER) deficient tumours, the Glutamate-to-Glutamine Ratio (GGR) of breast tumour tissues was higher than that of normal tissues, according to metabolomics research. Additionally, GGR stages were substantially correlated with ER deficiency and tumour grade. Because HER2-excellent breast cancer produces glutamate metabolism-related proteins such ASCT2, glutamate dehydrogenase (GDH) and GLS-1 significantly more than other subtypes, evidence implies that it has the highest glutamine metabolism activity (Table 2).¹⁶

Lipid Metabolism

The development and metastasis of breast cancer are also influenced by lipid metabolic programming and Fatty Acids (FAs). Because they may increase exogenous lipid and lipoprotein absorption as well as de novo cholesterol and lipid production, cancer cells can sustain a high rate of proliferation. They also have active lipid and cholesterol metabolisms. De novo synthesis of fatty acids is also necessary for cancer cells to support their accelerated growth and proliferation and to sustain their high

need for membrane metabolism (FAS). Fatty Acid Synthase (FASN), an important FAS enzyme, is expressed more frequently in breast cancer and is thought to be associated with cancer cell growth, recurrence and a poor prognosis in general. Patients with Triple Negative Breast Cancer (TNBC) tended to have more HER2 positive instances and had the lowest anatomical levels of acid synthase. FASN was discovered to be highest in HER2-positive breast cancer and lowest in TNBC at both the cellular and tissue levels. Breast cancer growth, metastasis and chemo resistance are thought to be aided by the "HER2-FASN axis," a two-way regulatory link between FASN and HER2. A lipogenic transcription factor called SREBP-1 interacts with the FASN promoter region to change the expression of FASN. Additionally, it is proposed that the signaling pathways PI3K, AKT, mTOR and mitogen-activated protein kinase regulate the expression of FASN (MAPK). As a result of the activation of AKT and SREBP-1 in breast cancer cells under hypoxic conditions, the FASN gene's expression is increased. It is possible to reduce FASN expression in breast cancer cells by blocking the MAPK pathway or with the mTOR inhibitor rapamycin (Table 3).^{17,18}

Glucose Metabolism

Glycolysis and Pentose Phosphate Pathway (PPP) are related metabolic routes in glucose metabolism, whereas serine and glycine metabolism is associated with glycolysis. Aerobic glycolysis, where glucose is first transported into the cells by glucose transporters and then transformed to pyruvate by a number of enzymes, is a pivotal stage in the glucose metabolism of cancer cells. Hexokinase II (HKII), pyruvate kinase and phosphofructokinase are the three major enzymes in this process (PK). The glycolysis-produced pyruvates are converted by the enzyme's pyruvate dehydrogenase and pyruvate carboxylase into Acetyl-CoA and oxaloacetate, respectively,

Table 2: Drugs that are being developed at various stages as amino acid metabolic treatments in breast cancer.

Target Protein and Pathway	Drug	Type	Indications
Glutaminase	CB-839	Phase I/Phase II	Advanced solid tumors/ advanced TNBC.
Indoleamine 2,3 dioxygenase (IDO1)	Indoximod	Phase I/Phase II	Metastatic breast cancer.
	Epacadostat	Phase I/Phase II	TNBC and other selected cancers.
Arginine deiminase (ADI)	ADI-PEG20	Phase I	Her2- metastatic breast cancer.

Table 3: Drugs that are being developed at various stages as lipid metabolic treatments for breast cancer.

Target Protein and Pathway	Drug	Type	Indication
FASN	TVB-2640	Phase II	Her2+ metastatic breast cancer resistant to trastuzumab and taxanes.
	Omeprazole	Phase II	Triple-negative breast cancer.
	Conjugated Linoleic Acid (CLA)	Phase I	Metastatic breast cancer.

in the mitochondria. From there, they enter the TCA cycle for Oxidative Phosphorylation (OXPHOS).¹⁹

