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In-silico study on plant determined flavonoids compounds for the synthetic medications against breast cancer growth

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ABSTRACT

Breast cancer is one of the genuine wellbeing worries in India bringing about the most elevated death rate in females, which happens because of uncontrolled cell division and can be metastasize to different parts of the human body, and different medications are accessible to its cure. Drugs like Tamoxifen and Herceptin can cure breast cancer however these medications have their unsafe impacts on human body. This study deals with the docking, toxicity, bioactivity and ADME expectation of flavonoids compounds with HER2 and estrogen receptor, to limit the utilization of existing medications. Lipinski's channel is utilized to screen the flavonoids compounds on the premise of five tenets. Out of 200 flavonoids compounds 15 compounds were screened on the premise of Lipinski's channel. The outcomes uncovered that the top positioning screened flavonoids indicates greatest docking and minimum binding energies with the HER2 and ER receptor when contrasted and the accessible medications. The above analysis demonstrated the compounds ST026594 (7-hydroxyflavone), ST070967 (2-(- 4-fluorophenyl)- 4n-chromen-4-one), ST086622 (3-hydroxyflavone) and ST055369 (8-methylflavone) were the best compounds indicating minimum binding energy in correlation with medication Tamoxifen with Estrogen receptor and compounds ST060160 (4-hydroxyflavone) and ST058442 (6,3-dimethylflavone) were the best compounds indicating minimum binding energy in examination with medication Herceptin with HER2 receptor, were likewise bioactive and non dangerous in nature with great pharmokinetics properties and drug likeliness.

Keywords: Flavonoids, Docking, ADME, Bioactivity, Toxicity.

INTRODUCTION

Breast cancer is one of the deadly ailments that bringing about higher death rates in females around the world. Breast cancer causes when cells in the breast cancer start to become wild and can be metastasize to different parts of the human body. Breast cancer can be estrogen positive and HER2 (human epidermal growth factor receptor) positive. There are different sorts additionally, however here we are managing (estrogen receptor) ER and HER2 positive breast cancer. In estrogen positive breast cancer the cells develop in light of hormone estrogen. Around 80% of the breast cancers are of estrogen positive cancer and about 20% of breast cancer is due to the cells makes excessively of protein known as human epidermal growth factor receptor 2 proteins [1]. HER2 quality makes HER2 protein, HER2 proteins are receptors on breast cells. In 25% of breast cancer the HER2 quality doesn't work legitimately and makes excessively numerous duplicates of it known as HER2 gene amplification. This makes breast cells develop and partition in an uncontrolled way (http://www.breastcancer.org/symptoms/diagnosis/her2). This sort of cancer is called HER2 positive. While in estrogen receptor positive cancer the cancerous cell are getting development signals from estrogen proteins. The most widely recognized receptor is estrogen receptor-α include in ER positive cancer [2]. In spite of the fact that these sorts of cancer are reparable if identified at early stage, different medications are accessible for the treatment of ER positive and HER2 positive breast cancer. Medications like Tamoxifen, Raloxifene, Toremifene are at present being used to help ER positive cancer and Herceptin is utilized as a part of treating HER2 breast cancer [3]. Ingestion of these medications causes many symptoms like blood clumps, strokes, uterine cancer, etc [4]. The side-effects of these medications made us to discover an option and conventional way to deal with breast cancer. Plant compounds are one of the alternative ways to treat various cancers [5]. Discovering new drug compound from the common flavonoids which are possessing anti-breast cancer activity and furthermore not having any symptoms to human ordinary cell [6, 7]. Flavonoids are plant compounds have high binding affinity for breast cancer receptors, flavonoids are group of natural polyphenolic compounds found in fruits, tea, red wine, cereals, vegetables and exhibit anti-oxidant, anti-carcinogenic, anti-inflammatory, anti-proliferative properties [8, 9].

