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Original Research Article

Promising reduction of *de novo* resistance to endocrine therapies in breast cancer by small molecules from natural origin: A structural approach

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Abstract

Purpose: *To investigate the pharmacokinetic properties and inhibitory binding interaction between naturally occurring phytochemicals and a mutated human estrogen receptor (hERα) using an in silico approach.*

Methods: *Naturally occurring small molecules, viz, myricetin, catechin, pinobanksin, pinocembrin, gelagin and pinostrobin, were investigated for their drug-likeness and pharmacokinetic properties. After that, molecular docking was used to study their binding affinities to Y537S (Tyr537Ser: a mutated estrogen receptor alpha, prominent in metastatic breast cancers). The structure of the ligand-binding domain (LBD) of human estrogen receptor was retrieved from Protein Data Bank while the structures of the studied compounds were collected from PubChem database. Using Schrodinger docking studio, the binding interactions of each phytochemical were investigated with the mutated estrogen receptor.*

Results: *All studied compounds were observed to be drug-like with good physicochemical properties. Myricetin, catechin, pinobanksin, pinocembrin, gelagin and pinostrobin showed good solubilities in human oral absorption and good intestinal permeability, which are the rate-limiting barriers for oral drug absorption. The distribution of the studied ligands and their plasma protein binding parameters were better than those of tamoxifen, which has previously been reported with high potential binding to albumin. None of the studied compounds showed central nervous system toxicity. The binding studies revealed good inhibition of the LBD of Y537S-hERα. This is a targeted approach to selectively inhibit this receptor which has been reported to confer ligand-independent functions to ERα. This inhibition prevents downstream signaling and metastasis, rendering breast cancer cells harboring such mutations susceptible to apoptosis upon treatment with endocrine therapies.*

Conclusion: *The compounds have the potential to mitigate de novo resistance in breast cancer cells harboring mutated estrogen receptors and should be further investigated as they are promising for oral delivery.*

Keywords: *Cancer, Mutation, Estrogen receptor, In silico, Schrodinger, Molecular docking*

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INTRODUCTION

The growth and progression of certain cancers like breast, endometrial and prostatic are dependent on hormone stimulation. More than 75 % of breast cancers (BC) in post-menopausal and more than 50 % of cancers in pre-menopausal women are hormone-positive [1]. These tumors are often managed in both adjuvant and palliative care with endocrine therapies. Endocrine therapies are the foremost treatment option for patients with estrogen receptor-positive breast cancers which are not rapidly progressing. They include the anti-estrogens (such as tamoxifen), or the aromatase inhibitors (such as letrozole, anastrozole, or exemestane). Unfortunately, *de novo* and acquired resistance have hampered patient's response to therapy, frustrating the overall therapeutic objective. Resistance to endocrine therapies in breast cancer is however a complex process that involves multiple mechanisms, including mutations in the ligand binding domain (LBD) of the estrogen receptor, alterations in hormone metabolism, upregulation of signaling pathways, epigenetic changes, and tumor microenvironment factors. This dilemma has stimulated research for more treatment options or possible modalities to subvert resistance and make cancer cells susceptible to death following treatment. This study investigated the binding interaction of potential small molecule inhibitors of the mutated human estrogen receptor alpha (Y537S-hERα-LBD).

Targeted therapy which focuses on directly or indirectly inhibiting a specific biomarker implicated in a specific type of cancer has been challenged by resistance which is due in part to mutation in the ligand binding domain of such clinical target [2]. One of the targets which has been implicated in the majority of breast cancer cases [3] is the human estrogen receptor alpha (hER), a central transcription factor that stimulates the proliferation of breast cancer cells, usually in the presence of estrogen. A prominent challenge in the treatment of estrogen receptor-positive cancer patients is the upsurge of resistance to endocrine therapies. This has resulted in about 50 % relapse with constitutively active forms of the receptor in the metastatic-resistance stage of BC. Activating mutations have also been acquired following estrogen deprivation therapies as a resistance mechanism of BC cells to escape hormonal control and promote cell proliferation through ligand-independent activation of Erα [4].

The most prevalent hERα mutation is a substitution of the amino acid Y537 in S, N or C and about 60 % of such mutations have been reported in metastatic breast cancer samples [5]. These mutations result in a conformational modification of the receptor, stabilize it in its agonist form and confer ligand-independent, constitutive activity to the mutated receptor. Y537S mutation with its typical conformational modification is due to replacement of the Y537-N348 interaction with an S537-D351 hydrogen bonding [6] which optimizes the h11-h12 loop in the agonist conformation, reducing its affinity for tamoxifen. In this conformation, coactivators can be recruited. According to Fanning *et al* [7], this binding interaction has been reported to occur with a high affinity for the Y537S mutant, even in the absence of estrogen. Hence, the mutation confers constitutive ligand-independent activity to Erα [4,8]. It also allows ERα to escape phosphorylation-mediated controls, providing cells with a potential selective advantage. However, if the mutated estrogen receptor is strongly inhibited, then downstream signaling will be impaired and such resulting conformation may enhance the affinity of the receptor to the administered endocrine therapy. Thus, this work was aimed at evaluating the binding interactions of each of myricetin, catechin, pinobanksin, pinocembrin, gelagin and pinostrobin with a mutated Y537S-hERα-LBD, following an investigation of their drug-likeness and predicted pharmacokinetic potential.