3-Phosphoglycerate (3PG), one of the intermediary metabolites created during glycolysis, is the first stage of the serine route. Phosphoglycerate Dehydrogenase (PHGDH) converts 3-Phosphoglycerate (3PG) to 3-Phosphohydroxypyruvate (pPYR), whereas phosphoserine aminotransferase transaminases pPYR to phosphoserine (pSER)(PSAT). From phosphorylated pSER, serine is produced by phosphoserine phosphatase. The Glycine Decarboxylase (GLDC), a crucial part of the glycine cleavage system, transforms glycine during the glycine metabolism into H-Protein-S-aminomethyl dihydrolipoylysine. The enzyme serine hydroxymethyltransferase establishes a reversible connection between Serine and glycine Metabolism (SHMT). By producing Nicotinamide Adenine Dinucleotide Phosphate (NADPH) for the synthesis of fatty acids and pentose phosphate for the synthesis of nucleic acids, it plays a key role in the survival and proliferation of cells. The oxidative and non-oxidative branches are its two subtypes. The oxidative branch generates Glyceraldehyde 3-Phosphate (G3P), sedoheptulose and fructose 6-phosphate in contrast to the non-oxidative branch, which generates ribulose-5-phosphate, CO₂ and NADPH (F6P). The production of Ribose-5-Phosphate (R5P), which is necessary for the synthesis of nucleic acids and amino acids, depends on these glycolytic intermediates. Trans Aldolase (TALDO), transketolase, Ribulose-5-Phosphate Epimerase (RPE) and Ribose 5-Phosphate Isomerase (RPI) mediate the non-oxidative branch, while 6-phosphogluconate dehydrogenase and Glucose 6-Phosphate Dehydrogenase (G6PD) mediate the oxidative branch (TKT) (Table 4).²⁰

Physiology

Like any other malignancies, breast cancer is brought on by a host who is it susceptible genetically and to an external (environmental) factor. Normal cells divide as often as necessary before ceasing to do so. They stay in tissues and adhere to other cells. Malignant

cells are those that have lost the capacity to control their division, adhere to neighboring cells, maintain their position and pass away when it is time.²¹

Healthy cells self-destruct when they are no longer required (programmed cell death). Up to that time, protein clusters and signaling pathways guard cells against programmed death. The RAS/MEK/ERK pathway and the PI3K/AKT pathway are two of the protective pathways. When a cell is no longer needed, it cannot naturally expire. These kinds of protective pathways that stop cancer when the genes in them are changed in a way that keeps them permanently "active" when paired with other mutations. The PI3K/AKT pathway is typically blocked by PTEN to prepare cells for programmed cell death. Some breast tumours with mutated PTEN protein genes maintain the PI3K/AKT pathway, which prevents the cancer cell from committing suicide. Estrogens exposure has been linked in studies to mutations that can cause breast cancer. Breast cancer and other diseases of the female reproductive system have also been connected to G-protein coupled estrogen receptors. By altering growth factor signaling at the stromal-epithelial cell interface, malignant cell proliferation can be facilitated. The overexpressed leptin presents in the adipose tissues of the breast promote which leads to cell proliferation and malignancy.²²

Normal cells will self-destruct when no longer needed (programmed cell death). Numerous protein clusters and pathways protect cells against programmed death up until that point. Two of the protective pathways are the RAS/MEK/ERK pathway and the PI3K/AKT pathway. Occasionally, the genes responsible for these defence mechanisms are altered in a way that permanently "turns" them "on," preventing the cell from destroying itself when it is no longer required. This is one of the processes that lead to cancer when paired with other mutations. The PI3K/AKT pathway is frequently blocked by the PTEN protein when the cell is getting ready for programmed cell death. Some breast tumours have mutated PTEN protein genes, which results in the PI3K/AKT pathway being permanently activated.²³

Table 4: Drugs that are being developed at various stages as glucose metabolic treatments for breast cancer.

Target Protein and Pathway	Drug	Type	Indication
SGLT-2	Dapagliflozin	Retrospective/Observational	Incidence of breast and bladder cancer.
Hexokinase	2-deoxy-D-glucose (2DG)	Phase I	Breast cancer and advanced solid malignancies.
TCA Cycle and MRC			
PDK	Dichloroacetate	Phase II	Metastatic breast cancer or NSCLC.
PDH/KGDH	CPI-613	Phase II	Advanced solid tumors.
	ME-344	Early Phase I	Her2- metastatic breast cancer.
Complex I	Metformin	Phase I/Phase II/Phase III	All breast cancer

Oestrogen exposure has been linked in experimental investigations to mutations that can cause breast cancer. Furthermore, a number of cancers of the female reproductive system, including breast cancer, have been linked to G-protein coupled oestrogen receptors. Malignant cell growth may be aided by abnormal growth factor signaling at the stromal-epithelial cell contact. Leptin excess in breast adipose tissue promotes cell division and the development of cancerous cells.²⁴