The objective of this study is to explain the auxiliary components of flavonoid derivatives against the receptor proteins by *in-silico* examination i.e. by performing docking, toxicity checking and ADME analysis.

The analysis should be possible by using the different bioinformatics tools and to decide the drug likeliness. This technique is known as Computer Aided Drug Discovery (CADD). *In-silico* CADD systems can be led as key to create and screen the compounds or medications to make compelling leads for treatment of various infections. Structure based drug designing philosophies includes the 3-D structure of protein on which docking analysis of a few particular small molecules have been endorsed so as to compute their docking score and binding affinity of ligands and their cooperating residues. The virtual screening and molecular docking of the medication hopefuls on check protein could find to settle the lead [10]. The study manages the docking of receptor with flavonoid derivatives taken after by bioactivity prediction by Molinsipiration online tool, Toxicity checking by lazar online tool and by toxicity checker and ADME analysis.

MATERIALS AND METHODS

Receptor protein as target

Breast cancer primarily of two sorts one Estrogen positive and other is HER2 positive, Estrogen positive is related with hormone estrogen and estrogen receptor while HER2 quality encodes HER2 proteins which are receptors on breast cells, in cancerous cell this quality makes excessively numerous duplicates of itself, HER2 quality advise breast cell to make HER2 receptor. Hence these two receptors were utilized as target protein with flavonoids in correlation with existing medications.

3D structure recovery of target protein

The three dimensional protein 3D structure of Human Estrogen Receptor and Human Epidermal growth factor receptor 2 (HER2) were recovered from PDB (http://www.rscb.org/pdb). The complex related with protein and unnecessary waters were removed by utilizing discovery studio.

The flavonoids were downloaded in 3D format from Pub-Chem database and downloaded flavonoids screened by using Lipinski's filter on the basis of Lipinski's rule of five is a rule of thumb to evaluate drug likeness which states that an orally active drug has no more than one violation of following criteria i.e., has not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular weight below 500 Daltons, partition co-efficient log P less than 5 [11].

Docking of protein receptor with the screened flavonoids subordinate.

The proteins arranged in above stride were utilized for docking by utilizing Auto-Dock 4.2.5 with the flavonoids alongside the medications Tamoxifen and Herceptin and thought about the outcomes. Those flavonoids which were demonstrating less binding energy like binding energy of with medications were thought to be more medications like compounds.

Bioactivity prediction of compounds by utilizing Molinspiration software

The docked flavonoids which demonstrated low binding energy with the protein receptors were broke down with molinspiration tool for anticipating bioactivity of the compounds to check whether the compounds were bioactive or not.

The bioactivity scores of compounds showed the likelihood of good to direct activity towards GPCR ligands, particle channel modulators, kinase inhibitors, molecular receptor ligands, protease inhibitors and other enzyme targets.

Active (bioactivity score>0),

Moderately active (-5.0-0.0) and

Inactive (<-0.5)

Toxicity determination of bioactive compounds

The compounds which are observed to be bioactive are analyzed further to check toxicity of compounds on human cells. To decide toxicity there were two tools utilized; first tool was Lazar prediction tool which decided the capacity of compounds to cross Blood Brain Barrier (BBB) and to check the cancer-causing nature of the compounds and second tool was Toxicity checker which utilizes SMILES format of the compounds or ligands and molecular structure was drawn and was checked for poisonous substructure.

ADME examination

The ADME (ingestion, dispersion, digestion and discharge) examination was done by utilizing Swiss ADME tool accessible online which decides the lipophilicity, water dissolvability, pharmacokinetics properties like GI retention and drug likeliness of compounds.

RESULTS

Structure Retrieval

3D structures of estrogen receptor (PDB ID 5T92) and HER2 receptor protein (PDB ID 5JIH were recovered from PDB showed in Fig.2 (a) and 2(b).

