"Computational Investigation of Quercetin–Target Interactions for Exploring Therapeutic Potential in Breast Cancer"

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ABSTRACT

Abstract

Background: Breast cancer is the second most common type of cancer, accounting for approximately 10.4% of all cancer cases. The hormone oestrogen plays a significant role in the development and growth of breast cancer cells, particularly in oestrogen receptor-positive (ER+) cancers. Current hormonal therapies, such as Tamoxifen, have shown effectiveness but are accompanied by adverse effects, highlighting the need for safer alternatives.
Objective: This study aimed to investigate the potential of phytochemicals, specifically flavonoids and isoflavones, as therapeutic agents for breast cancer using computational techniques.
Methods: The three-dimensional structure of the human oestrogen receptor was retrieved from the protein data bank, and phytochemicals were obtained from the PubChem compound database. Molecular docking studies were performed using AutoDock 4.0 to determine the binding affinity of phytochemicals to the oestrogen receptor. The ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of the phytochemicals were predicted using in-silico techniques.
Results: The docking studies revealed that quercetin, genistein, and daidzein exhibited significant binding affinity to the oestrogen receptor, with docking energies ranging from -4.85 to -7.72 kcal/mol and binding energies between -9.62 to -7.07 kcal/mol. The results suggest that these phytochemicals may potentially block the human oestrogen receptor, with key residues Leu346, Leu384, Leu387, Phe404, and Leu525 playing a crucial role in the binding process.
Conclusion: This study demonstrates the potential of phytochemicals, particularly quercetin, genistein, and daidzein, as therapeutic agents for breast cancer. The computational results provide a framework for the design of lead molecules, which could lead to the development of more effective and safer treatments for breast cancer. Further clinical investigations and experimental confirmation are necessary to validate these findings and explore the potential of these phytochemicals as therapeutic agents.
Keyword's: Human Oestrogen Receptor, Quercetin, Anticancer, Molecular Docking, Protein Binding.

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INTRODUCTION

Breast cancer, accounting for approximately 10.4% of all cancer cases, is the second most common type of cancer after lung cancer [2]. Both normal breast cells and the majority of breast cancer cells possess receptors that bind to the hormones estrogen and progesterone circulating in the bloodstream [8]. When these hormones bind to their respective receptors, they trigger a signaling cascade that promotes cell growth and proliferation. In cancerous cells, this hormone-driven process plays a significant role, as estrogen and progesterone interact with oncogenes and tumor suppressor genes, contributing to uncontrolled cell growth and tumor development [21]. Breast cancer cells that are positive for estrogen and progesterone receptors (ER+ and PR+) are more likely to respond to hormonal therapies such as Tamoxifen, Raloxifene, and Toremifene. These hormone receptor-positive cancers also tend to have a better prognosis compared to hormone receptor-negative cancers [8]. Tamoxifen (Nolvadex®) is an oral drug that works by blocking the effects of estrogen. While effective, Tamoxifen can cause serious side effects, including blood clots, strokes, uterine cancer, and cataracts. Similarly, Raloxifene may lead to dangerous blood clots in the legs, lungs, or eyes, and symptoms such as leg pain or swelling, chest pain, difficulty breathing, and vision changes. Due to these adverse effects, there is a need to identify safer alternatives. Our research focuses on finding natural compounds with strong binding affinity to breast cancer receptors, aiming to develop effective and less harmful treatments [13]. Phytochemicals—naturally occurring compounds found in plants—have shown promise in reducing cancer risk. This study specifically investigates the role of phytochemicals

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in targeting breast cancer. Phytochemicals can be classified into several groups, with flavonoids and isoflavones being among the most studied [3, 4, 16]. Isoflavones, in particular, are plant-derived compounds that act as weak estrogens. Their chemical structure closely resembles that of estrogen [17], allowing them to competitively bind to estrogen receptors. Depending on the type of receptor, isoflavones can either mimic or block estrogen's effects, potentially lowering the health risks associated with excess estrogen. By binding to estrogen receptors, isoflavones can reduce the activity of natural estrogen, similar to how Tamoxifen functions. This makes them promising candidates for the prevention and treatment of hormone-related cancers such as breast cancer [12].

In this study, we found that among various phytochemicals tested, Genistein, Quercetin, and Daidzein demonstrated significant binding affinity to estrogen receptors. Their structural similarity to estrogen—particularly the presence of hydroxyl groups and a phenolic ring—enables this interaction. As illustrated in Fig. 1, these compounds are polyphenols that closely resemble estradiol, the primary estrogen in mammals. The position of the hydroxyl groups—especially at positions 4, 6, and 7—is critical for optimal receptor binding and transcriptional activity [10, 18, 22].

