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IN SILICO MOLECULAR DOCKING OF RICE QUERCETIN AS A POTENTIAL ANTI-CANCER TARGET IN HER2 AND ER α -ASSOCIATED BREAST CANCER

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ABSTRACT

Breast cancer remains one of the most prevalent invasive cancers affecting women worldwide and is a leading cause of cancer-related deaths. The Estrogen Receptor alpha (ER α) and human epidermal growth factor receptor 2 (HER2) protein serves as a crucial therapeutic target in the treatment of this disease. In the current study, a virtual screening approach was employed to evaluate rice quercetin as a potential anti-cancer natural drug using molecular docking techniques. The basic molecular properties of quercetin, like MW (302.24 Dalton), HBA (=7), HBD (=5), TPSA (131.36 Å), and rotational bond (=1), suggest that it has more drug-like properties. Moreover, its human intestinal absorption is 77.20%, which indicates it has strong ADME properties. The docking analysis revealed that quercetin has strong binding affinities to ER α (-8.2 kcal/mol) and HER2 (-7.6 kcal/mol), along with an RMSD value of zero. Quercetin has high biological activities related to breast cancer, like HIF1A expression inhibitor has 0.96, CYP1A1 substrate/inducer/inhibitor has 0.94. Again, Quercetin interacted with the ER α receptor at several residues, including ASP 426 (bond length: 3.4 Å), PRO 399 (2.3 Å), ALA 430 (2.4 Å) and ARG 436 (2.5 Å) (Fig. 1c). Similarly, in HER2 protein at GLN 56 (2.4 Å), CYS 233 (2.3 Å), GLN 35 (2.5 Å), GLY 270 (2.2 Å), and ALA 271 (2.0 Å). These findings suggest that rice quercetin may play a significant role in the prevention and treatment of breast cancer through targeted HER2 inhibition.

Key words : Breast Cancer, Estrogen receptor, Human epidermal growth factor receptor 2, Quercetin.

Introduction

Cancer is counted among the most serious, life-threatening, non-communicable disease that brings profound disruption in the life of the diagnosed individual (Pandey *et al.*, 2024). One of the most prevalent malignancies is the breast cancer in case of women (Aizaz *et al.*, 2023). It contributes about 10% of all types of cancer globally and is the second leading reason for malignancies related mortality (Siegel *et al.*, 2023). It was divided into three major groups based on the presence or absence of hormone receptors. The first group includes

tumors, which are positive for either progesterone receptor (PR) or estrogen receptor (ER). The second group constitute tumors, show positive result for human epidermal growth factor receptor 2 (HER2), where ER and PR may or may not be positive. Whereas, the third group includes triple-negative breast cancer (TNBC), where ER, PR and HER2 show negative result (Goldhirsch *et al.*, 2013; Miziak *et al.*, 2023).

About 75% of breast cancer are found to be ER positive (Heo *et al.*, 2019). These estrogen receptors are activated by estrogens (estrone, estradiol, estriol and

estretol). They are synthesized in the rough endoplasmic reticulum and travel through blood stream, crossing biological membranes and getting attached to the nuclear ER (Patel *et al.*, 2018). These are of two types *i.e.*, 1. Nuclear ER, 2. G protein coupled estrogen receptor 1. Nuclear ER has two isoforms, namely, ER α and ER β (Arao *et al.*, 2021). Any alteration in the ER α expression can lead to develop tumors in ovary, uterus and breast epithelial cells (Liu *et al.*, 2020). Whereas, ER β inhibits the ER α and estradiol mediated gene expression and cell proliferation (Miziak *et al.*, 2023). Generally, the ratio between ER α to ER β regulate the activity of estrogen and breast cancer development in the women (Matthews *et al.*, 2006; Sotoca *et al.*, 2008). ER α regulates cell growth, division and differentiation through downstream signal transduction in presence of estrogens (Shanle *et al.*, 2010). So, ER α signaling pathway is the main therapeutic target for the treatment of breast cancer (Miziak *et al.*, 2023).