EXPERIMENTAL

Computer hardware and software

The molecular docking simulation was performed on Lenovo Precision workstation 6.1.7600 running Intel® Core™ i5 Duo Processor, 4.0 GB RAM, 436 GB hard disk and AMD Radeon graphics card (Lenovo PC HK Limited, China). The 3D structures of small molecules (myricetin, catechin, pinobanksin, pinocembrin, gelagin and pinostrobin) were obtained from the National Centre for Biotechnology Information, Pubchem database (www.ncbi.nlm.nih.gov/pccompound) in SDF format and prepared with Maestro, using ligprep version 3.6 (LigPrep 2015). The solution x-ray crystal structure of the human ERα (3UUD, 1.60 Å resolution) was retrieved from the protein databank (www.rcsb.org) using Discovery Studio visualizer 4.5 (Accelryls, USA). Protein-ligand docking simulation was performed using the Schrodinger molecular docking suite version 2018-4.

Preparation of ligands and protein

The ligands were prepared using LigPrep, a utility of Schrodinger software suit that combines tools for generating 3D structures from 1D (Smiles) and 2D (SDF) representation. Molecular mechanics force fields, and optimized potentials for liquid simulations-2005 (OPLS_2005) with default settings were employed for the ligand minimization and the ligands were thereafter filtered for computational studies. The crystal structure of Y537S-hERα was prepared using Schrodinger protein preparation wizard tool (Glide) following visualization in Discovery Studio as earlier reported [3].

Prediction of pharmacokinetic properties and drug-likeness of studied flavonoids

The drug-likeness of the investigated molecules was examined using Lipinski's rule of five and certain pharmacokinetics descriptors [9] were evaluated using qikProp module of Schrodinger Suite, a program designed by Professor William L Jorgensen [10]. In addition to predicting physical significance and pharmaceutically relevant molecular descriptors, qikProp also provides ranges for comparing the predicted descriptors of each compound with those of 95 % of drugs known for oral use. The pharmacokinetic descriptors evaluated were: molecular weight (Mwt), total solvent accessible surface area (SASA), Donor hydrogen bond (DonorHB), number of acceptable hydrogen bonds (Accept HB), predicted octanol/water partition coefficient (QPlogPo/w), predicted aqueous solubility (QPlogS), predicted apparent Caco-2 cell permeability (QPPCaco), predicted brain/blood partition coefficient (QPlogBB), number of likely metabolic reactions ($^{\#}$metab), human oral absorption, Van der Waals surface area of polar nitrogen and oxygen atoms (PSA) and prediction of plasma protein binding (Khsa). Cytochrome P450 inhibitory promiscuity and inhibition of the human either-a-go-go-ralted gene were also accessed via the admerSAR web server. The prepared ligands were used as input structures and their pharmacokinetics profiles with respect to properties shared by 95 % of drugs known for oral use were evaluated.

Docking studies

Docking studies were carried out using Glide XP of Schrodinger Suite (Maestro version 11.8 and Glide version 8.0, 2018-4) docking program following the reported standard procedures [3]. Each ligand was individually docked onto the LBD of hERα using Glide extra precision (XP) mode. In the course of docking, several binding poses were generated for each ligand and the best binding pose was selected at the end of docking process.

Calculation of ligand-free energy of binding with hERα

The Prime MM-GBSA or 'molecular mechanics energies combined with generalized Born and surface area continuum solvation' approach was used in the post-assessment of free energy of binding of ligands-hERα complex [11]. This approach uses OPLS_2005 all-atom force field for protein residues, ligands and cofactors. The input structures for these calculations were taken from a pose viewer file Glide output after the docking study.

The following descriptors were generated by the prime MM-GBSA approach:

i. MM-GBSA_∆G_bind (ligand binding energy (ΔG_{bind})

ii. MM-GBSA_E_complex (energy of the complex ($G_{complex}$)

iii. MM-GBSA_E_protein (energy of the receptor without the ligand ($G_{protein}$) and

iv. MM-GBSA_E_ligand (energy of the unbound ligand (G_{ligand}).

