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VIRTUAL SCREENING AND IDENTIFICATION OF PLAUSIBLE NOVEL THERAPEUTIC *EGFR* INHIBITORS AGAINST BREAST CANCER

Megana KSNM, Suneetha Y*

Department of Zoology, Sri Venkateswara University, Tirupati 517502.

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Computational tools

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ABSTRACT

Present days increasing concern about the identification of potential non-toxic drug candidates against several cancers is very important. The current study was carried out to discover the novel phytochemicals as effective anticancer agents against the selected protein (i.e., *EGFR*), which is a promising target for moderating triple-negative breast cancer (TNBC). Various studies showed that the natural constituents have a strong anti-tumor capacity and inhibiting tumor growth. Here structure-based virtual screening and molecular docking studies have been recognized as rational tactics for the recognition of novel drug candidates against the binding domain of *EGFR* (PDB code: 3GKW & 5FEE). Furthermore, the drug-likeness, adverse effects, and toxicogenomics effects were assessed with the help of various computational tools. Virtual screening was reported that 4 drug candidates i.e., CID: 65064; CID: 5280443; CID: 440735, and CID: 5280343 showed reliable consequences with fewer side effects and more efficient for the selected proteins. The overall effects indicated that renowned hits could be developed as reference skeletons for novel inhibitors envisaging *EGFR* to ameliorate TNBC.

* Corresponding author

E-mail: ysuneethareddy4@gmail.com (Dr. Y. Suneetha)

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1 Introduction

Breast carcinoma is the most prevalent disease in females around the world and it is the third deadliest cancer after lung and cervical cancers (Benson et al., 2012). Various factors including biological, genetic, and environmental factors are intricate in the progression of breast malignancy. Age, hormonal replacement therapy, family history, Obesity, genetic changes, etc., are some of the general factors that confer the threat of breast carcinoma (WHO 2014). According to the data from the IARC registry assessed new female breast cancer cases in the year, 2020 is 11.7%, and 6.9% of breast cancer-related death occurs in low-and middle-income economies (Hyuna et al., 2021). Under the data from ICMR-PBCR, carcinoma of the breast is common among women living in Indian states and metropolitan cities like Delhi, Kolkata, and Mumbai (National Centre Registry Programme 2016). The above reports powerfully recommend the implications of lifestyle factors as the most providers to develop breast cancer.

Usually, the dysregulation of the steroid hormones estrogen (ER), and progesterone (PgR) is associated with the risk of breast tumors. The family comprises 4 receptors *EGFR1*, Her2, Her3, and Her4. Epidermal growth factor receptors are highly expressed in tumors of breast cancer, pancreas, head, prostate, ovarian, and colon cancer. The overexpression of EGFRs relates to the pathogenesis and development of several human cancers, which make them good therapeutic targets for both diagnosis and therapy (Dai et al., 2016; Amaia et al., 2019).

Phytochemicals are naturally active non-nutritive chemicals. Nowadays, natural compounds are frequently investigated in modern medicine. Numerous reports have suggested that dietary compounds such as fiber, lignin's, phytoestrogens, soy protein, phenols, fruits, etc., can play a prominent role in cancer treatment and prevention (Alok et al., 2019). Presently most of the efficacious anti-cancer drugs are derived from traditional compounds or their analogs. The eating of raw vegetables and vitamin-rich fruits are useful for control the risk of breast cancer.

One of the active compounds used to treat cancer is eriodictyol (ER) [(S)-2-(3, 4-dihydroxy phenyl)-5,7-dihydroxychroman-4-one), a natural flavonoid compound (Marin et al., 2017), and a bitter-masking flavone, which is extracted from the plant *Eriodictyon californicum*. The compound is found in *Eupatorium arnotianum* (Clavin et al., 2007) and its glycosides (eriodictin) on rose hips (*Rosa canina*). Other natural plant-derived compounds that can be used for breast cancer treatment are EGCG, resveratrol, quercetin, curcumin, apigenin, daidzein, etc., (Wamidh et al., 2020). EGCG is a powerful antioxidant, and it has been used as a breast cancer chemopreventive phytochemical candidate found in green tea (*Camellia sinensis* (Theaceae) (Sumio et al., 2020). EGCG (-)-Epigallo Catechin gallate, (-) -Epicatechin gallate

(EGC), EGC, and Epicatechin (EC) are the important polyphenol natural compounds which are reported in high quality in green tea (Yao et al., 2008; Lambert & Elias, 2010; Musial et al., 2020).