Human epidermal growth factor receptor 2 (HER2) is another important predictive biomarker for breast cancer. HER2-positive breast cancer is highly aggressive and can invade rapidly (Obeagu *et al.*, 2023). About 15-20% of cases are HER2 overexpressing type. The expression of HER2 vary between primary malignancy and metastasis (Niikura *et al.*, 2012). In severe cases, these may cause systemic and brain metastasis spreading all over the body (Exman *et al.*, 2021). It is a tyrosine-protein kinase receptor, encoded by ERBB2 gene, lacking in specific ligand and present in open configuration enables it to dimerize with HER1, HER3, and HER4 (Asif *et al.*, 2016). Further, it activates the signal transduction cascade involving PI3K/Akt and the Ras/Raf/MEK/MAPK pathway (Arteaga *et al.*, 2012). It is associated with rapid growth, proliferation, and differentiation of cells leading to the development of a tumor. Thus, dimerization of HER2 is the primary step for activation of the intracellular signaling cascade for the development of HER2-positive BC (Asif *et al.*, 2016) and down regulation of HER2 could block the development of BC. So, it makes HER2 as a potential therapeutic target.

With the ongoing technological advancement, many approaches have been developed for the treatment of cancer including chemotherapy, radiation therapy, immunotherapy, and surgery. However, phytotherapy has been surfaced as a potential alternative approach (Enioutina *et al.*, 2017). These days it is gaining the attention of many researchers. In phytotherapy, different bioactive plant products like Quercetin (3, 3', 4', 5, 7-pentahydroxy flavanone) and flavanone-type flavonoid (Nayak *et al.*, 2025) with anti-cancer properties can be

used as therapeutic agents (David *et al.*, 2016). These products commonly available in many fruits, vegetables, tea, wine, and cereal grains like rice (Ezzati *et al.*, 2020). Rice is a staple food for half of the global population (Mahapatra *et al.*, 2026; Mondal *et al.*, 2025) and a rich source of quercetin (Sen *et al.*, 2020). Rice embryo, endosperm, pericarp and aleurone layer contain approximately 24.5, 2.6, 31.4 and 31.2 $\mu\text{g g}^{-1}$ of quercetin, respectively, which is higher than other crops (Ti *et al.*, 2015). Quercetin is known to obstruct carcinogenesis at multiple stages by influencing multiple signal transduction pathways (Ezzati *et al.*, 2020). It also involves in scavenging different types of ROS and prevents oxidative cell damage (Biswas *et al.*, 2022). In addition to this, it induces the expression of P53 (tumor suppressor gene) which arrests cell cycle by modifying G1 and G2/M phase (Choi, 2008). The anti-proliferative role of Quercetin was also reported previously by studying the expression of P38MAPK (marker of cell proliferation) (Ranganathan *et al.*, 2015). It also prevents malignant type cell proliferation by inhibiting the shortening of telomeres (Tawani and Kumar, 2015).

The idea of using quercetin as an anticancer agent in breast cancer treatment needs deeper understanding and feasibility assessment (Wu *et al.*, 2025). Wet lab analysis can be a tedious, labor-intensive and resource-draining method to assess the therapeutic properties of quercetin compound (Passi *et al.*, 2025). Molecular docking can give authentic results within a limited period of time and resources (Cruz *et al.*, 2021). So, here we aim to get a detailed insight into the therapeutic potential of quercetin in breast cancer treatment using molecular docking method. It involves, studying of binding affinity, specificity, and stability assessment of quercetin with different targeted receptors such as ER α and HER2, which regulate breast cancer development.

Materials and Methods

The three-dimensional structure of these proteins were retrieved from Protein Data Bank (RCSB PDB) (<https://www.rcsb.org>). Specifically, two proteins were selected for this investigation: (i) Estrogen receptor alpha (ER α) (PDB ID: 3ERT (Shiau *et al.*, 1998), (ii) HER2 (PDB ID: 5K33 (Lobner *et al.*, 2017). Quercetin was selected as the ligand for this study due to its known anti-cancer properties. The SDF format of Quercetin retrieved from PubChem database (PubChem CID: 5280343) (Fig. 2b & 3b) converted to its Open Babel PDB format (O'Boyle *et al.*, 2011).