Screening of ligand on the premise of Lipinski's rule of five

The Fifteen flavonoids compounds were screened on the premise of lipinski's lead of five criteria i.e., a compound has not more than 5 hydrogen bond donors, not more than 10 hydrogen bond acceptors, molecular weight beneath 500 Daltons, partition co-efficient log P under 5, which is showed in below table (1).

Visualization of docking results of receptors and flavonoids by PYMOL.

The Docking of compounds or ligands with that of receptors (HER2 and estrogen receptor) is done by utilizing Auto Dock 4.2.5 and the outcomes were imagined by utilizing Pymol (fig.1 (a) and (b)). The out of fifteen compounds 8 compounds showed least minimum binding energy with ER receptor while 6 compounds showed least minimum binding energy with HER2 receptor in comparison with minimum binding energy scores with the accessible medications, which is showed in table (2).

Bioactivity expectation by Molinsipiration

The molinspiration comes about demonstrates that screened compounds were bioactive. Demonstrate the activity of compounds showing minimum binding energies with the receptors shown in table (3).

Toxicity Checking of Ligand compounds

The compounds were additionally examined for toxicity checking by an online tool Lazar toxicity prediction and by Toxicity checker. The lazar toxicity prediction tool decides the blood brain barrier ability and the cancer-causing nature of the compounds, showed in table (4). While the toxicity checker decides (shown in Fig. 3) the presence of any Toxic substructure was checked by the online tool Toxicity checker molecule by putting SMILES Sequence of the compounds.

The lazar toxicity confirmed that flavonoids compounds with ID ST070967 and ST086622 are Carcinogenic in Nature. Subsequently not appropriate for Drug designing.

