International Research Journal of Engineering and Technology (IRJET) e-ISSN: 2395-0056
Volume: 09 Issue: 09 | Sep 2022 www.irjet.net p-ISSN: 2395-0072

In-Silico study of Flavonoid Compounds And its Modifications for the Medications against Breast Cancer Growth.

Dixita Zod[1], Shrutika R. Talpe[1]

Department of Biotechnology, School of Bio Science and Technology, Vellore Institute of Technology (VIT), Vellore, Tamil Nadu, India.

Abstract - *Breast cancer is one of the greatest global issues causing to increase in death rates in females due to uncontrolled growth of a tumor that can metastasize to different parts of the human body. The binding of Estrogen receptor (ER) and Human Epidermal Growth Factor Receptor 2 (HER-2) with breast cancer cells is mainly responsible to cause malignant tumor that regulates the transcription of various genes and act as a transcription factor. Maximum of the drugs used to cure breast cancer have a negative effect on body so, we focused on natural flavonoids such as Chrysin, Equol, Hesperetin and Naringenin and modified these flavonoids which will interact with breast cancer cell receptors, such as Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2), showing less toxic effect to human body. The new way to deal with the immune system studies that combine techniques of systems biology with data provided by information-driven prediction methods. The structure information of these flavonoids were collected from PubChem and the structural data of HERα and HER-2 receptor were collected from Protein Data Bank (PDB). The four ligands were modified using the Corina classic tool and drug-likeness and molecular properties of all the flavonoids' original structure and modified structures were examined using the Molinspiration server to check if all the flavonoids satisfy "Lipinski's Rule of Five." Computational docking allows to study of the biomolecular interactions and ligand interactions with thousands of compounds and this virtual screening method is done using the Auto Dock tool. This study focused on the molecular docking of modified flavonoids (ligands) with breast cancer cell receptors and the best-modified ligand against each receptor were analysed and evaluated to cure breast cancer. The best-modified flavonoid of Hesperetin is (2S)-8-amino-2-(3-hydroxyphenyl)-6-iodo-3,4dihydro-2H-1benzopyran-4-one whose highest interaction energy is -6.3 Kcal/mol and -7.0 Kcal/mol respectively, with HERα and HER2 receptor of breast cancer. All the best-modified structures of Naringenin, Chrysin, and Equol flavonoid did not show potential significant difference between the original and modified structure activation energy.*

Keywords: Flavonoids, activation energy, breast cancer, auto dock, naringenin, chrysin, equol, and hesperetin.

1. Introduction:

Breast cancer is one of the major malignant growths affecting adult women between the ages of 20 and 59 and the underlying cause of the highest mortality rate among women in India. Over the nation, the highest rates of illiteracy were found among females who are engaged in household activities where the illiteracy rate is 8% to 46%. The explanation incorporates the need for value instruction, individual lifestyle tendencies, and reproductive age [Gupta et al.,2015; Torre et al.,2017].

Estrogen receptors have been developed to be the best objective and effective for breast cancer treatment since endogenous estrogens are assumed to have a significant role in the advancement of breast cancer [Debeb et al.,2015]. ER fundamentally exists in 2 types: ER beta and ER alpha. Estrogen receptor α (ER) is the major driver of ~75% of breast cancers and plays an important role in controlling the transcription of nuclear DNA necessary for mammary [Siersbæk et al., 2018].HER2 amplification was first noted in human breast cancer and was subsequently identified in ovarian cancer [Berchuck et al. 1990; Slamon et al. 1987, 1989; Zhang et al. 1989].HER2 protein expression is mainly increased due to the HER2 gene amplification mechanism, which prompts overexpression of the receptor and disturbs typical control mechanism, possibly prompting the development of aggressive tumor cells [Salmon et al., 1989; Hynes et al., 1994; Hung et al., 1986]. This situation along these lines requests the advancement of better HER2-TK inhibitors with minimal toxicity issues to be presented as focused anti-cancer therapeutics [Chandrika et al., 2016].

Correct cancer treatments are those that are specifically tailored to the individual's needs in order to provide the most effective treatment. The first PARP inhibitor has been approved for clinical use [Bryant et al., 2005]. The tamoxifen citrate drug has a widespread role in treating the metastatic breast cancer (Manni et al., 1982). The use of an LH-RH agonist (zoladex) it was used with the combination with Tamoxifen as the observation was not good and there were unpredictable endocrinological responses [Klijn et al., 1984]. The serious side effects of these artificial drugs used in breast cancer are uterine cancer which causes a small increased risk, stroke vision problems, the drugs are anticancer drugs in breast cancer but are a carcinogenic agent in the endometrium which affects the female genital tract, and a high risk of endometrial malignancy [Fleming et al., 2018]. Paclitaxel and carboplatin are also used in the treatment of breast cancer and have some urinary symptoms in females, there were worsening of existing urinary continence and an overflow [Stemmler et al., 2008].