ADMET and Drug Likeness properties

The open-access online platforms pkCSM (<http://>

structure.bioc.cam.ac.uk/pkcs) and SwissADME (<http://www.swissadme.ch/index.php>) were employed to evaluate the ADMET properties and medicinal potential of the target compound, quercetin. A key consideration in the early stages of drug development is Lipinski's Rule of Five (Lipinski *et al.*, 2004), which helps in predicting a compound's oral bioavailability. According to this rule, a molecule is likely to have poor absorption or permeability if it violates more than two of the following parameters: (i) molecular weight (MW) should <500; (ii) Hydrogen bond donors (HBD) <5; Hydrogen bond acceptors (HBA) < 10; log P value <5 and polar surface area (PSA) should be within below range of 140 Å².

Pass Computer Program

The PASS (Prediction of Activity Spectra for Substances) software was used to predict quercetin's potential anti-cancer properties. It is a computational tool designed to assess the possible biological activities of phytochemical compounds. It provides predictions in the form of probable activity (Pa) and probable inactivity (Pi). A compound is considered likely to exhibit a specific pharmacological effect if its Pa value is greater than its Pi value.

Active Site prediction

Accurate identification of the active site is a crucial step in molecular docking. In this study, the active sites of the target proteins—Estrogen receptor alpha (ER α) (PDB ID: 3ERT (Shiau *et al.*, 1998) and HER2 (PDB ID: 5k33 (Lobner *et al.*, 2017).—were predicted using Biovia Drug Discovery Studio Visualizer 2020.

Molecular Docking

Protein-ligand docking analysis was carried out using AutoDockVina, a highly preferred tool for these studies. It involves eliminating water molecules, identifying the active site, and adding polar hydrogens with the help of BIOVIA Studio Visualizer. The inhibitor was then removed to accelerate the binding activity of the receptor to the active site of ligand. The 3D structure of the protein was purified using the BIOVIA Discovery Studio 2025 Client. In this purification process water is removed along with other ligands and cofactors. After that, AutoDockTools v1.2.7 add polar hydrogens along with Gasteiger charges and the receptor/protein was saved in a .pdbqt file. For preparing ligand, hydrogen was added along with Gasteiger charges. Then rotatable bonds were added for flexibility by adding a torsion tree to detect root and rotatable bonds. After that ligand was saved as .pdbqt file.

Subsequently, grid coordinates were determined based on the location of the co-crystallized inhibitor within the

receptor. In this study, we set the grid parameter for Estrogen receptor alpha (ER α) receptor for binding ligand poses 3D box (74 Å wide (X), 96 Å tall (Y) and 84 Å deep (Z), centered at coordinates (24.579, 6.538, 18.775)). Similarly, grid parameter for human epidermal growth factor receptor 2 (HER2) set as 126 Å for X, Y and Z axes; coordinates as (16.941, 41.129, 39.842) with spacing for 0.5 Å. Exhaustiveness for each docking procedure was set at 8 for accurate binding.

Results and Discussion

ADMET analysis

Proper concentration and distribution are obligatory for a molecule to become a drug. Its biological activity should persist long enough to make desired biological changes. The drug development process follows a stringent procedure like absorption, distribution, metabolism, excretion and toxicity (ADMET), in which many potential compounds' physical samples are unavailable. In this scenario, computational models serve as practical alternatives to laboratory experiments. For this, the SwissADME web tool was used. It provides reliable predictive models for assessing pharmacokinetics, drug-likeness, physicochemical properties and medicinal chemistry suitability. This tool uses advanced in-house techniques like iLOGP, Bioavailability Radar and BOILED-Egg.

Based on the ADME/T analysis (Andrade *et al.*, 2016) of Quercetin, the compound meets the criteria outlined by Lipinski's rule of five. Its molecular weight is 302.24 g/mol, well below the 500 Da threshold, which is essential for optimal absorption and bioavailability in the body. A potential drug should have a molecular weight should be <500 Dalton, as small molecules generally have better ADME properties (Hasan *et al.*, 2022). However, too large molecules may struggle with permeability and bioavailability. HBA (Hydrogen Bond Acceptors) and HBD (Hydrogen Bond Donors) should be in the range of ≤ 10 and ≤ 5 for better membrane permeability and oral bioavailability. In our ligand quercetin, HBA and HBD are 7 and 5, both within the acceptable range, suggesting strong binding affinity. Again, according to this rule, LogP (Partition Coefficient) should be in the range of 0–5, which measures the lipophilicity, which shows the partition of compound between water and lipid. Our ligand has logP 1.23, which falls within the ideal range (below 5), supporting efficient absorption. Molecules having high TPSA (Topological Polar Surface Area) can hinder a molecule's ability to cross cell membranes. Its value should be <140 Å². Interestingly quercetin has 131.36 Å². For good oral bioavailability rotational bond should

Table 1 : Basic Molecular Properties of Quercetin.