The total free energy (ΔGbind) of binding is expressed as:

$\Delta G_{bind} = G_{complex} - (G_{protein} + G_{ligand})$ …….. (1)

The other parameters for the complex were:

i. Prime Coulomb energy (ΔG_{bind} coulomb)

ii. Prime Van der Waals energy (ΔG_{bind} vdW)

iii. Prime Hydrogen Bond (ΔG_{bind} H-bond)

RESULTS

Considering hydrogen bond interactions of the studied molecules with active amino acids of estrogen receptor, from the results, 7-OH of gelagin (Figure 2 a and b) formed one hydrogen bond with Glycin 521 at a distance of 1.89 Á and π-cation interactions with phenylalanine 404 and histidine 524. The 3^1- OH and 4^1- OH groups of myricetin (Figure 2 c and d) each established 1H bond with glutamic acid 353 residue at distances of 1.59 and 1.74 Á respectively. A firm interaction was also observed with Arginine 394 by 4^1 -OH of myricetin at distances of 1.97 and 2.26 Á. The

8- OH of myricetin also established 1H bond with histidine 524 and glycin 521 at 1.90 Å. There was also a π-interaction of this ligand with phenylalanine 404 and histidine 524 (Figure 2 c and d). In Figure 3 a and b, 1H bond each was established between 8-OH of pinobankskin and Glycine 521 and Methionine 388 at distances of 1.78 and 1.89 Å respectively. A pi-pi interaction was also observed between the ligand and phenylalanine 404 as well as histidine 524. A pi-pi interaction was formed between pinostrobin and phenylalanine 404 of hERα while its 8- OH group formed one hydrogen bond with glycine 521 at 1.78Å (Figure 3 c and d). Pinocembrin (Figure 4 a and b) established a pi-cation interaction with phenylalanine 404 and histidine 524 while its 5-OH group formed 1H bond with leucine 387 at 1.89 Å. A strong interaction was observed between its 8-OH group and glutamate 353 at 1.57 Å. Tamoxifen, on the other hand, established 1H bond with Arginine 394 at 2.34 Å and a pi-cation interaction with phenylalanine 404 and histidine (Figure 4 c) while estradiol, the native ligand had 1H bond each with glutamate 353 and histidine 524 at distances of 1.80 and 2.04 Å, respectively (Figure 4 d). A pi-pi interaction was also observed with histidine 524 and phenylalanine 404.

Binding energy analysis

From the prime energy calculations, the quantity of free energy of binding, (ΔG)-bind calculated from Equation (1) was in the following order: estradiol > myricetin > catechin > gelagin > pinobankskin > pinocembrin > pinostrobin (Figure 5). Other components that contributed to electrostatic interaction like the quantity of prime coulomb energy of the complex ((ΔG)_bindcoulomb), prime van der Waals energy of complex interaction ((ΔG)_bindvdW), the quantity of prime hydrogen bonding interaction are as presented in Table 2.

DISCUSSION

Approximately 30 – 50 % of BC recurrences harbor activating mutations in ligand binding domain (LBD) of human estrogen receptor alpha [5]. These mutations which are rarely found in primary ER+ breast cancers, have been shown to confer ligand-independent functions, including transcriptional regulation, growth, and proliferation of ER mutant breast cancer cells both *in vitro* and *in vivo*. A prominent mutation is the substitution of amino acid; Y537 in S, N or C. About 60 % of Y537 mutations have been reported in metastatic breast cancer samples [7,8] and are implicated in resistance to endocrine therapies [5]. Endocrine therapies include aromatase inhibitors (AIs), selective estrogen receptor modulators (SERMs), and selective estrogen receptor degraders (SERDs). Studies have shown differential expression of thousands of genes provoked by ER mutations in comparison to estrogen treatment of wild-type (WT) cells [12]. Several studies have observed ligand-independent transcriptional regulation, growth, and proliferation of ER mutant breast cancer cells both *in vitro* and *in vivo* [8]. The postulation is that if a strong binding inhibition of the studied molecules with LBD of Y537S-hERα exists, then the molecules under investigation would be promising to relieve endocrine resistance.