Resveratrol (*trans*-3, 4', 5-trihydroxy stilbene) is a member of the stilbene family and it's also a polyphenol compound like flavonoids. Resveratrol was first discovered longer than sixty years ago by Takaoka, in the cohesive substance of *Veratrum grandiflorum* oleo's (John 2019). RES is highly available in dietary foods, including grapes, peanuts, berries, red wine, dark chocolate, and traditional oriental medicinal plants (Berman et al., 2017; Bahare et al., 2018; Xiao et al., 2019). High RES (resveratrol) concentrations are present in grapes, perhaps because of *Vitis vinifera*, which are responsive to fungal infections (Li et al., 2015; Nawaz et al., 2017). Many scientific reports concluded that RES has shown several beneficial effects on the health of human beings and could be useful to defend against several pathologies (Wahab et al., 2017; Abhay et al., 2018). RES also acts as a preventive and chemotherapeutic agent against various human disorders (Sinha et al., 2016). Various wet biology experiments have been described that the RES exhibits activation in both hormonal sensitivity and resistance in breast cancer cells. This bioactive molecule is a potential phytoestrogen and acts as an agonist and antagonist for control ER+ breast carcinoma (Sandipan et al., 2013; Roca et al., 2014). Hence, the prediction of novel potential drug candidates is very essential for future utilization. The selected natural ligands: Eriodictyol (Pubchem CID: 440735); Resveratrol (CID: 445154); Epigallo Catechin 3-gallate (CID: 65064); Piceatannol (CID: 667639); p-Coumarin acid (CID: 637542); Curcumin (CID: 969516); Quercetin (CID: 5280343); Apigenin (CID: 5280443); Daidzein (CID: 5281708) has outstanding anti-cancer activity, better PK, and ADMET properties. Based on their parameters, these phytochemicals were chosen for the current study. This study aimed to predict the best breast cancer inhibitors by using *in silico* studies and exploration of the molecular docking simulations against the selected *EGFR* receptors.

2 Materials and methods

2.1 Structure Retrieval

A crystallographic macromolecular structure of EGFR (Epidermal growth factor receptor) was downloaded from PDB (www.rcsb.org/pdb). The structure identified in PDB by the ID of 5FEE and 3GKW, Res: 1.85Å & 2.70Å as receptor models for docking studies.

2.2 Retrieval of ligands

The structure of all compounds in this study was retrieved from the Pub Chem compound database (<http://pubchem.ncbi.nlm.nih.gov/>).

The selected chemical structures were downloaded in 3D SDF file format. After that, the downloaded molecules were minimized by using the Software open Babel, and the energy difference is less than 0.1. All the optimized ligands were converted to PDBQT format in the Pyrx Interface for docking studies.

2.3 Molecular docking simulations and grid parameter file

Molecular screening is the most important approach in the structure-based drug designing process (Dallakyan & Olson, 2015). Docking simulation studies were done using the AD Vina in PyRx interface open-source software for selected optimized hits against the active site of the macromolecule. The active site dimensions selected as a grid center $x=-3.6117$, $y=18.9549$, $z=-21.7196$, and grid dimensions $x=43.1664$ Å, $y=47.1486$ Å, $z=59.2543$ Å for 5FEE; While for 3GKW the active site dimensions as a grid center $x=2.8973$, $y=-5.4929$, $z=-17.4551$ and grid dimensions $x=71.1868$ Å, $y=54.1961$ Å, $z=45.2106$ and the free energy function and Lamarckian genetic algorithm were used for docking with 8 exhaustiveness iteration for every selected ligand poses. The Root mean square deviation value 0.0 with binding energy was considered as the best docking fit for ligand and macromolecule interactions. The grid parameters that are essential to creating such a grid were stored in the Grid Parameter File with GPF extension. The grid dimensions of both the macromolecules are shown in figure 1.