Parameter	MW	HBA	HBD	TPSA	Rotatable Bonds	LogP	Fraction Csp ³	Drug Likeness
Value	302.24	7	5	131.36 Å ²	1	1.23	0	Yes

Table 2 : Summary of ADMET Properties of ligand Quercetin.

Parameters	Absorption Intestinal (Human) Absorption	Distribution									Excretion Total Clearance	AMES Toxicity
		Log BB	LogPS	2D6	3A4	1A2	2C19	2C9	2D6	3A4		
Value	77.207	-1.098	-3.065	NO	NO	Yes	NO	NO	NO	NO	0.407	No

be in the range of ≤ 10 . Our ligand has rotational bond 1, which is good. Overall, Quercetin satisfies all the parameters of Lipinski's rule, including favorable absorption, distribution, metabolism, and excretion profiles, indicating good oral bioavailability (Chen *et al.*, 2020).

Moreover, toxicity evaluations showed that Quercetin is non-mutagenic and non-carcinogenic. Its acute oral toxicity falls within category II, with a rat acute toxicity value of 3.020, suggesting that its toxicity remains within acceptable limits based on computational studies. However, further clinical validation is necessary to comprehensively assess its safety profile. Overall, Quercetin demonstrates a promising balance of efficacy and safety compared to standard reference drugs.

Human absorption percentage refers to the predicted human intestinal absorption (HIA). It represents how well a compound is absorbed from the gastrointestinal tract after oral administration. Different range for absorption are presented here and those are high absorption: $> 70\%$; Moderate: $30\text{--}70\%$; Low: $< 30\%$ (Fagerholm, 2007). Quercetin has high absorption (77.2%) (Table 2), which is desirable for oral bioavailability. Similarly, Log BB (Blood-Brain Barrier Permeability) indicates the ability of a compound to cross the blood-brain barrier (BBB). Different ranges of BB represent the penetration ability. Log BB > 0.3 shows high brain penetration, the range between -1 and 0.3 shows moderate penetration and < -1 shows poor penetration (Kunwittaya *et al.*, 2013). Our ligand value (-1.098) (Table 2) indicates poor BBB penetration, which could be good or bad depending on the target. Here, metabolism (Cytochrome P450 Enzymes Inhibition) is mostly favorable, excretion value indicates the rate at which the drug is eliminated from the body and higher values show faster clearance (might reduce efficacy). 0.407 is moderate — not too fast or slow, but would need to be evaluated against dosing frequency and half-life. From this analysis, we found that Quercetin is non-mutagenic, which is very good for drug development

PASS predictions for Anti-Cancerous activity

Pa determines the probability, a compound exhibit

with a specific biological activity, and Pi determines the probability that a compound do not exhibit that activity. If $Pa > 0.7$, the compound is highly active for that property. The range between $0.5 < Pa < 0.7$ depicts a moderate chance of activity; potential for novelty (less well-known but promising) and $Pa < 0.5$, depicts low probability of activity means the result is less reliable but not impossible (Goel *et al.*, 2011).

In our study, Quercetin has high biological activities with $Pa > 0.7$ in HIF1A expression inhibitor(0.96, may reduce tumor growth); CYP1A1 substrate/inducer/inhibitor(0.94, relevant in estrogen metabolism and detox pathways); MAP kinase stimulant(0.93); AR expression inhibitor (0.887); CYP19 inhibitor(0.873); CYP1B1 inhibitor (0.872), NOS2 expression inhibitor(0.850); JAK2 expression inhibitor (0.787); Anticarcinogenic (0.757); MMP9 expression inhibitor (0.734) (Table 3). These activities show strong potential for anticancer properties. Biological activities having Pa value moderated are RELA expression inhibitor (0.695); Antineoplastic (breast cancer, 0.577); Estrogen antagonist (0.549); Estrogen receptor beta antagonist (0.546).