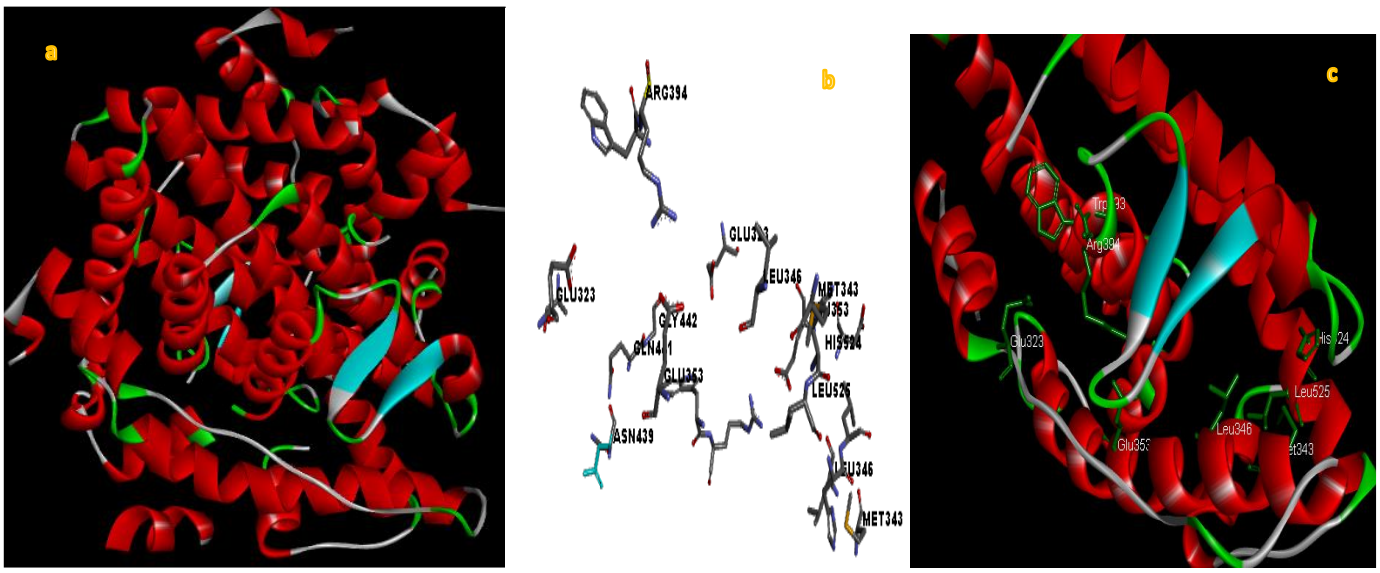


Figure 1: Ligand binding domain of Y537S-hERα: (a) Complete x-ray structure of Y537S-hERα shown in the cartoon, (b) Active amino acid residues, (c) Ligand binding domain with amino acids shown in green

Table 1: Pharmacokinetic properties of studied molecules

Compound	MW[A]	SASA[B]	Donor HB[C]	Accept HB[D]	QPlog Po/w[E]	QP log SF	QPP Caco[G]	QP log BB[H]	#meta[I]	% Human oral absorption (%)[J]	PSA[K]	KHSA[L]	Rule of Five[M]
Myricetin	318.24	522.36	5	6	-0.28	-2.56	7.66	-2.82	6	28.19	161.31	-0.49	1
Estradiol	272.39	510.23	2	2.45	4.00	-4.67	12221.94	-0.37	4	100	43.69	0.44	0
Catechin	290.27	513.73	5	5.45	0.47	-2.65	53.25	-1.90	7	60.57	115.49	-0.42	0
Pinobanksin	272.26	492.52	2	4.95	1.47	-3.08	211.88	-1.17	5	77.19	97.06	-1.68	0
Pinocembrin	256.26	486.98	1	3.25	2.38	-3.68	431.99	-0.83	5	88.07	77.67	0.136	0
Gelangin	270.24	488.02	2	3.75	1.79	-3.30	193.62	-1.22	3	78.36	95.96	-0.04	0
Pinostrobin	270.28	509.44	0	3.25	3.08	-3.84	1427.9	-0.35	5	100	63.41	0.18	0
Tamoxifen	371.52	725.07	0	2.75	6.53	-5.83	2203.13	0.37	3	100	11.49	-7.4	1

Note: Range for 95% known drugs: A (Molecular weight = 130.0 - 725.0); B (Total solvent accessible surface area = 300.0 - 1000.0); C (Donor HB = 0.0 - 6.0); D (Accept HB = 2.0 - 20.0); E (Predicted octanol/water partition coefficient = -2.0 - 6.5); F (Predicted aqueous solubility = -6.5 - 0.5); G (Predicted apparent Caco-2 cell permeability ≤ 25 poor, > 500 great); H (Predicted brain/blood partition coefficient = -3.0 - 1.2); I (Number of likely metabolic reactions = 1 - 8); J (% Human oral absorption ≥ 80 % → High, < 25 % → Poor); K (Van der Waals surface area of polar nitrogen and oxygen atoms = 7.0 - 200.0); L (Human serum albumin = -1.5 - 1.5); M (Number of violations of Lipinskis Rule of Five; mol MW < 500, QPlogPo/w < 5, donor HB ≤ 5, accept HB ≤ 10. Compounds that satisfy these rules are considered drug-like