Cancer cells will in general dodge apoptosis, a process by which cells undergo through the programmed cell death by harming DNA, which thus restricts the cell proliferation [Evan et al.,1998; Hanahan et al., 2011]. In this way, apoptosis induction is one of the best techniques to stop cancer, which is used in most anticancer techniques, for example, irradiation and chemotherapy treatment [Fulda et al.,2006]. But due to side effects and constraints related to these therapies, for example, cardiovascular toxicity and neuropathy, the need to discover new chemo preventive agents with the least side effects is growing in demand [Monsuez et al.,2010 ; Rivera et al.,2015].

So, Kawaii (1999) and Pouget (2001) discovered an alternative approach for the treatment of breast cancer by the use of traditional herbal drugs called flavonoids that have anti-breast cancer activity and show fewer side effects against human normal cells. Naturally, occurring flavonoid products are derived from plants and are found in various parts of plants [Havsteen et al., 2002]. Flavonoids are classified as flavones, flavonols, anthocyanidins, flavanols, flavanines, flavanonols, aurones, furan chromones, isoflavones, isoflavanones, biflavones, xanthones, chaocones and dihydrochalcones (fig 1) [Wang et al., 2018].

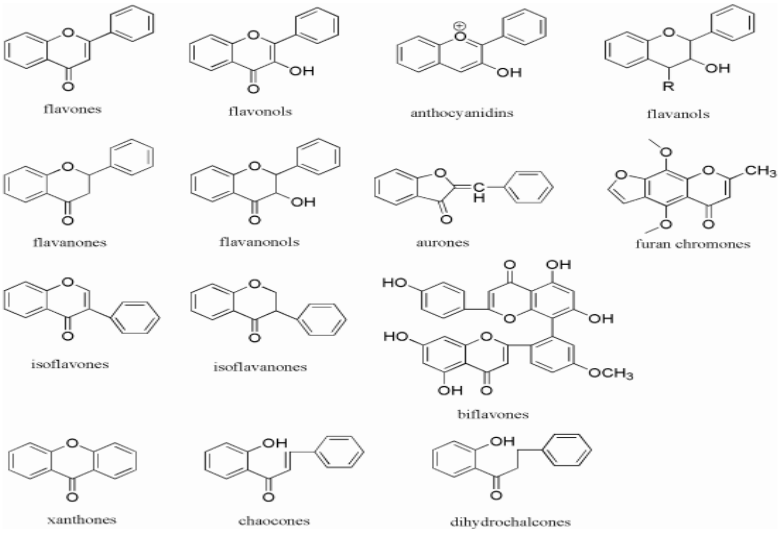


Figure 1:- Flavonoids classifications (Wang et al., 2018)

Flavonoids are well known for their antioxidant properties [Mishra et al., 2013], anti-bacterial & anti-viral activities [Wu et al.,2008; Wang et al., 1998], anti-inflammatory and anti-thrombogenic properties [Alcaraz et al., 1987], anticancer activity [Sheikh et al., 2020]. In cancer therapy, apoptosis is the known target pathway of chrysin and it affects different molecular pathways [Moghadam et al., 2020]. Hence chrysin can be used as an anti-tumor agent [Yadav et al., 2018; Wang et al., 2020; Zhang et al., 2020]. Prakash et al (2020) demonstrated the anticancer activity of hesperetin for cervical cancer. Naringenin is a potential agent for anti-tumor as demonstrated by Hughes et al (2008), Erdogdu et al (2009), and Verbeek et al (2004). Shi et al (2011) This study demonstrated that equol can be used to inhibit the expression of nuclear factor-kappa B in human breast

cancer cells. Many studies have found that high intakes of flavonoids may reduce the risk of cancer in humans. [Hui et al., 2013].

Flavonoids used in this project are Chrysin, Equol, Hesperetin, and Naringenin against two breast cancer cell receptors, Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2(HER-2). *In silico* study of Chrysin and Equol flavonoid is done by Suganya et al (2014) against receptor Human Estrogen Receptor Alpha (HERα), also the *In silico* study of Hesperetin and Naringenin flavonoid against Human Epidermal Growth Factor Receptor 2 (HER-2) was conducted by Chandrika et al (2016). So, we modified all the four flavonoids 10 times each and all modified flavonoids successfully satisfied Lipinski's rule of five. All the modified structures of each flavonoids were docked against the receptors HERα and HER-2 and successfully the best-modified flavonoid results were obtained by comparing the activation energy of original structure of flavonoids and modified structure of flavonoids with HERα and HER2 receptors using the Auto Dock tool, and the best-modified flavonoid was selected having more activation energy than original flavonoid, which can be used to cure breast cancer with no side effects.