2.4 Hydrogen bond and molecular interaction analysis

The receptor and ligand molecule interactions were investigated by using the software tool Pymol molecular viewer (Lill & Danielson, 2011; Pymol 2015). The better affinity compounds were evaluated along with hydrogen bond interactions, and interaction residues with atoms involved in hydrogen bonds for both the macromolecule and chemical compounds. Because hydrogen bond interactions are involved in molecular stabilization and lead to function by interaction.

2.5 Screening of bioactive ligands on the principle of RO5

The selected bioactive compounds were screened on the premise of Pfizer's lead of five criteria i.e. the drug candidates have the number of HBA $\leq$ 10, HBD is not more than 5, Partition coefficient

log P under five($\leq$ 5), and MW $\leq$ 500 Daltons (Lipinski et al., 2001). Other parameters such as water partition coefficient, volume, rotatable bonds, number of atoms, violations, drug-likeness, drug score, ADME, etc. were predicted using *in silico* methods. The best binding affinity values of ligands with the target receptors were investigated for its drug parameters, and adverse effects with the help of five different bioinformatics analytical tools, i.e., Admet Sar tool an inclusive source and free online tool for calculation of ADMET parameters available at <http://lmmd.ecust.edu.cn/admetSar> (Cheng et al., 2012), Molinspiration (<http://www.molinspiration.com/>), Swiss ADMEonline tool (<http://www.swissadme.ch/index.php>) (Daina et al., 2017), DruLiTo and OSIRIS property explorer programs, respectively.

3 Results and Discussion

3.1 Assessment of Physicochemical parameters

Analysis of pharmacological profiles of chemicals is imperative assortments before going for preclinical analysis and these ligands act as promising druggable compounds towards the therapy of various diseases. These consequences shall delineate what are the noticeable functionalities linked with their structures and how these chemical ligands act as drug-like candidates. Therefore, propitious pharmacological properties & toxicity profiles of molecules were precisely evaluated by molinspiration, DruLiTo software, and Osiris programs. According to table 1, all leads are verified for Pfizer's rule and the obtained parameters revealed that all the chemical molecules can satisfy RO5. Atomic and knowledge-based methods were used to predict the partition coefficient between n-Octanol and water (log Octanol/water) (Malkia et al., 2004) measuring the hydrophobicity of all complexes and it was reported the ranged between 1.49 to 2.46 (log P $\leq$ 5) which indicates all molecules are easily permeable. High lipophilic compounds are poorly permeated through membranes, as they get wedged in the lipophilic bilayer. High hydrophilic molecules cannot pass through membranes, as they hardly enter the hydrophobic interior of the lipophilic bilayer (Tsaion & Kates, 2013). It is suggestive that the Partition coefficient value must be

Figure 1 The grid dimensions of (a) 5fee (b) 3gkw.

Table 1 Prediction of Drug properties of best-docked complexes

	EGCG	Apigenin	Quercetin	Eriodictyol
<i>Physicochemical Properties.</i>				
Log P	2.05	2.46	1.834	1.63
TPSA	197	90.89	127.45	107.22
MW	458.08	270.24	302.04	288.06
AMR	120	80.15	83.44	80.13
nON	11	5	7	6
n-atoms	33	20	22	21
noHNH	8	3	5	4
nviolations	2	0	0	0
n rotatable bonds	4	1	1	1
volume	367.57	224.05	240.08	238.28
uwQED	0.158	0.755	0.467	0.629
wQED	0.197	0.722	0.458	0.618
<i>Toxicity risks</i>				
Mutagenic	None	YES	YES	None
Tumorigenic	None	None	YES	None
Irritant	None	None	None	None
Reproductive effect	None	None	None	None