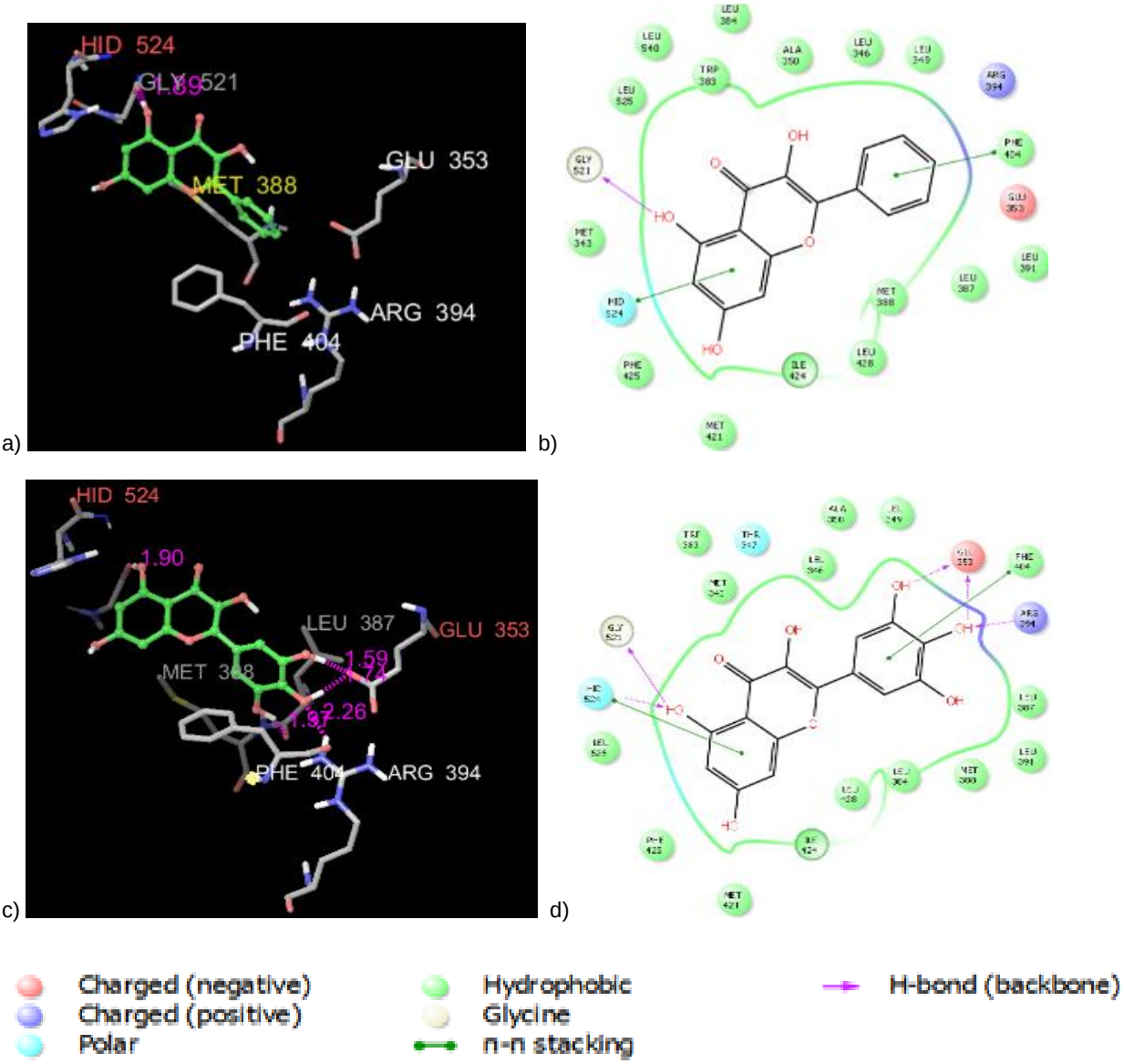
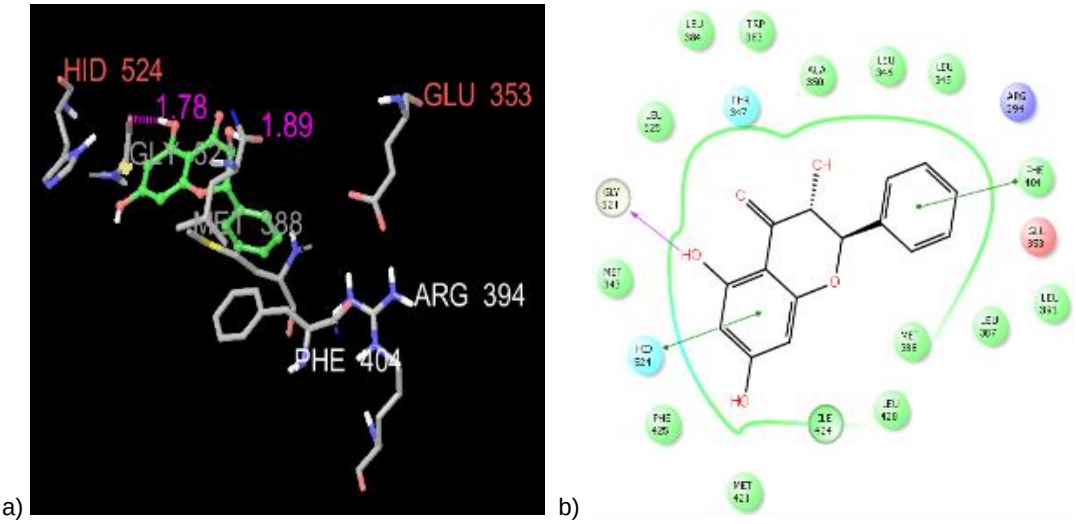