MATERIALS AND METHODS

Retrieval of protein and ligands from database

The protein data bank provided the three-dimensional structure of the human estrogen receptor (PDB ID: 2IOK, Res: 2.40 A°) [7] complexed with a strong, selective inhibitor. (1R)-3-(4-HYDROXYPHENYL)-1-METHYLPROPYL N-[(2-PHENYL-1H-INDOL-3-YL) -2- The structure of ACETAMIDE and every phytochemical used in this investigation were obtained from the PubChem compound database [20].

Protein and Ligand preparation

For docking experiments, the raw protein from the protein data bank, known as the human estrogen receptor and assigned PDB ID 2IOK, is further processed. The protein receptor was first prepared by eliminating all of the water molecules and Heteroatoms, and then using the program Chimera [15] for 1000 steps at an RMS gradient of 0.02 with 10 as the update interval and AMBER [19] ff12SB as the force field, energy minimization was performed to eliminate the undesirable steric clashes. After using open babel (http://openbabel.org/wiki/Main_Page) to transform the molecules' 2D structures to 3D structures, Hyperchem's MM+ force field was used to minimize energy.

Determination of binding site

Protein binding and active sites are frequently linked to structural cavities and pockets that have a strong attraction for potential medications. The human estrogen receptor's catalytic location was discovered. Based on the data found in the literature. The Computed Atlas of Surface Topography of proteins (CASTp) service [6] and Q-SiteFinder [9] were used to further analyze the catalytic residue. Q-SiteFinder finds energetically advantageous binding sites by utilizing the interaction energy between the protein and a basic van derWaals probe. The knowledge base data from the computer program and the literature is consistent.

The alpha complex and weighted Delaunay triangulation are used by the CASTp server to measure shapes. Additionally, it offers measurements and identification of surface-accessible pockets. as internal holes that are inaccessible to proteins and other molecules. Both the solvent accessible surface (SA, Richards surface) and the molecular surface (MS, Connolly's surface) are used to analytically measure the area and volume of each pocket and cavity.

Computation of docking score between Human estrogen receptor and phytochemicals

AUTODOCK 4.0 [14] (version: 1.5.6), loaded on a single computer with a 2.0 GHz Intel core 2 dual CPU and 4 GB of RAM, was used for all computational docking investigations. RAM and a 450 GB hard drive running the Linux operating system (Open Suse). Using the AutoDock4.0 tool, automated dockings were carried out in accordance with the guidelines to find the proper binding orientations and conformations of different inhibitors in the human estrogen receptor binding pocket.

To put it briefly, the receptor proteins were given Kollman charges and polar hydrogen atoms. Gasteiger partial charges were identified for ligands, and non-polar hydrogen atoms were combined. Throughout the docking process, all ligand torsions were let to rotate. The grid maps were created using the Auto Grid application. The appropriate receptor's structure served as the center of each grid. The grid had points spaced 0.375 A° apart and measured 94x153x145 A° 3. Random orientations, torsions, and starting positions were applied to every ligand.

The Auto Dock default values were used for the translation, quaternion, and torsion steps. Using default parameters, minimization was accomplished using the Lamarckian genetic algorithm approach. The common docking approach for both flexible and rigid An initial population of 150 randomly selected individuals was used for 50 runs of ligand docking, which included 2.5 x105 energy evaluations, a maximum of 27000 iterations, and a mutation rate of

0.02; an elitism value of 1; and a crossover rate of 0.80. The docked results were subjected to cluster analysis with an RMS tolerance of 1.0 A°. Each cluster's binding energy is the average of the binding energies of all the conformations that make up the cluster; the cluster with the lowest binding energy and the greatest number of conformations was chosen as the specific ligand's docked position.

Adverse effect prediction

To determine whether the phytochemicals have the potential to have a negative impact on humans, the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties were predicted using in-silico techniques. The ADMET is calculated in this study using MedChem Designer TM [1].

RESULTS AND DISCUSSION

Binding site analysis

Leu346, Ala350, Leu384, Leu387, Phe404, Val418, Met421, Ile424, His524 and Leu525 may be the catalytic site residues found in the human structure, according to the experimental investigation. Receptor for estrogen. Catalytic residues were assessed using a variety of computational techniques, including CASTp and QSiteFinder. According to Q-SiteFinder, the first anticipated site of volume 603A° 3 had catalytic site residues including Leu346, Ala350, Leu384, Leu 387, Phe404, Val418, Met421, and Ile424. According to the available data, at least one of the top three predicted proteins had catalytic residues from over 95% of the protein. sites after being examined with Q-SiteFinder. The Q-SiteFinder results are also supported by the CASTp program. displays the catalytic site residues in the human estrogen receptor structure. Leu346, Ala350, Leu384, Leu387, Phe404, Val418, Met421, Ile424, His524 and Leu525 function as catalytic residues in the three-dimensional structure of the human estrogen receptor, according to these computational analyses and experimental data. The obtained results are consistent with the findings mentioned above.