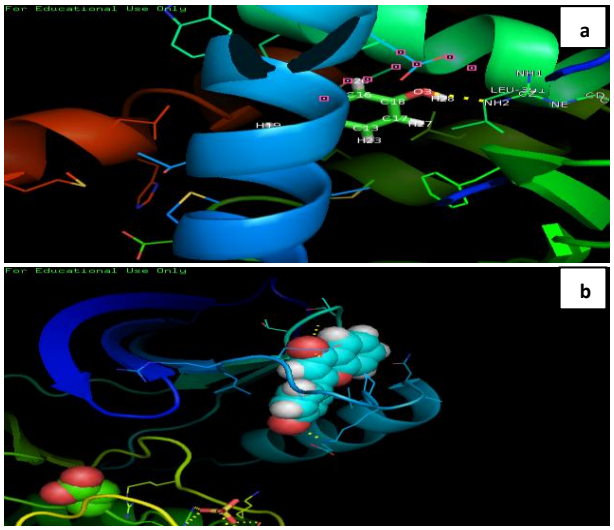


Figure 1: (a) ST026594 with ER; **(b)** ST060160 with HER2

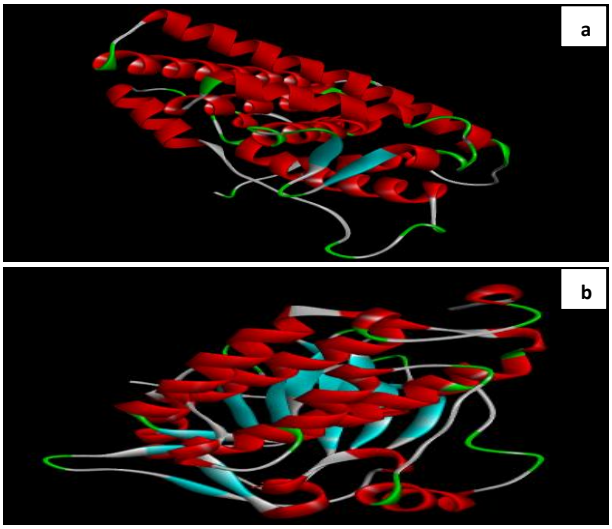
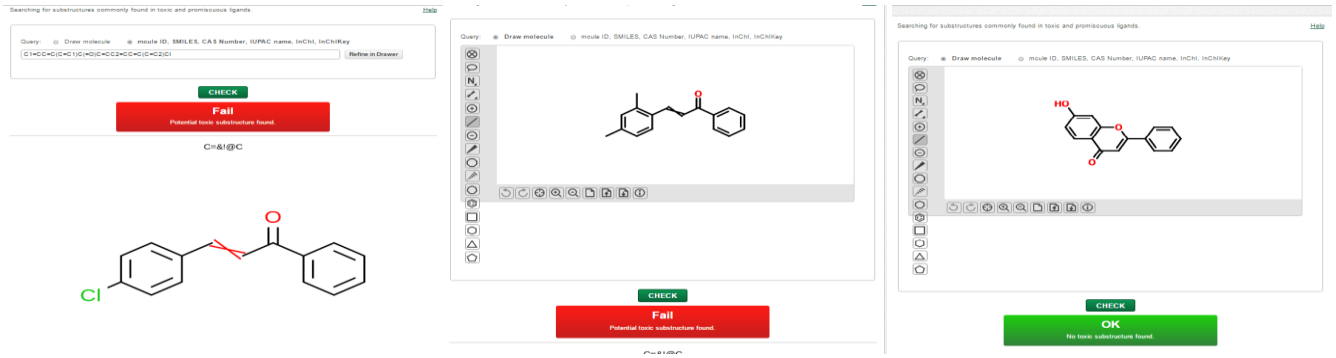
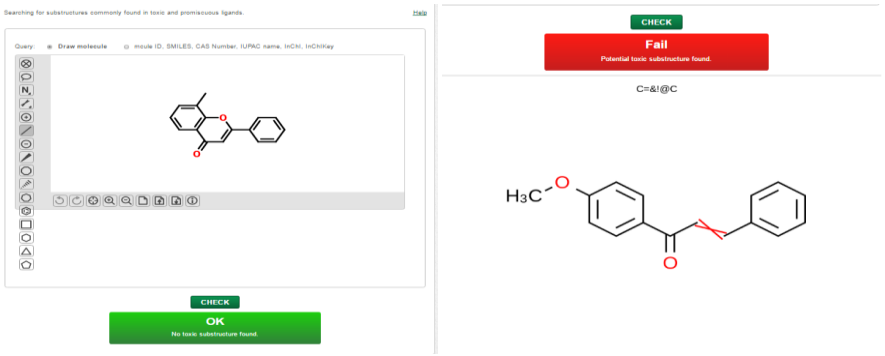


Figure 2: (a) 3D structure of Estrogen receptor; **(b)** 3D structure of HER2 receptor



1. ST001473 **2. ST019933** **3. ST026594**



4. ST055369 **5. ST059919**

Figure 3: Showing few flavonoids compounds with toxic substructure determined by toxicity checker.

Table 1: Flavonoids compounds screened by using Lipinski's filter

S No	Ligands (timtec ID)	Chemical Formula	Molecular Mass	Hydrogen Bond donors	Hydrogen Bond acceptors	LogP
1.	ST001473	C15H11ClO	242.71	0	1	3.891119
2.	ST019933	C17H16O	236.32	0	1	4.199539
3.	ST026594	C15H10O3	238.25	1	3	3.008399
4.	ST055369	C16H12O2	236.27	0	2	3.611218
5.	ST055369	C15H12O3	240.26	1	3	3.098699
6.	ST059082	C15H10O3	238.25	1	3	3.008399
7.	ST059919	C16H14O2	238.29	0	2	3.591299
8.	ST060160	C15H10O3	238.25	1	3	3.008399
9.	ST069348	C16H12O2	236.27	0	2	3.611218
10.	ST070967	C15H9FO2	240.24	2	3	2.993899
11.	ST072640	C15H12O3	240.26	2	3	2.993899
12.	ST079153	C15H12O3	240.26	1	3	3.098699
13.	ST086622	C15H10O3	238.25	1	3	3.188499
14.	ST019949	C18H18O	250.34	0	1	4.507959
15.	ST058442	C17H14O2	250.3	0	2	3.919639