Figure 2: Molecular interactions of gelagin and myricetin at the Y537S-hERα-LBD: (a) 3D binding interaction of gelagin, (b) 2D interaction of gelagin, (c) 3D binding interaction of myricetin, (d) 2D interaction of myricetin



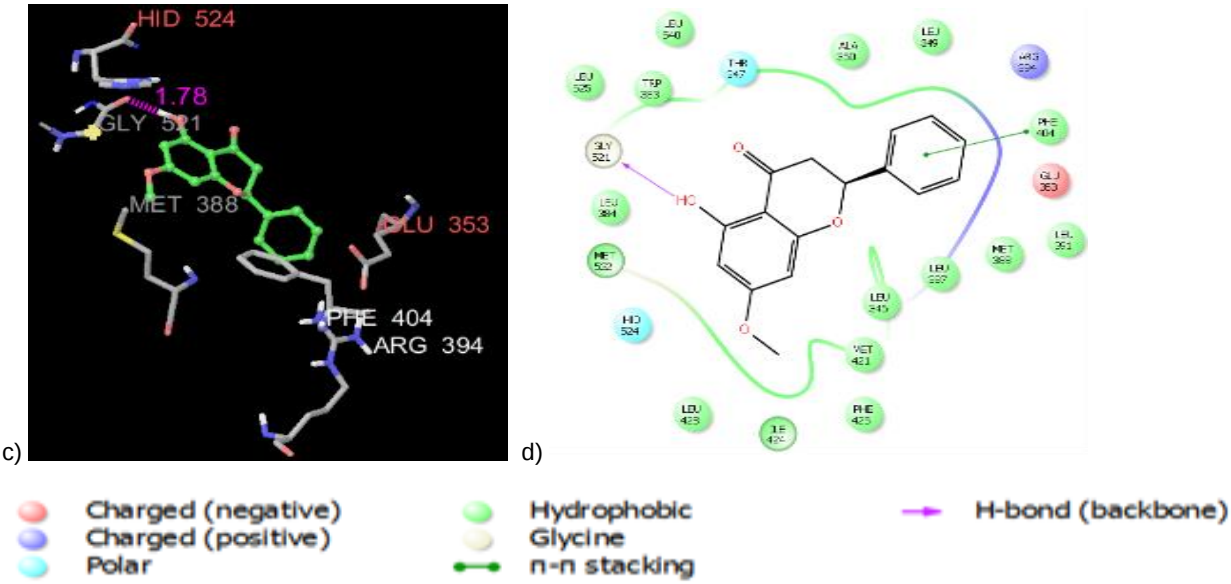


Figure 3: Molecular interactions of pinobanksin and pinostrobin at the *Y537S-hERα-LBD*: (a) 3D binding interaction of pinobanksin, (b) 2D interaction of pinobanksin, (c) 3D binding interaction of pinostrobin, (d) 2D interaction of pinostrobin