A first- or second-degree relative who also has one of these diseases is present in 10-20% of American women with breast cancer or ovarian cancer. Male breast cancer risk is increasing. The tendency to acquire these tumours is referred to as the "hereditary breast-ovarian cancer syndrome." The BRCA mutations, the most well-known of these, raise the lifetime risk of breast cancer by 60-85% and ovarian cancer by 15-40%, respectively. Cancer is associated with some mutations in DNA repair systems, such as p53, BRCA1 and BRCA2. These mutations can be inherited or developed after birth in an individual. The evidence for residual risk variation across families with carriers, which extends much beyond heritable BRCA, is, nonetheless, overwhelmingly strong. This is due to unknown risk factors. This shows that several causes, including those related to the environment, may cause breast cancer. Hereditary mutations in the BRCA1 or BRCA2 genes may make it more difficult to repair DNA double strand breaks and cross linkages (known functions of the encoded protein). These substances can damage DNA, resulting in double strand breaks and DNA crosslinks, which are frequently repaired by BRCA1 and BRCA2 processes. However, BRCA gene mutations only account for 2 to 3% of all breast cancers. According to Levin *et al.*, not all people with BRCA1 and BRCA2 mutations will get cancer. Unknown genes are responsible for about 50% of hereditary breast-ovarian cancer illnesses. It's also possible that the BRCA1

gene expresses less by some latent viruses, increasing the risk of breast cancer (Figure 3).^{25,26}

Computational Pharmacokinetics (drug-likeness)

When creating and developing new medications, it is crucial to consider the prediction and pharmacokinetics of ADME (absorption, distribution, metabolism and excretion). Using online calculations from SwissADME (<http://www.swissadme.ch>), the drug-likeness and pharmaceutical characteristics. The drug-likeness prediction based on several principles, particularly Lipinski, Veber and Egan, has been examined for each candidate in order to determine a molecule's capacity for oral bioavailability. Number of Hydrogen Bond Donors (HBDs) ≤ 5 , Molecular Weight (MW) ≤ 500 , number of Hydrogen Bond Acceptors (HBAs) ≤ 10.6 and octanol/water partition coefficient (AlogP) ≤ 5 are often used parameters to determine if a molecule may be ingested orally or not. These ligands may be the most effective medication candidates to treat breast cancer, according to the ADME prediction. The projected values for skin permeability (LogKp) and water and intestine solubility (log mol/L, % absorbed) demonstrated efficient skin permeability in comparison to the usual value ($>30\%$ abs and -2.5 LogKp). Effective chemical absorption results in effective potency since the target molecule is passively penetrated.²⁷

Despite having excellent anti-proliferative capabilities, a molecule will not be permitted to go into pre-clinical research if it has weak drug-likeness and poor ADMET characteristics. For a molecule's drug-likeness to be determined, it must go through the pipeline of drug development and one of the primary streams is its ADME characteristics. A breakthrough in the treatment of triple-negative breast cancer has been made using parviflorons compounds. Many planned compounds fall short of becoming medicines.^{28,29} Ineffectiveness and systemic safety are the two main