Table 2: Binding energy of flavonoids compounds with ER and HER

S No	Compound ID	Binding energy with ER (kcal/mol)	Binding Energy with HER2 (kcal/mol)
1.	Tamoxifen	-8.92	-
2.	Herceptin	-	-8.98
3.	ST001473	-8.5	-7.5
4.	ST019933	-8.3	-7.3
5.	ST026594	-8.7	-6.1
6.	ST055369	-8.9	-6.01
7.	ST059080	-7.5	-7.3
8.	ST059082	-7.4	-7.5
9.	ST059919	-8.7	-8.8
10.	ST060160	-6.7	-8.9
11.	ST069348	-7.4	-7
12.	ST070967	-8.87	-7.3
13.	ST072640	-7.7	-8.72
14.	ST079153	-6.8	-7.2
15.	ST086622	-8.9	-8
16.	ST019949	-8.89	-9
17.	ST058442	-6.3	-8.83

Table 3: Shows Bioactivity of Selected flavonoids compounds

I D	GPCR ligand	Ion-channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
ST001473	-0.34	0.16	-0.51	0.45	0.5	0.13
ST019933	0.29	0.28	-0.1	0.37	-0.3	0.15
ST026594	-0.20	-0.17	0.0	0.10	-0.45	0.14
ST055369	0.12	0.21	0.18	0.23	-0.1	-0.21
ST059919	0.23	-0.24	0.45	0.3	-0.32	0.2
ST070967	0.22	0.0	-0.12	0.46	-0.02	0.23
ST060160	-0.17	-0.13	0.00	-0.08	0.2	0.12
ST072640	0.32	-0.01	0.11	0.39	-0.2	0.4

ST086622	0.05	0.30	0.02	0.37	-0.13	-0.21
ST019949	0.02	-0.21	0.0	0.32	0.5	-0.19
ST058442	-0.19	-0.29	-0.19	0.0	0.37	0.2
Tamoxifen	0.3	0.0	-0.01	0.57	0.0	0.32
Herceptin	0.32	0.12	-0.12	0.49	0.0	-0.23

Table 4: Shows Blood brain carrier capacity and carcinogenicity of the compounds

Compound ID	Blood Brain Barrier	Carcinog-enicity
ST001473	Penetrating	Active
ST019933	Penetrating	Active
ST026594	Penetrating	Inactive
ST055369	Penetrating	Inactive
ST059919	Penetrating	Active
ST060160	Penetrating	Inactive
ST070967	Penetrating	Inactive
ST072640	Penetrating	Active
ST086622	Penetrating	Inactive
ST019949	Penetrating	Inactive
ST058442	Penetrating	Inactive
HERCEPTIN	Penetrating	Inactive
TAMOXIFEN	Penetrating	Inactive

Table 5: Shows ADME pharmokinetics properties of the compounds

Ligand ID	Liphophilicity	Water solubility	Pharmokinectics		Drug likeliness
			GI absorption	Blood brain barrier	
ST001473	2.82	-4.01(moderately soluble)	HIGH	YES	YES
ST019933	2.96	-4.39(moderately soluble)	HIGH	YES	YES
ST026594	2.22	-4.19(Partially soluble)	HIGH	YES	YES
ST055369	2.73	-4.37(partially soluble)	HIGH	YES	YES
ST059919	2.20	-3.92(soluble)	HIGH	YES	YES
ST060160	2.65	-4.25(moderately soluble)	HIGH	YES	YES
ST070967	2.19	-4.23(partially soluble)	HIGH	YES	YES
ST072640	1.91	-3.85(soluble)	HIGH	YES	YES
ST086622	2.44	-4.05(partially soluble)	HIGH	YES	YES
ST019949	3.18	-4.7(moderately soluble)	HIGH	YES	YES
ST058442	3.07	-4.65(partially soluble)	HIGH	YES	YES
HERCEPTIN	2.19	-3.92(soluble)	HIGH	YES	YES
TAMOXIFEN	2.22	-3.8(soluble)	HIGH	YES	YES

Bioactivity expectation by Molinsipiration

The molinspiration comes about demonstrates that screened compounds were bioactive. Demonstrate the activity of compounds showing minimum binding energies with the receptors shown in table (3).