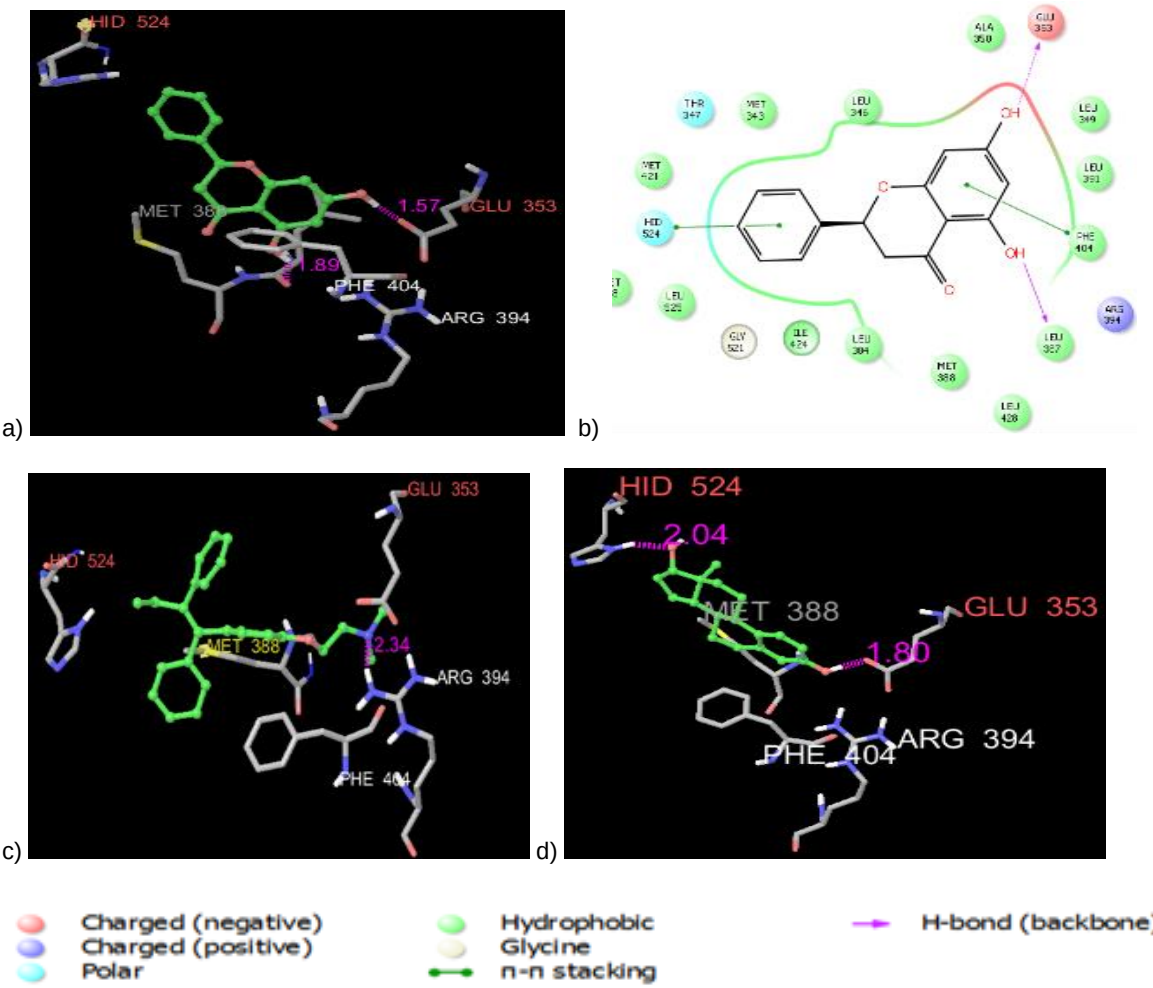


Figure 4: Molecular interactions of pinocembrin, tamoxifen and estradiol at the *Y537S-hERα-LBD*: (a) 3D binding interaction of pinocembrin, (b) 2D interaction of pinocembrin, (c) 3D binding interaction of tamoxifen, (d) 3D interaction of estradiol

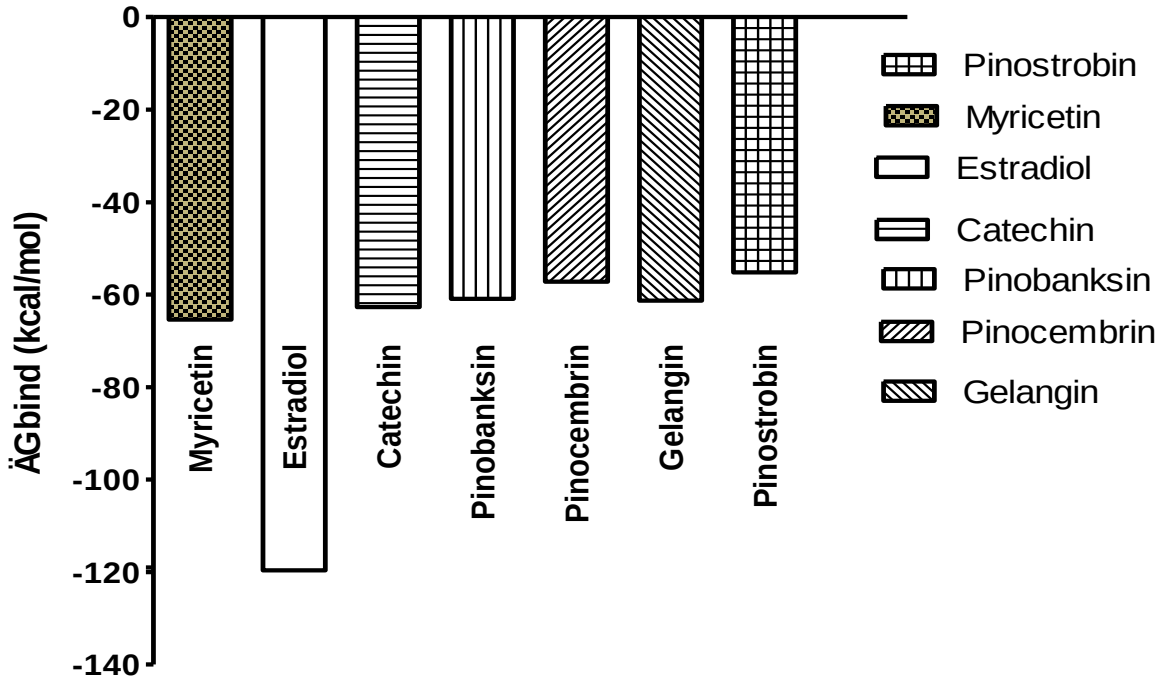


Figure 5: Free energy of binding ΔGbind (kcal/mol) for the studied ligands with the hERα binding site