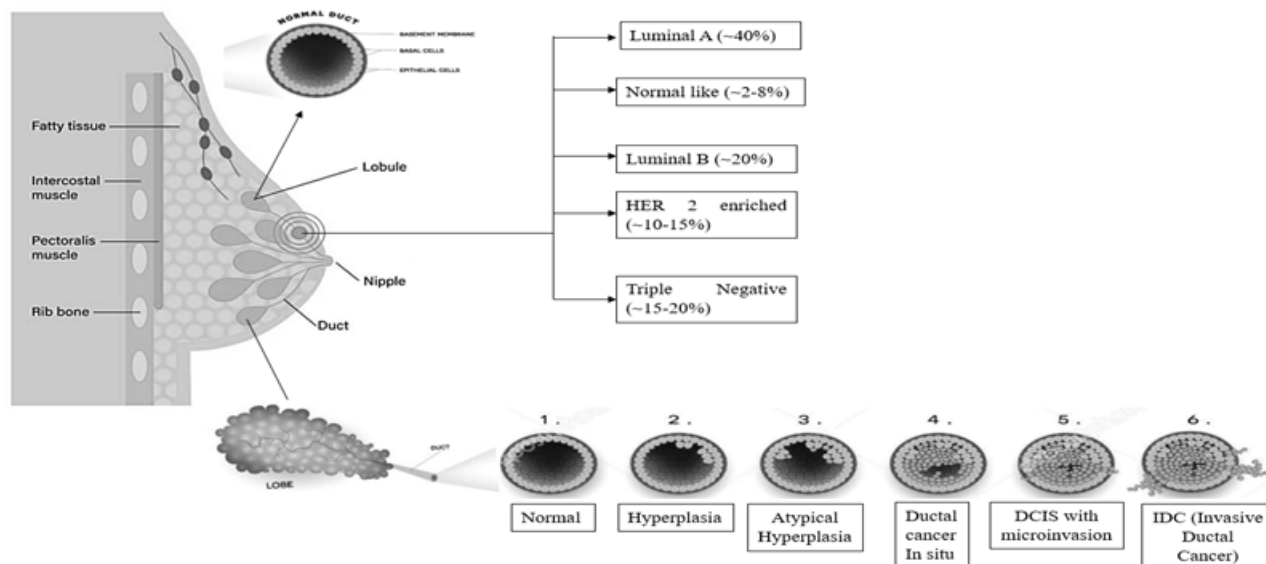


Figure 3: Overview about Breast carcinoma.

causes of therapeutic failure, which implies that a compound's properties of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) have a substantial influence on each step of the drug discovery process. Therefore, it is essential to find powerful molecules with useful ADMET characteristics. being present in biology Radar first scans the molecule for drug-like characteristics. The findings of a pharmacokinetic study on the newly developed Parvifloron compounds (ADME and other physicochemical parameters) showed that all of them passed the drug-likeness test. The ability of the compounds to move on to the next phase of a pre-clinical research shows a significant advancement in medicine's search for effective, long-lasting treatments for breast cancer (MCF-7 cell line). To determine which compounds, vary from the ideal parameters needed for drug similarity and anti-proliferative activity, the physicochemical properties of the title compounds have mostly been predicted based on theoretical methodologies. pKa, QPPCaco (Predicted apparent Caco-2 permeability in nm/sec), QPlogBB (Predicted brain/blood partition coefficient) and QPPMDCK (Predicted apparent MDCK cell permeability in nm/sec) are a few instances of descriptive terms. Additionally provided are the predicted octanol/water partition coefficient (QPlogP o/w), pKa, QPPCaco and polar surface area (PSA). A crucial molecular characteristic and element in the production of medications is lipophilicity.³⁰

However, there are potent and effective substances that exhibit anticancer activity while having a high molecular weight and low lipophilicity. Particularly, lipophilicity has a big impact on the anticancer activity. pKa is another essential and fundamental factor to consider while developing effective anticancer medications. A molecule's potential for many various properties, such as solubility, distribution, permeability, metabolism, excretion, protein binding, etc. are measured by a property called charge, or pKa. The pKa of the molecule and the biology of the tumor have an impact on the cellular uptake and retention of chemicals.³¹

Challenges

A worldwide problem that needs immediate action is breast cancer. Although there is a global concern, current projections indicate that in the coming decades, underprivileged populations will account for a large portion of breast cancer incidence and mortality. The healthcare systems of Low- and Middle-Income (LMIC) countries must deal with this difficulty given their constrained resources. In these circumstances, it is difficult to diagnose the disease at an earlier stage, which results in worse outcomes from late diagnosis and identifies considerable discrepancies in stage at presentation. Additionally, there is a dearth of basic radiation, surgery and systemic care, all of which have an effect on how well a patient respond to treatment. Because only a small fraction of their budget is designated for healthcare, LMICs must maximize their resources by focusing on cost-effective solutions that can yield the best results. A healthier,

more educated and, most crucially, more productive society that benefits future generations results from investments in women's health. A collaborative effort including all stakeholders should be sparked by addressing disparities in order to develop context-adapted solutions to improve healthcare outcomes.³²

Women frequently feel terrible if they do develop breast cancer since there is so much emphasis on educating them about lifestyle modifications that can have a negligible effect on preventing it. Even though the majority of breast cancer cases are caused by uncontrollable factors, such as genetics or naturally occurring background radiation, some women decide that their own cancer was caused by a poor diet, a lack of exercise, or another aspect of their lifestyle that could have been changed. Adopting such a notion might provide them a stronger feeling of self-control. Unintentionally, greater awareness leads to more victim blame. Women who reject breast self-examination or screening mammography are subjected to peer pressure, scare tactics, guilt and threats from certain doctors to end the patient relationship. Similar to the emphasis on early detection, many women mistakenly hold themselves responsible for their cancer's late detection.³³