HIF1A expression inhibitor functions in a hypoxic condition by limiting the catalytic functions of PHD (prolyl hydroxylase), FIH and restraining HIF-1 α hydroxylation and degradation, thereby activating the HIF pathway (Strowitzki *et al.*, 2019). Subsequently, HIF-1 α is involved in angiogenesis, glucose metabolism, cancer cell invasion and metastasis, and immune escape by regulating the expression of target genes (Zhi *et al.*, 2024). Quercetin suppressed the HIF-1 α accumulation during hypoxia in human breast cancer SkBr3 cells (Lee *et al.*, 2008). CYP1A1 hydroxylates 17 β -estradiol (E2) into 2-hydroxyestradiol, a less estrogenic metabolite. However, an imbalance favoring 4-hydroxyestradiol, a product of CYP1B1, can lead to oxidative DNA damage and promote cancer (Li *et al.*, 2017). CYP1A1 expression is often upregulated in breast tumors, particularly in estrogen receptor-positive (ER⁺) subtypes, through the aryl

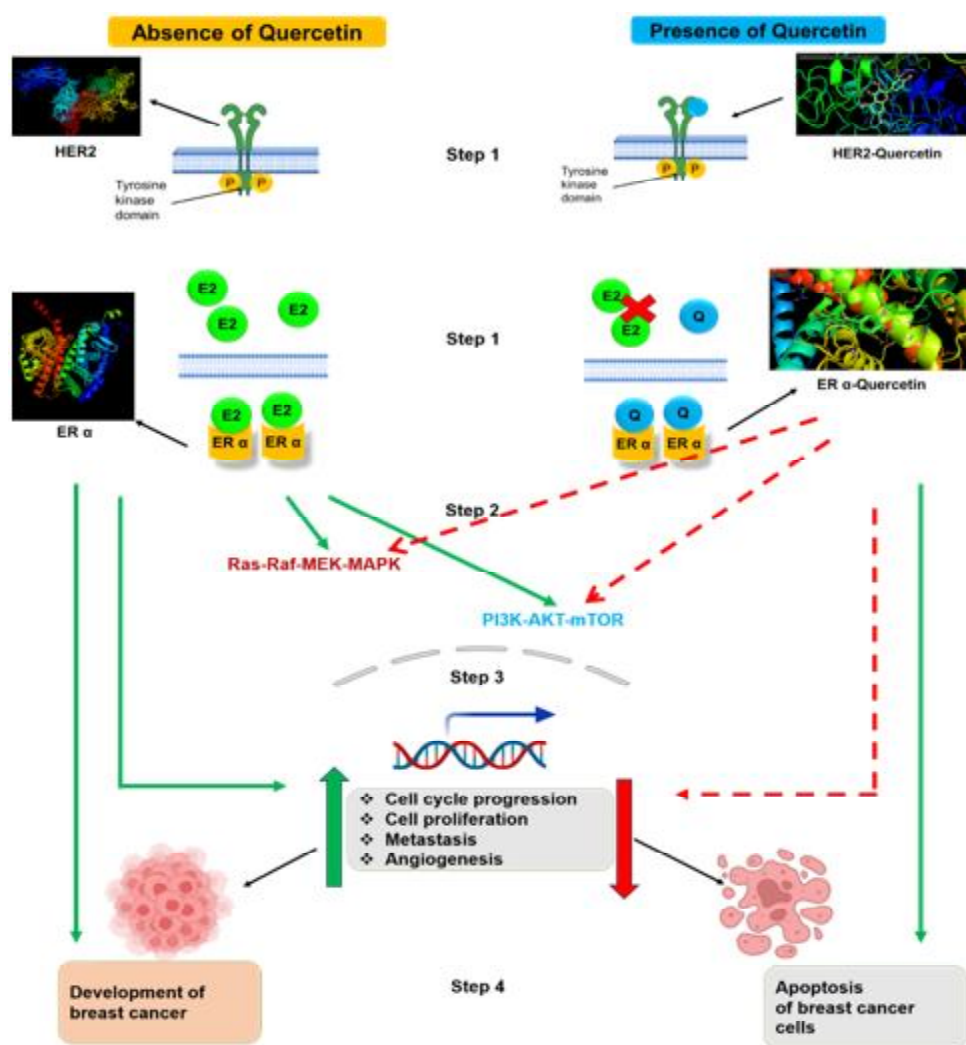


Fig. 1 : Quercetin in prevention of HER2 and ER α induced breast cancer.