Table 2: Output properties from a Prime MM-GBSA calculation for the studied ligands

Molecule	ΔGbind Coloumb	ΔGbind Hbond	ΔGbind lipophylic	ΔGbind vdW
Myricetin	-34.658	-2.235	-34.511	-33.239
Estradiol	-20.097	-2.048	-66.632	-47.059
Catechin	-28.643	-2.949	-39.082	-23.324
Pinobanksin	-13.609	-0.092	-36.347	-35.558
Pinocembrin	-14.970	-0.990	-36.565	-26.755
Gelangin	-9.446	-0.165	-34.435	-37.534
Pinostrobin	-5.321	-0.239	-41.357	-25.884

Investigation of pharmacokinetic profile is a vital approach in drug discovery and poor profile has been blamed for the high attrition rate of new chemical entities [13]. The studied molecules have been shown to possess good physicochemical properties in comparison to 95 % of orally available drugs [8]. *In silico* prediction of aqueous solubilities and human oral absorption had been reported to correlate well with *in vivo* bioavailability [14]. The studied molecules showed good solubilities and human oral absorption as well as intestinal permeability, which are the rate-limiting barriers for oral drug absorption. To predict the distribution of studied ligands, their plasma protein binding and blood-brain barrier penetration were investigated. Unlike all compounds that showed good distribution, tamoxifen, however, did not comply within the range, indicating its high potential binding to albumin. This observation was in line with previous report on the high protein binding affinity of tamoxifen to serum albumin [15,16].

Considering blood-brain barrier permeation, studied compounds showed no tendency to cross it. Hence, central nervous system toxicity is not evident. The studied molecules were also investigated to predict the possible number of biotransformations that could point to potential toxicities. From the results, all the compounds complied with the range of metabolic reactions displayed by 95 % of orally available drugs. These *in silico* predictions of pharmacokinetic-related profiles of intended drug molecules help to reduce the rate of attrition of new chemical entities in clinical trials, thus, reducing the cost of bringing a candidate drug to the market.

Inhibition of LBD of Y537S-hERα is a targeted approach of directly inhibiting a specific ER implicated in breast cancer. This gives specificity in approaching BC, a heterogenous malignancy with over 20 characterized subtypes. Awareness of ERα conformational changes related to

mutations has been brought to the fore with emerging biophysical techniques, inspiring understanding of the ERα response to estrogen and antiestrogens. According to *in vitro* studies, Y537S mutations that confer ligand-independent activity to ERα remain sensitive to tamoxifen and fulvestrant when therapeutic doses are increased [17]. Hence, the need for more potent options suitable to overcome endocrine resistance.

The competitive inhibition observed with the studied small molecules to LBD of Y537S-hERα, altered the conformation of the mutated ER+ receptor, distorting the positioning of regions within its ligand-binding pocket. This observation will prevent downstream signaling and render cancer cells harboring Y537S mutation and exposed to these phytochemicals susceptible to apoptosis. The residues of estrogen receptors that partook in this binding interaction were earlier reported to play critical roles in the inhibition of the ligand binding domain of hERα [18]. These molecules may be harnessed as promising agents that subvert resistance to endocrine therapies in breast cancers.

CONCLUSION

Estrogen receptor alpha (Erα) is involved in breast cancer development. By directly inhibiting Erα or reducing circulating estrogen, endocrine therapy has been a strategy against luminal breast cancers. However, endocrine resistance exists in a significant number of patients, raising public health concerns. A prominent mechanism enabling tumor cells' resistance to hormonal therapy is a mutation of Erα. This development of resistance towards the standard of care promotes the need for more potent and selective agents against Erα in its native and mutated forms. These studies revealed promising small molecules with good pharmacokinetic properties and unique inhibitory potential against Y537S-hERα-LBD, a commonly mutated Erα and may be harnessed in the bid to subvert endocrine resistance in breast cancer.

DECLARATIONS

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Ethical approval

None provided.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors. Imaobong Etti conceived the idea, carried out the experiments, and analyzed the data, Arifah Kadir and Rasedee Abdullah prepared and edited the manuscript while Esther Uweh and Cecilia Okuku participated in the research.

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