The activities, mindsets and values that surround and influence breast cancer in the public are collectively known as the "pink ribbon culture" or "breast cancer culture".³⁴ The guiding principles are optimism, cheerfulness, solidarity and selflessness. It is in favor of doctors, drugs and mammograms. Health care providers are sources of information, but women with breast cancer should not seriously challenge the validity of their advice. Patients are not urged to inquire about the funding of research or the status of efforts to find a "cure" by the research community. By selecting it she-oes based on the level of suffering they have endured, the pink ribbon culture transforms breast cancer into a rite of passage rather than a sickness, making women whose treatments are less painful or incapacitating feel alienated and worthless. Initiating women into the inner circle of breast cancer culture, the suffering, especially the prolonged agony of months of chemotherapy and radiation treatment, takes the form of a metaphorical experience or rite of passage. Although there is a global concern, current projections indicate that in the coming decades, underprivileged populations will account for a large portion of breast cancer incidence and mortality.³⁵

Advance Research

Although ER-targeted therapy has lately been utilized to treat breast cancer that has already been diagnosed, whether it is adjuvant or has progressed to other parts of the body, its main application has been the treatment of this disease. Tens of thousands of women took part in big, international chemoprevention trials that produced level 1 evidence of benefit for two SERMS (raloxifene and tamoxifen) and growing evidence of benefit for two AIs.³⁶

Tamoxifen (vs placebo) was taken for 5 to 8 years and four randomized trials including over 23,000 pre- and postmenopausal women in North America and Europe indicated that it had favorable preventive effects. Tamoxifen has been demonstrated to reduce the risk of breast cancer by around one-third, with research indicating a 10-year reduction in risk. Both invasive and non-invasive breast cancer are similarly impacted by the benefits, which are only noticeable in the risk of ER-positive breast cancer, which is decreased by half. Despite the large relative risk decrease, the absolute advantages are very small (2-4% in the research groups) and they are accompanied by a higher risk of endometrial cancer, thromboembolic events, cataracts and hot flashes. With the exception of the most disadvantaged women, the net benefit is consequently insignificant. As a result, many medical professionals are hesitant to recommend tamoxifen to most women who would benefit from it and many women are hesitant as well.^{37,38}

The effect of an AI (exemestane, anastrozole) against medication were examined in two recent trials. Invasive breast cancer risk was reduced by around half to two-thirds in both studies. These drugs' toxicities in the adjuvant setting were less severe than anticipated, with little to no effect on quality of life and no evidence of an elevated risk of fracture. Determining the relative advantages of these medications in comparison to tamoxifen is difficult because both trials used placebo as a comparison arm.^{39,40} However, because AIs have a favourable adverse effect profile in the preventative setting, they may be used more frequently. Tamoxifen is the only drug that has been shown to prevent breast cancer in premenopausal women. Raloxifene and the AIs are promising choices for postmenopausal women.⁴¹ In postmenopausal women, individual patient features (including prior hysterectomy) and preferences should drive agent selection; modelling benefits and hazards may help with this. Breast cancer prevention that is both effective and widely accepted is still elusive.^{42,43} Women who are healthy have a lower tolerance for toxicity, especially catastrophic events like cancer and thrombosis. Finding ways that are both successful and have a reasonable risk-benefit ratio will remain a challenge. The following prescription drugs were discovered utilizing computational drug techniques: Gefitinib, Erlotinib, Sorafenib, Lapatinib, Abiraterone and Crizotinib. Research on anticancer drugs has thus far advanced quickly, with new hopeful findings coming from computational and AI technologies.⁴⁴ The optimization of SR13668 using the PH4 design, which comes from Indole-3-Carbinol (I3C), is a good example. SR13668 demonstrated a powerful effect on a number of cancers throughout phase I. Recently, a Machine Learning (ML)-based technique developed by Rodrigues *et al.* using physicochemical and pharmacophore attributes successfully identified a potent 5-lipoxygenase inhibitor. With the advancement of AI, the design of anticancer medications *in silico* has made remarkable progress. Modern deep learning algorithms can offer novel molecules the desirable chemical features they need.^{45,46} Similar

to this, Jann *et al.* created the first variational auto encoder-based anti-cancer chemical generator and showed that the production of the molecule may be selective toward compounds with high expected inhibition to a particular malignancy. This suggests that models could be created to provide drug candidates with highly desirable efficacy (IC_{50}) against an interest target. By utilizing the bimolecular aspect of the disease to increase the possibility that a lead molecule will be found, this discovery could revolutionize the development of *in silico* cancer therapies shown in (Figure 4).^{47,48}