Toxicity Checking of Ligand compounds

The compounds were additionally examined for toxicity checking by an online tool Lazar toxicity prediction and by Toxicity checker. The lazar toxicity prediction tool decides the blood brain barrier ability and the cancer-causing nature of the compounds, showed in table (4). While the toxicity checker decides (shown in Fig. 3) the presence of any Toxic substructure was checked by the online tool Toxicity checker molecule by putting SMILES Sequence of the compounds. The lazar toxicity confirmed that flavonoids compounds with ID ST070967 and ST086622 are Carcinogenic in Nature. Subsequently not appropriate for Drug designing.

ADME analysis

An extensive number of information including lipophilicity, water solvency, GI absorption and drug likeliness were controlled by utilizing Swiss ADME online tool. The outcome demonstrated that compounds were partially soluble, moderately soluble or soluble in water in correlation with the medications, likewise demonstrated the compound is for the most part medication like and prone to ingest through Gastro Intestinal tract shown in table (5).

DISCUSSION

The anticipated 15 regular flavonoid compounds utilized for docking studies. The after effects of the interactivity between the catalytic site deposits of target Human Estrogen Receptor protein and Human epidermal growth factor receptor protein and 15 Flavonoid compounds were showed in the Table 2. By analyzing the docking interactivity, ST026594 (7-hydroxyflavone), ST070967 (2-(- 4-fluorophenyl)- 4n-chromen-4-one), ST086622 (3-hydroxyflavone) and ST055369 (8-methylflavone) were found to have the most noteworthy initiation binding energy in kcal/mol scores of -8.7, -8,87, -8.9 and -8.9 with estrogen receptor in comparison with drug tamoxifen which has binding energy score of -8.92, which is almost equal to the binding energies of the above flavonoids compounds similarly with HER2 receptor the flavonoids compounds with ID ST060160 (4-hydroxyflavone) and ST058442 (6,3-dimethylflavone) were demonstrating minimum binding energies scores of -8.9 and -8.83 in correlation with drug Herceptin which has score of -8.98 which is similar as scores of above two flavonoids compounds. In this manner the docking results were analyzed lastly revealed that among the six plant compounds, displays the best binding affinity with the human Estrogen Receptor and HER2 and further it could be helpful for distinguishing proof and advancement of new preventive and restorative medication against breast cancer [12]. A study also reported the similar results in which they found two flavonoid compounds which exhibits highest binding affinity with the human estrogen receptor [13].

CONCLUSION

The present work recognizes the potential medication that focuses against the receptor protein (ER and HER2) as a characteristic solution to cure breast cancer. The study reveals that flavonoids can go utilized as medication to cure cancer. Main aim of this study is to limit the harmful impact of accessible medications to the normal human cell. The study demonstrated the compounds ST026594 (7-hydroxyflavone), ST070967 (2-(- 4-fluorophenyl)- 4n-chromen-4-one), ST086622 (3-hydroxyflavone) and ST055369 (8-methylflavone) were the best compounds indicating minimum binding energy when we compared Tamoxifen with Estrogen receptor and compounds ST060160 (4-hydroxyflavone) and ST058442 (6,3-dimethylflavone) were the best compounds demonstrating minimum binding energy in correlation with Herceptin with HER2 receptor, were additionally bioactive and non poisonous in nature with great physiochemical properties and drug likeliness. In future one can go for drug outlining of these compounds including clinical trials.

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Conflict of interest – Authors have no conflict of Interest.

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