Table 2 Molecular properties of selected macromolecules

S. No	Molecular properties	5FEE	3GKW
1	Classification	Transfer Inhibitor	Immune system
2	Structure Weight	37.86	48.24
3	Molecule	EGFR	EGFR
4	Chain	A	H
5	Length	328	222
6	UniProt ID	P00533	-
Source			
7	Organism	Homosapiens	Homosapiens
8	Common Name	Human	Human
Ligand/Chemical Component			
9	Identifier		
10	Formula	C ₂₅ H ₂₇ F ₃ N ₄ O ₂	C ₁₀ H ₂₂ O ₆ , C ₄ H ₁₀ O ₃
11	Name	~{N}-[7-methyl-1-[(3~{R})-1-propanoylazepan-3-yl]benzimidazol-2-yl]-3-(trifluoromethyl)benzamide	PENTAETHYLENE GLYCOL, DI(HYDROXYETHYL)ETHER

less than 5 (Vyas et al., 2013). The calculated values of Log P of these four compounds are within the limit of 5. Toxicity assets of ligands are informative and observable values. The top complexes i.e. Pub Chem CID: 65064, CID: 5280443, CID: 5280343, and CID: 440735 do not show irritation & reproductive effect, and Pub Chem CID: 5280343 might be tumorigenic. Osiris explorer model for mutagenicity the CID: 65064 (Epigallo Catechin 3-gallate), CID:440735 (Eriodictyol) are non-mutagens, and CID:5280443, CID:5280343 might be mutagens (low reliability).

3.2 Analysis of macromolecule properties

Overexpression of this protein receptor (EGFR) has been shown to associate with tumor menace and a bad prognosis for cancer patients (Mendelsohn & Baselga, 2006). The coordinates of the epidermal growth factor receptor have been deposited at the RCSB Protein data bank with the PDB accession Code: 3GKW & 5FEE (Talavera et al., 2009). The epidermal growth factor receptor PDB ID: 5FEE contains 2.70Å resolution and 37.86 MW with one identical chain A, 328 amino acid lengths with 2353 atom count. While the *EGFR* target PDB entry 3GKW contains 2.50Å contain

one chain H, 222 amino acid lengths, and 48.24 MW with the source organism *Homo sapien*. They exemplified the molecular properties of both the receptors in table 2.

3.3 Drug targets

A total of selected natural bioactive molecules were identified from the Pub med literature search that showed inhibitory properties of the selected molecules against the breast cancer cells. The 3-Dimensional structures of phytochemicals were downloaded in SDF file format. The structures of both proteins and chemical scaffolds used in this study are presented in figure 2.

3.4 Study of Pharmacokinetic & ADMET properties of compounds

Pharmacokinetics assets of compounds are informative evident values, which include all competitors to restrain the higher human gastrointestinal absorption (% HIA). Zhao et al. (2001) stated that most of the absorption data found in the published reports were based on excretion in urine, bioavailability, and oral administration. The most crucial tactic of the chemical & pharmaceutical industry to

Figure 2 List of chemical structures used in this study

overcome its efficacy crisis in drug discovery is to consider the most molecular features for ADME (Nazarshodeh et al., 2015; Wang et al., 2016). Plausible compounds were subjected to ADME, and probability scores assessment using the robust Swiss ADME and ADMETSAR programs. As per the results given in table 3, the pharmacokinetics properties of the top complexes i.e. CID: 65064, CID: 5280443, CID: 5280343 & Eriodictyol (CID: 440735) were showed good permeability for most of the parameters i.e. Blood-brain barrier coefficient was detected in 0.6047 & 0.6364 in best-hit compounds, CID:65064 & CID: 5280443 compared to other phytochemicals. CaCo_2 permeability, HIA (%), and the major cytochrome enzymes involved through CYP450 family genes were also predicted by using structural data (Reichel & Begley, 1998). Coming to excretion & toxicity, the obtained results of best hits were recorded as non-carcinogens with good probability scores of 0.9617, 0.9181, 0.9450, & 0.9513 compared to other ligands. The molecules CID: 65064, CID:

5280443 & CID:440735 having well drug scores, i.e. 0.7, 0.47 & 0.41 when compared to other ligands. The aqueous solubility is significantly affected by solubility. Lower the solubility, the lesser the absorption. The CID:65064 & CID: 440735 depicted maximum solubility (-3.52 & -3.62) while the second and third compounds were least soluble when compared to other molecules. The best drug scores, drug-related values such as drug-likeness properties, solubility, and rat oral dose (LD50) were evaluated for individual leads that are entered in figure 3. The pictorial representations of bioavailability radars are shown in figure 5. The overall findings of the current study revealed that the four docked complexes have the highest binding affinity values and acceptable biological features with less adverse effects; So based on that consequences they may be used as hopeful druggable candidates for human *EGFR* toward moderating the progression of triple-negative breast cancer (TNBC) and other malignancies associated with the *EGFR* and their biological pathways.