QSAR Descriptors

To recognize and comprehend the Structure-Activity Relationship, molecular characteristics and biological activity must be correlated (SAR). The most and least significant molecular descriptors for the anticancer activity may be taken into consideration in order to discover the optimal match. A variety of online tools can be used to calculate the molecular descriptors, including those that compute chemical descriptors like surface area, volume, charge and dipole moment as well as those that compute molecular property descriptors like lipophilicity.^{49,38} The Quantitative Structure-Action Relationship (QSAR) is a significant and well-known computer software for anticipating anticancer activity and establishing the relationship between molecular characteristics and biological activity. The Schrodinger Ligprep module was used to design the chemical structures of all the compounds in the title and the structures were all reduced in accordance with the procedure.⁵⁷ The Schrodinger's Qi prop module predicted molecular descriptors after ligand synthesis. To forecast the features of the compounds that are similar to those of drugs, Qi prop develops about 46 physically relevant descriptors.⁵⁸ The descriptor in the QSAR model with the highest weight was VsurfDW13, which was connected to hydrophilicity and hydrophobia as well as vsurfID3 and vsurfIW7, which reflected the compound's lowest hydrophilic energy. While vsurfID3's positive contribution was indicative of the opposite circumstance, vsurfDW13 and vsurfIW7's positive contributions showed that the compounds' hydrophilicity was advantageous to their activities.^{59,60}

Molecular Docking

Molecular docking simulations were done using the SurfLex-Dock module of Sibyl X 2.1 to look at the binding interactions and forecast the bioactive conformations of withanolide analogues.⁶¹ The crystal structure of α -tubulin (PDB code 4IHJ)³² was used as the ligands and the dataset of compounds was employed as a potential therapeutic target for treating cancer. The SurfLex-Dock scoring method was used to assess the potency of the interactions between the ligand and protein.⁶² This scoring algorithm incorporates energy components to take hydrophobicity, polarity, repulsiveness, entropy and solvation into account. Simulations were done using flexible ligands but rigid protein structures, with

Subtype	Overview	Standard care
<p>HR+: Luminal-A</p> <p>Luminal-B</p>	<p>This subtype is characterised by hormone receptor positivity and may account for up to 75% of breast cancer tumour cases. 50–60% of all breast cancers are Luminal A breast tumours, which are identified as ER+ and/or PR+, HER2-, and low Ki67 (14%). These tumours typically have a fair prognosis, a low histological grade, and little mitotic activity. ER+ and/or PR+/- (PR20% + Ki6714%) with HER2- as well as ER+ and/or PR+/- (any PR+ and any Ki67) and HER2+ are the definitions of luminal B tumours, which make up 15-20% of breast cancers. These tumours differ from Luminal A tumours in that they often have a more aggressive phenotype and a higher histological grade and proliferative index. In spite of the fact that Luminal B tumours react to neoadjuvant chemotherapy better, they typically have worse prognoses.</p>	<p>Having a response rate of only 50–60% to hormone-focused therapies, this patient group is sensitive. The two most frequently prescribed medications used as first-line therapies in clinical practise are aromatase inhibitors and tamoxifen (TMX, Novaldex®). The success of the treatment is, however, constrained by long-term toxicities as well as innate or acquired resistance to the medication.</p>
<p>HER2- Enriched</p>	<p>constitutively active, causing dysregulated cell proliferation and aggressive biology and clinical behaviour in 20–30% of breast tumours. They are classified as ER-, PR-, and HER2+ tumours.</p>	<p>HER2 extracellular domain monoclonal antibodies and small kinase inhibitors have been humanised. Patients with HER2-enriched breast cancer frequently experience acquired resistance to therapy.</p>
<p>Basal-Like</p>	<p>TNBC tumours are classified as ER-, PR-, HER2-, CK5/6+, and/or EGFR+, making for about 80% of basal-like tumours and 10-15% of breast carcinomas.</p>	<p>Despite limited efficacy and poor survival outcomes, chemotherapy is the current gold standard for advanced TNBC. Various targeted therapies are under development.</p>

Figure 4: Classification of breast cancer and recommended treatments.⁵⁰⁻⁵⁶

all docking parameters set to their default values. By measuring the hydrogen bond contacts, hydrogen bond length and hydrophobic interactions, docked molecules were graphically analyzed.^{63,64}