hydrocarbon receptor (AhR) pathway (Rodriguez and Potter, 2013). Quercetin inhibits the induction of CYP1A1 expression in human mammary epithelial cells exposed to BaP. This inhibition reduces the formation of BaPDE and subsequent DNA adducts, potentially decreasing the risk of carcinogenesis (Wang *et al.*, 2018; Kumar *et al.*, 2012). Quercetin reduces the oxidative stress induced by BaP and reduce the formation of DNA adduct (Bukowska and Duchnowicz, 2022; Yeh *et al.*, 2006). The inhibitory effect of quercetin on CYP1A1 expression is mediated through the aryl hydrocarbon receptor (AhR) pathway. Quercetin competes with BaP for AhR binding, thereby reducing the activation of CYP1A1 and limiting the formation of carcinogenic metabolites (Perepechaeva *et al.*, 2017; Nguyen and Bradfield, 2009). Dietary flavonoids like quercetin act as ligands of the AhR although quercetin is more effective in attenuating the activation of TCDD (Ciolino *et al.*, 1999). TCDD (2,3,7,8-Tetrachlorodibenzo-p-dioxin): A highly toxic environmental pollutant and a strong AhR activator. It's often used in

research as a model compound to study AhR activation (Avilla *et al.*, 2020). For MAP kinase stimulant, Quercetin plays as anti-proliferative in MCF-7 cells by reducing the phosphorylation of P38MAPK as a hallmark of cell proliferation (Bulavin *et al.*, 2004; Ranganathan *et al.*, 2015).

The Human epidermal growth factor receptor 2 (HER2) present on the cell membrane dimerises leading phosphorylation of tyrosine kinase domain and activates a downstream signalling cascade involved in breast cancer development (step 1). Another receptor ER α (Estrogen receptor α) activated by estrogen (E2; estradiol) also involved in breast cancer development (step 1). Both the receptors are known to activate the Ras-Raf-MEK-MAPK and PI3K-AKT-mTOR signalling cascade (step 2). This leads to activation of gene expression involved in cell cycle progression, cell proliferation, metastasis, and angiogenesis (step 3). This stimulates the breast cancer development in women (step 4). While in presence of quercetin, the HER2 receptor forms complex with

Table 3 : Biological activity prediction of Quercetin based on Pa and Pi scores.

S. no.	Pa	Pi	Biological activity related to Breast cancer
1	0.969	0.002	HIF1A expression inhibitor
2	0.940	0.003	CYP1A1 substrate
3	0.933	0.001	MAP kinase stimulant
4	0.930	0.001	CYP1A1 inducer
5	0.924	0.007	CYP2C12 substrate
6	0.909	0.001	CYP1A1 inhibitor
7	0.909	0.003	CYP1A2 inhibitor
8	0.910	0.004	CYP1A2 substrate
9	0.887	0.002	AR expression inhibitor
10	0.873	0.001	CYP19 inhibitor
11	0.872	0.001	CYP1B1 inhibitor
12	0.850	0.002	NOS2 expression inhibitor
13	0.787	0.009	JAK2 expression inhibitor
14	0.757	0.007	Anticarcinogenic
15	0.734	0.005	MMP9 expression inhibitor
16	0.695	0.002	RELA expression inhibitor
17	0.601	0.004	CYP19A1 expression inhibitor
18	0.577	0.012	Antineoplastic (breast cancer)
19	0.549	0.004	Estrogen antagonist
20	0.546	0.004	Estrogen receptor beta antagonist
21	0.370	0.017	CYP1A2 inducer
22	0.305	0.004	Estrogen beta receptor agonist
23	0.265	0.005	Estrogen alpha receptor agonist
24	0.216	0.008	CYP19 substrate
25	0.166	0.010	Aromatase inhibitor
26	0.114	0.008	Estrogen-related receptor alpha antagonist

quercetin and it downregulates the further signalling (step 2). The binding of Quercetin (Q) with ER α prevent the binding of ER α with E2 by blocking the binding site (step 1). This leads to deactivation of the signaling cascade (step 2). This leads to downregulation of genes involved in cell division, cell proliferation, metastasis and angiogenesis (step 3). Thus, Quercetin involved in apoptosis of HER2 and ER α induced breast cancer cells and prevent breast cancer development (step 4).