Table 3 ADMET Profiles of ligand molecules

	65064		5280443		5280343		Eriodictyol	
	Result	Probability	Result	Probability	Result	Probability	Result	Probability
Absorption								
Blood-Brain Barrier	BBB-	0.6047	BBB+	0.6364	BBB-	0.5711	BBB-	0.5784
Human intestinal Absorption	HIA+	0.8867	HIA+	0.9887	HIA+	0.9650	HIA+	0.9223
Caco2 Permeability	Caco2-	0.8957	Caco2+	0.8541	Caco2-	0.8957	Caco2-	0.8576
Distribution & Metabolism								
CYP450C9 Substrate	Non-substrate	0.8225	Non-substrate	0.7813	Non-substrate	0.7898	Non-substrate	0.7669
CYP450D6 Substrate	Non-substrate	0.9057	Non-substrate	0.9126	Non-substrate	0.9116	Non-substrate	0.8782
CYP450A4 Substrate	Non-substrate	0.6299	Non-substrate	0.6907	Non-substrate	0.6530	Non-substrate	0.5849
CYP inhibitor promiscuity	Low CYP Inhibitory Promiscuity	0.8067	High CYP Inhibitory Promiscuity	0.7316	High CYP Inhibitory Promiscuity	0.5822	Low CYP Inhibitory Promiscuity	0.5488
Excretion & Toxicity								
Human Ether-a-go-go-related gene inhibition	Weak inhibitor	0.9847	Weak inhibitor	0.9559	Weak inhibitor	0.9781	Weak inhibitor	0.9756
AMES Toxicity	Non-Ames toxic	0.9040	Non-Ames toxic	0.8906	Non-Ames toxic	0.7220	Non-Ames toxic	0.7215
Carcinogens	Non-carcinogens	0.9617	Non-carcinogens	0.9181	Non-carcinogens	0.9450	Non-carcinogens	0.9513
Acute oral toxicity	IV	0.3764	III	0.7012	II	0.7348	II	0.4796

Figure 3 Drug properties of best virtual leads

Figure 5 The bioavailability radars of the best virtual hits

3.5 Visualization of screening results of proteins and bioactive ligand molecules

The virtual screening of ligands with a protein target of *EGFR* (5FEE & 3GKW) is used by employing AD Vina in the PyRx interface, and the outcomes were imaged by utilizing the Pymol visualization tool (figure 4). Out of nine active bio compounds i.e., Pub Chem CID: 440735; CID: 445154; CID: 65064; CID: 667639; CID: 637542; CID: 969516; CID: 5280343; CID: 5280443; CID: 5281708. Among these phytochemicals, five docking scaffolds showed the least

minimum binding affinity values, i.e. -5.6, -6.6, -7.0, -7.0, and -7.7 kcal/mol ΔG binding energies with the 5FEE receptor. Whereas three complexes showed minimum binding energy values, i.e. -5.7, -7.0, -7.1, with the target protein PDB ID: 3GKW compared to other molecules used in these studies. The top four molecules, i.e. CID:65064 (EGCG); CID:440735 ((S)-2-(3,4-dihydroxy phenyl)-5,7-dihydroxychroman-4-one); CID: 5280343 (3,3',4',5,7-Pentahydroxyflavone); CID: 5280443 (5,7-Dihydroxy-2-(4-hydroxyphenyl)-4H-chromen-4-one) displayed the highest binding affinities and showed inhibitory activity against breast cancer.