Targeting Strategies

Cell Targeted Therapy

Mesenchymal Stem Cells (MSCs) have become a potent therapeutic tool for BCSC targeting in cell targeted treatment for breast cancer. MSCs are specialized in tumor tissues, have a wide range of differentiation abilities and a low immunogenicity.⁶⁵ They are an essential part of the breast cancer microenvironment and can be influenced by a variety of stimuli to migrate to breast cancer locations. MSCs can prevent BCSCs from proliferating, block the development of EMT and reduce angiogenesis, which, in turn, has a profound inhibitory effect on the growth and spread of breast cancer, according to studies by Mandal *et al.* Due to their low immunogenicity and intrinsic anti-inflammatory properties, MSCs can also be used to load novel Nano-chemotherapy drugs in order to achieve the goal of targeted delivery to breast cancer cells.^{66,67}

The proliferation of CSCs can be controlled by long non-coding RNA (lncRNA) and microRNA (miRNA), which is essential for the treatment of HER2-negative breast cancer. Studies have shown that TNBC and BCSCs overexpress CCAT2.⁶⁸ It promotes the development and spread of breast cancer by raising OCT4-PG1 expression and activating the Notch signaling system. MiR-200c

expression levels have been found to be downregulated whereas miR-300c expression levels have been raised in metastatic breast cancer tissues, which may point to patient BCSC enrichment. Therefore, concentrating on lncRNA or miRNA could aid in the development of new BCSC treatments (Table 5).^{69,70}

Nano-Delivery Targeted Therapy

Recent research has shown that molecularly focused nanotechnology can be used to create BCSCs tailored medications with precise control over drug release. It has the potential to enhance medication growth and dissemination in breast cancer cells in addition to improving drug absorption by CSCs. The mechanism is to increase drug retention and prolonged release while decreasing the expression of Sox2 and ABCG2. Additionally, it can make breast cancer cells more responsive to medications when combined with taxanes.^{71,72}

Delivering anti-miRNA via RNA nanotechnology is a unique method of treating TNBC. The proliferation of TNBC cells can be significantly slowed down by these therapeutic RNA nanoparticles' binding to the CD133 receptor, which lowers the expression of miR21 and increases the expression of the tumor suppressor genes PTEN and PDCD4.⁷³

A novel and efficient way of drug delivery in order to treat breast cancer has been made possible by the development of nanotechnology. Combining drugs with currently available breast cancer treatments can increase drug efficacy and lessen adverse

Table 5: A list of repositioning medications authorised for the treatment of breast cancer.

Category	Chemical name	Commercial name
Alkylating agent	Cyclophosphamide	Cytoxan, Clafen, Neosar.
	Thiotepa	Thioplex, Tespa, Thiophosphoamide, TSPA, Tepadina.
Anthracyclins	Doxorubicin	Adriamycin, Caelyx, Rubex
	Capecitabine	Xeloda
	Fluorouracil	Adrucil, Carac
Antimetabolite	Gemcitabine	Gemzar
	Methotrexate	Mexate, Folex, Rheumatex
CDK 4/6 inhibitor	Palbociclib, Palbonix	Ibrance
	Tamoxifen	Nolvadex, Apo-Tamox, Tamifen, Soltamox
HT-SERM	Toremifene	Fareston
	Raloxifene	Evista
	Exemestane	Aromasin
	Letrozole	Femara
HT-SERD	Fulvestrant	Faslodex
HT-LHRH agent	Goserelin	Zoladex
mTOR inhibitor	Everolimus, Votubia, Evertor	Afinitor
	Docetaxel	Taxotere
	Paclitaxel	Taxol, Onxol
Mitotic inhibitor	Vinblastine	Velban, Velsar, Adria, Velbe.

effects, which is crucial for breast cancer diagnosis, treatment and prognosis.^{74,75}

Chemotherapy

Chemotherapy is frequently used in medical settings. However, nonspecific medication distribution, Multidrug Resistance (MDR) and the heterogeneity of disease make chemotherapy's therapeutic potential completely insufficient. As a result, combined therapy based on chemotherapy and nanotechnology is currently popular in clinical research.⁷⁶ This therapy can significantly boost therapeutic effectiveness while having few adverse effects on normal tissues. Nano-agnostic, which integrates diagnosis with the therapeutic process and permits precise pre-diagnosis and real-time tumor monitoring, is a promising area of cancer treatment research.^{77,78}

Gene Therapy

It is anticipated that gene therapy will be a useful therapeutic strategy for advanced breast cancer.⁷⁹ Four categories can be used to categories the strategies used in current clinical protocols: 1) transfer of tumour-suppressor genes or oncogene suppression; 2) strengthening of the immune system; 3) transfer of genes that cause suicide; and 4) use of drug resistance genes to safeguard bone marrow. Gene therapy for Multidrug Resistance (MDR) has started a clinical trial. Docetaxel was used to treat metastatic breast cancer in patients who had already had high-dose chemotherapy, autologous Peripheral Blood Stem Cell Transplantation (PBSCT) and MDR1-infected hematopoietic cells. So far, two people have received docetaxel treatment and had their MDR1-transduced cells enriched *in vivo*. Both patients received the MDR1 gene transfer and both are now completely remission-free.⁸⁰