Molecular Docking

We used blind docking by taking the whole receptor molecule to find out the possible target sites. The grid

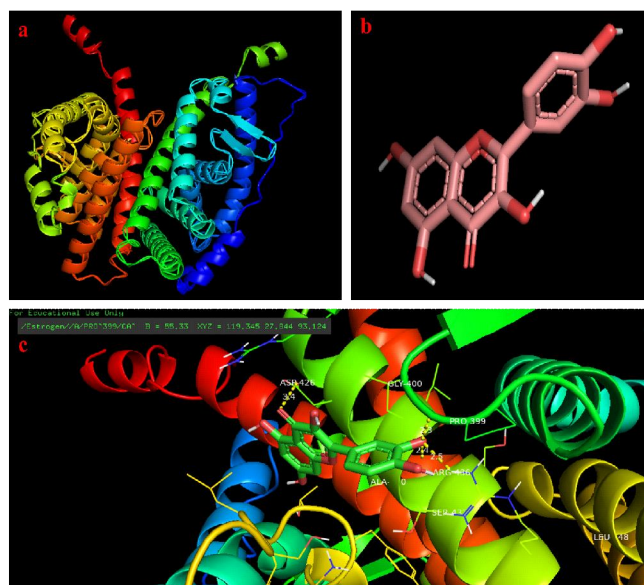


Fig. 2 : Complex of Estrogen receptor alpha (ER α) with quercetin (a) 3D structure of the protein 3ERT (b) 3D structure of ligand quercetin (c) ER α and quercetin complex after docking.

box parameter was set accordingly so that the whole receptor molecule can act as potential target site for quercetin. Then molecular docking was performed using AutoDockVina. The affinity of the receptor molecule with the ligand is expressed as Kcal/mole

In our docking results total nine models were found with different affinity and RMSD(Root Mean Square Deviation) of lower bound and upper bound. When both L.B and U.B RMSDs are low, the prediction is considered stable and accurate.

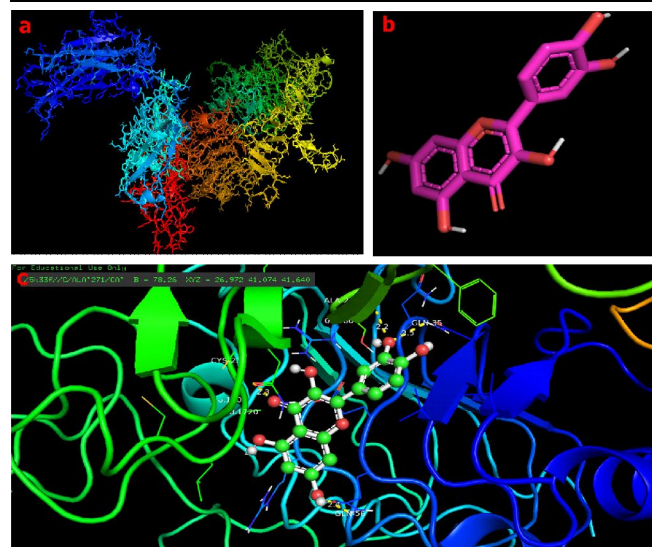
Model no 1 found to be powerful and complex due to its high affinity energy (-8.2 kcal/mol) for ER-Alpha+ Quercetin complex and -7.6 kcal/mol for HER2+ Quercetin complex (Table 4).

If we compare this binding energy with other standard drugs like Tamoxifen and Toremifene, then it was found -4.81 and -5.49 kcal/mol, respectively (Hasan *et al.*, 2022). Tamoxifen is a standard drug used to block the estrogen receptors on breast cancer cells (Criscitiello *et al.*, 2010). Likewise Toremifene exerts its anticancer effect by competitively binding to estrogen receptors, thereby inhibiting estrogen-mediated proliferation of breast cancer cells (Vogel *et al.*, 2014).