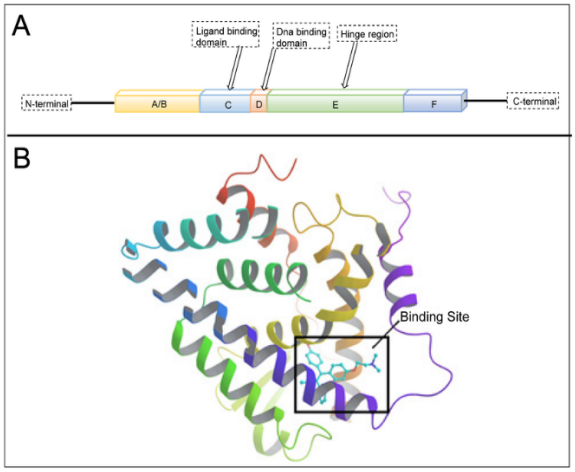


Figure: Binding Site Human Estrogen Receptor

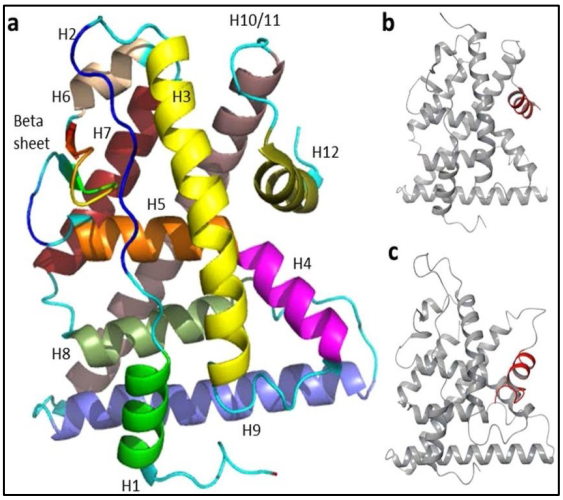
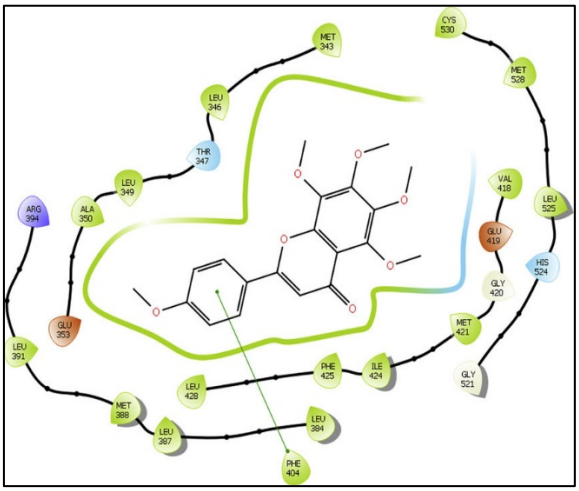


Figure: Human Estrogen Receptor

Docking studies of Human estrogen receptor with phytochemicals

Docking studies of human estrogen receptors (ERs) with quercetin indicate that quercetin can bind effectively to both ER alpha (ERα) and ER beta (ERβ) subtypes, exhibiting notable binding affinity which suggests potential modulatory effects.



In silico molecular docking and dynamics simulations reveal favorable and stable interactions of quercetin with ERs, particularly showing high affinity for ERβ and its associated steroidogenic enzymes, while binding less strongly to ERα. These interactions involve key residues within the ligand-binding domain that are critical for receptor activation and coactivator recruitment.

The docking scores and binding energies for quercetin typically range from moderate to strong, supporting its characterization as a selective estrogen receptor modulator (SERM) with possible implications in hormone-related therapeutic applications like cancer prevention and reproductive health regulation. Post-docking analyses show quercetin stabilizes through hydrogen bonds and hydrophobic interactions within the active site of ERs. Moreover, molecular dynamics simulations further support the stability and favorable binding profile of quercetin to estrogen receptors, highlighting its potential for functional modulation of estrogen signaling pathways essential in neuroprotection, cancer, and metabolic diseases.