CONCLUSION

There are multiple examples where the combined methods of molecular docking-based predictions and QSAR have demonstrated efficacy in the field of drug discovery and design, all of which have statistical support. Through QSAR research and pharmacokinetics analysis, parvifloron derivatives were found to be a more effective anti-breast cancer candidate against the MCF-7 cell line. According to statistical analysis the stastical approximation based mathematical model originated from QSAR studies refer an increase in the magnitude of MLFER BO, nX and GATS5e descriptors always results in simultaneous enhancement in the anti-proliferative activity of Parvifloron derivative. On the other hand, decreasing MATS3e value potentiate the proliferative activities and serve as a common anti-breast cancer agent. It is anticipated that additional two-phenylacrylonitriles will have an impact on the AhR transcription factor, which has been identified as a suitable target for the drug delivery aimed for futuristic breast cancer treatment regimens. The appropriately modelled cytotoxicity of several 2-phenylacrylonitriles and its derivatives against MCF-7 human breast cancer cells has been studied.

According to the results of this study, 2-(4-fluorophenyl)imidazole-5-one derivatives showed to be a more reliable anti-cancer therapy candidate against the MCF-7 cell line in a number of QSAR analyses, molecular docking evaluations and pharmacokinetics investigations. This is an example of an amazing medical advancement in the fight against breast cancer (MCF-7 cell line).

This review proposes to continue the investigation of QSAR based breast cancer research that to optimize the incorporation of various malignant cells, further clinical studies that to propose to considered patient compliance by scaling to mass production of drugs through QSAR studies and the challenges that has to be considered.

Finally, it can be said, that QSAR based breast cancer research has demonstrated various effective biomedical application in a great diversity and more come on its advancements.

ACKNOWLEDGEMENT

The authors are very much grateful to Prof. Monaj Ranjan Nayak, president, Siksha o Anusandhan for his inspiration and facilities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

QSAR: Quantitative structure-activity relationship; **PR:** Progesterone receptor; **ER:** Estrogen receptor; **AhR:** Aryl Hydrocarbon Receptor; **HER2:** Human epidermal growth factor receptor 2; **TNBC:** Triple negative breast cancers; **GA:** Genetic algorithm; **NADH:** Nicotinamide dinucleotide; **ASCT2:** Alanine-serine-cysteine transporter 2; **GDH:** Glutamate dehydrogenase; **MSCs:** Mesenchymal Stem Cells; **MDR1:** Multidrug resistance.

SUMMARY

Breast carcinoma is the world's most prevalent type of cancer. The building of predictive cytotoxicity breast cancer models assists permanent synthetic activities and give critical information about structure-activity of novel structure design through a Quantitative Structure-Activity Relationship (QSAR) modelling application. Quantitative Structure-Activity Relationships (QSAR) present a model that links pharmacological and biological activities to chemical structures and molecular docking research reveals the medication's interaction with its targeted enzymes. This review is dedicated for the detailed study of models for designing highly effective breast anticancer MCF7 cells. The Per-ARNT-SIM transcription factor family includes the Aryl Hydrocarbon Receptor (AhR), which is a member recognized as a viable novel aim for the cure of breast cancer. The development of a series of 2-phenylacrylonitriles that target AhR has showed enticing and discerning efficacy against malignancy cells while preserving healthy and non-cancerous cell lines. This study aims to use estimating techniques such molecular docking studies, Quantitative Structure-Activity Relationship (QSAR) and QSAR model parameters to more advanced design new effective molecules and analyse the pharmacokinetics "drug-likeness" assets of the new compounds before they could progress to pre-clinical trial. These investigations also showed that derivatives of 2-(4-fluorophenyl) imidazole-5-one were more potent anti-cancer therapeutic candidates against the MCF-7 cell line. This exemplifies a remarkable medical breakthrough in the fight against breast cancer (MCF-7 cell line).

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Cite this article: Mohapatra R, Panda P, Rout SS. Qsar Based Drug Repurposing: A New Paradigm in Breast Cancer Research. *Indian J of Pharmaceutical Education and Research.* 2024;58(3):695-708.