The possible interaction of quercetin with ER α is at ASP 426 with a bond length of 3.4 Å, PRO 399 at 2.3 Å, ALA 430 at 2.4 Å and ARG 436 at 2.5 Å (Fig. 2c). Similarly, quercetin made five interactions with the HER2 protein. First is at GLN 56 with a bond length of 2.4 Å. Similarly, at CYS 233 at 2.3 Å, GLN 35 at 2.5 Å, GLY 270 at 2.2 Å and at last ALA 271 at 2.0 Å (Fig. 3c).

Table 4 : Molecular docking binding energy of Quercetin with Er α and HER2 protein.

Mode	ER α +Quercetin			HER2+ Quercetin		
	Affinity (Kcal/Mol)	RMSD (Dist from L.B)	RMSD (Dist from U.B)	Affinity (Kcal/Mol)	RMSD (Dist from L.B)	RMSD (Dist from U.B)
1	-8.2	0	0	-7.6	0	0
2	-7.2	1.42	3.113	-7.6	10.245	15.185
3	-7.1	1.629	7.096	-7.5	12.611	15.32
4	-6.8	22.106	24.31	-7.1	1.451	7.113
5	-6.5	17.207	18.786	-7	39.615	40.724
6	-6.4	16.88	17.543	-6.8	15.073	17.54
7	-6.4	16.484	17.633	-6.7	14.045	17.06
8	-6.2	15.476	17.948	-6.4	1.85	2.264
9	-6.2	15.390	18.239	-6.4	17.140	18.512

**Fig. 3 :** Complex of human epidermal growth factor receptor 2 with quercetin (a) 3D structure of the protein 5k33 (b) 3D structure of ligand quercetin (c) HER2 and quercetin complex after docking.

Organic compounds can associate with proteins by forming chemical bonds and engaging in non-covalent interactions between the ligand and the protein (Grabowski, 2020; Brylinski *et al.*, 2018). Among these, hydrogen bonding and hydrophobic interactions are key factors in determining binding affinity and the potential pharmacological effectiveness of a new drug candidate. Hydrogen bonds are particularly crucial for maintaining the structural stability of many biological molecules, such as proteins and DNA (Abelian *et al.*, 2021; Pace *et al.*, 2014) and for facilitating drug-receptor interactions. These bonds are commonly observed between ligands and proteins, enhancing biological activity by promoting chemical interactions. A bond is classified as a hydrogen bond when an appropriate donor–acceptor pair is within

an optimal distance, with stronger hydrogen bonds typically approaching ideal geometric configurations (Chen *et al.*, 2016; Basu *et al.*, 2024). When a ligand binds to a protein, it establishes direct interactions and often leads to the displacement of water molecules at the binding site (Dyson *et al.*, 2006).

For Quercetin and the target proteins, the observed bond distances mostly averaged around 2.63 Å, ranging between 2.3 to 3.4 Å for Er α , and average bond length for HER2 is 2.28 Å, ranging from 2.0 Å to 2.5 Å, which is considered favorable compared to the interaction distances of standard reference drugs (Jeffrey *et al.*, 1997). Hydrophobic interactions occur when the non-polar side chains of protein amino acids come into close proximity with the lipophilic regions of the ligand (Dyson *et al.*, 2006). These interactions are known to play a significant role in enhancing the binding affinity of ligands that possess prominent lipophilic characteristics.

Conclusion

In this study, we explored the potential therapeutic anti-cancer properties of rice Quercetin. It favors the possible binding affinity with Er α and HER2 compared to standard drugs. We evaluated several antineoplastic activities (targeting breast cancer). The findings from our study may contribute to the design and development of novel compounds with enhanced inhibitory effects against multiple diseases. Rice Quercetin also exhibited favorable drug-like characteristics, showing no signs of carcinogenicity or mutagenicity. Given their versatility, Quercetin and its derivatives represent promising drug candidates; however, further validation through wet lab experiments is essential to confirm their therapeutic efficacy, safety profile, and drug interaction potential in human health.

Declaration of competing interest

There is no conflict of interest.

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Authors contribution

JKN and BP hypothesized and conceptualized experiments. JKN performed the dry lab experiments and analyses. BP and JKN drafted the manuscript. SM, DM, DM and PS reviewed and edited the MS. JKN and BP finalized the MS.

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