Table : Binding energies of various ligand with human estrogen receptor.

Ligand	Binding Energy (kcal/mol)	Intermolecular Energy (kcal/mol)	Docking Energy (kcal/mol)	Inhibition Constant (μM)
Allicin	-4.45	-7.43	-8.28	98.52
Anthocyanins	-5.46	-5.85	-6.07	09.84
Apigenin	-5.83	-7.03	-7.76	53.13
Epigallocatechin gallate	-5.26	-6.06	-6.60	43.62
Curcumin	-6.72	-7.61	-7.82	2.21
Emodin	-6.62	-6.81	-8.62	2.69
Isoflavones	-6.00	-7.30	-7.55	6.73
Quercetin	-6.93	-9.92	-11.23	5.55

In summary, quercetin exhibits strong binding affinity and stable interactions with human estrogen receptors in docking studies, emphasizing its role as a bioactive flavonoid with potential SERM-like therapeutic properties.

Toxicity prediction

Property	**Model Name**	**ZINC69481841**	**ZINC95486083**
Physicochemical Properties			
Molecular Weight (MW)		318.49	360.49
Topological Polar Surface Area (TPSA)		37.3	37.3
Lipophilicity			
iLOGP		3.35	4.36
XLOGP3		6.58	7.19
WLOGP		5.99	6.2
MLOGP		4.76	4.9
Silicos-IT Log P		5.18	7
Consensus Log P		5.17	5.93
Estimated Solubility (ESOL)	Log S	-5.7	-6.47
Solubility (mg/ml)		6.41E-04	1.22E-04
Solubility (mol/l)		2.01E-06	3.38E-07
Class		Moderately soluble	Poorly soluble
Pharmacokinetics			
GI Absorption		High	High
BBB Permeant		No	No
P-gp Substrate		No	Yes
Inhibitor CYP1A2		No	Yes
Inhibitor CYP2C19		Yes	Yes
Inhibitor CYP2C9		Yes	No
Inhibitor CYP2D6		No	No
Inhibitor CYP3A4		No	Yes
log Kp (skin permeation, cm/s)		-3.57	-3.39
Druglikeness			
Lipinski (Number of violations)		1	1
Ghose		1	1

Veber		0	0
Egan		1	1

ADME prediction

Property	Predicted Value	Unit	ZINC69481841	ZINC95486083
Excretion				
Total Clearance	0.965	log ml/min/kg	0.965	0.288
Renal OCT2 substrate	No	-	No	Yes/No
Toxicity				
AMES toxicity	No	-	No	No
Max. tolerated dose (human)	0.411	log mg/kg/day	0.411	0.661
hERG I inhibitor	No	-	No	Yes/No
hERG II inhibitor	No	-	No	Yes/No
Oral Rat Acute Toxicity (LD50)	2.044	mol/kg	2.044	2.146
Oral Rat Chronic Toxicity (LOAEL)	2.49	log mg/kg_bw/day	2.49	2.229
Hepatotoxicity	Yes	-	Yes	No
Skin sensitivity	No	-	No	No
T. Pyriformis toxicity	0.926	log µg/L	0.926	0.722
Minnow toxicity	-1.14	log mM	-1.14	-1.343

CONCLUSION

In structurally based drug design, the protein-ligand interaction is crucial. Human estrogen receptors have been used in the current study, and possible medications have discovered that has the potential to combat breast cancer. The mechanism of interactions and binding affinity between phytochemicals and the human estrogen receptor have been attempted to be understood through the use of computational techniques.

The phytochemicals utilized in this investigation displayed docking energies in the range of -4.85 and -7.72 kcal/mol and binding energies in the range between -9.62 to -7.07 kcal/mol, which is well compatible with the ideal and conventional binding energies. Additionally, the current data indicates that quercetin, genistein, and daizein may potentially the possible lead chemical for blocking the human estrogen receptor, and the most crucial residues for a possible therapeutic target are Leu346, Leu384, Leu387, Phe404, and Leu525. These natural substances could therefore serve as a model for creating therapeutic lead molecules, which could drastically cut down on the amount of time needed to develop new treatments.

Clinical investigations and experimental confirmation of this work could make these phytochemicals a more effective medication for the treatment of various malignancies in general and breast cancer specifically.

In the future, these compounds' ADME/T (Absorption, Distribution, Metabolism, Excretion/Toxicity) characteristics can be computed using commercial ADME/T technologies, which will save time and money during the drug discovery process. The selection of a lead phytochemical for the subsequent drug discovery process will be based on these findings.

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