Figure 4 Visualization of top docked complexes

Table 4 Binding affinities of ligand molecules that can be used in these study

Pubchem ID	Molecule name (IUPAC)	ΔG binding energy (kcal/mol)		Interacting residues	
		5FEE	3GKW	5FEE	3GKW
440735*	(2S)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one.	-7.7	-8.1	MET ⁷⁹³ , LYS ⁷⁴⁵	GLY ⁴² , GLN ⁴³
445154	5-[(E)-2-(4-hydroxyphenyl)ethenyl]benzene-1,3-diol.	-6.6	7.0	THR ⁸⁵⁴ , PRO ⁷⁹⁴	GLN ⁴²
65064*	[(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate.	-8.6	-8.4	ASP ⁸⁵⁵ , CYS ⁷⁹⁷ , ARG ⁸⁴¹	GLY ⁴² , GLN ³⁸ , GLY ⁴¹ , GLU ¹⁴⁸ , GLN ⁴³
667639	4-[(E)-2-(3,5-dihydroxyphenyl)ethenyl]benzene-1,2-diol.	-7.0	-7.1	GLY ⁹¹⁷ , ILE ⁹¹⁸ , TYR ⁹¹⁵ , ARG ⁸⁴¹ , SER ⁹¹²	THR ³⁹ , GLY ⁴² , SER ⁷
637542	(E)-3-(4-hydroxyphenyl) prop-2-enoic acid.	-5.6	-5.7	LEU ⁷⁶⁰	SER ¹⁰
969516	(1E,6E)-1,7-bis(4-hydroxy-3-methoxyphenyl)hepta-1,6-diene-3,5-dione	-7.0	7.6	-	SER ⁷ , LYS ¹⁰³
5280343*	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-on	-7.7	-7.6	MET ⁷⁹³ , LYS ⁷⁴⁵ , LEU ⁷¹⁸	GLN ⁴³ , GLN ⁴² , ALA ⁴⁰
5280443*	5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one	-7.7	-8.3	LYS ⁷⁴⁵ , MET ⁷⁹³	ALA ⁴⁰ , GLY ⁴²
5281708	7-hydroxy-3-(4-hydroxyphenyl)chromen-4-one	-7.1	-7.6	LYS ⁷⁴⁵ , GLU ⁷⁶²	GLY ⁴²

3.6 Binding mode analysis of best natural compounds with the protein structure

In this regard, the current study identified four Pub Chem compounds i.e., [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate (CID:65064); 5,7-dihydroxy-2-(4-hydroxyphenyl)chromen-4-one (CID:5280443); 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one (CID:5280343); (2S)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydrochromen-4-one (CID:440735) might be chosen as novel inhibitors for EGFR and these compounds having anti-tumor properties and have the high human epidermal growth factor receptor protein binding capability. The structures of these natural molecules with EGFR (5FEE) CID: 65064 having good binding energy value i.e.-8.6 kcal/mol. These shown interactions with ASP⁸⁵⁵, CYS⁷⁹⁷, and ARG⁸⁴¹. CID:5280443 contains a binding energy value of -7.7 kcal/mol this was shown to interact with LYS⁷⁴⁵, MET⁷⁹³. CID: 440735 having a better affinity value i.e. -7.7 kcal/mol, this shows the interaction with MET⁷⁹³, LYS⁷⁴⁵, and another EGFR Protein (3GKW) CID: 65064 having ameliorated affinity value is -8.4 kcal/mol. This was shown to interact with GLY⁴², GLN³⁸, GLY⁴¹, GLU¹⁴⁸, and GLN⁴³. CID: 5280443 having a binding energy value is -8.3 kcal/mol. This was shown an interaction with ALA⁴⁰ and GLY⁴². The interacting residues and binding

energy values of all compounds that can be used in this study are elucidated in table 4. The receptor and ligand interacting residues of top complexes are shown in figure 4. Hopefully, these results may be used for novel breast cancer drugs against EGFR.

Conclusion

The present study recognized the potential medication that emphasis against the target protein (EGFR) as a characteristic solution to prevent breast carcinoma. The focal objective of the virtual screening and *in silico* based assessments used in this study was to portray as rational strategies for recognition of novel natural inhibitors for human EGFR. The binding affinity values and the interacting residues of the protein-ligand complexes showed that 2 natural compounds have greater binding affinities, respectable drug scores, and fewer adverse health effects. Based on these criteria, it can be suggested that the characterized leads may act as intense druggable inhibitors against EGFR and can be used as anti-cancerous agents to treat breast cancer. It can be concluded that our novel comparative strategies can reveal potential leads and non-toxic molecules that may proficiently act as promising templates against EGFR for reducing TNBC. The research work will be continued on cell lines in wet biology experiments and then *in vivo* studies.

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Conflict of interest

No conflict of interest is associated with this work.

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