2. MATERIALS AND METHOD:

2.1) Protein preparation

The 3D crystallographic structure of the receptor Human Estrogen Alpha (HERα) having Protein ID:2IOG and Human Epidermal Growth Factor Receptor 2 (HER-2) having Protein ID: 3PP0 was retrieved from Protein Data Bank (PDB). All the hydrogen atoms present in the proteins were merged and all the non-essential water molecules and heteroatoms were removed during docking analysis using the Auto Dock tool. Hence these two were the target proteins that were docked against the four flavonoids.

2.2) Ligand preparation

PDB format, two- and three-dimensional structures of flavonoids: Chrysin, Equol, Hesperetin, and Naringenin were obtained from PubChem for docking analysis against HERα and HER-2 receptors. [Suganya et al., 2014;Chandrika et al., 2016].

2.3) Ligand modifications

All four flavonoids, Chrysin, Equol, Hesperetin, and Naringenin, were modified using a Corina classic tool. Three-dimensional structures of each modified flavonoid were generated using this tool. Each flavonoid was modified 10 times, each of which was tested against the two receptors. Naming modified flavonoids using the King Draw tool.

2.4) Lipinski rule of five of ligand molecule

The molecular properties and drug-likeness of all the flavonoids' original structures and modified structures were examined using the Molinspiration server. Christopher A Lipinski formulated a thumb rule to assess the property of drug-likeness, it has criteria such as a partition co-efficient log P which is less than 5 and not more than 5 hydrogen bond donors, and the molecular weight should be below 500 Daltons.

2.5) Molecular docking using the Auto Dock tool

The active site residues were determined after the protein and the modified ligand were prepared, providing information about the protein's secondary structure and the protein-ligand interaction, and preserving the protein and ligand in PDBQT format. The X, Y, and Z coordinates were recorded when the grid box was created using the Auto Dock tool, which identifies the residues implicated in the active site. The updated ligand and the protein were stored as the configuration file as input as conf.txt, and the dock was run using the command prompt. The distance from the best mode and the affinity (Kcal/mol) were determined [Sandeep et al., 2011] [Morris et al., 2008].

3. RESULTS:

3.1) Target protein structure

The main target of the breast cancer cell were Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2). Both the receptors 3D structures were recovered from Protein Data Bank (PDB) and the crystallography structure were visualized in PyMol software as shown in figure2 and figure 3.

Figure 2:- Human Estrogen Receptor Alpha (HERα) with PDB ID:2IOG

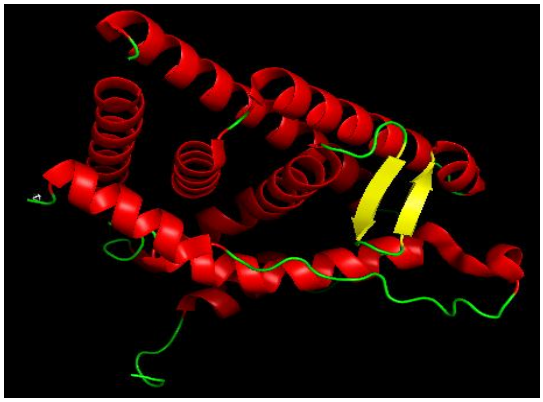
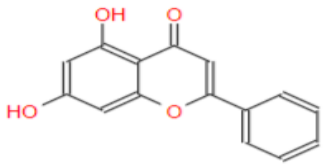
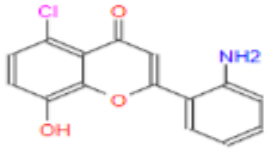
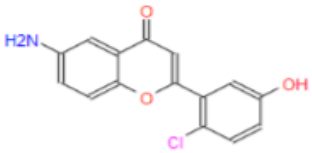
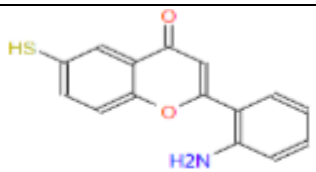
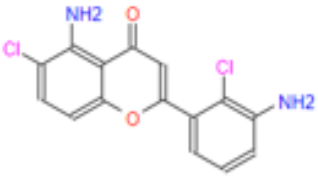
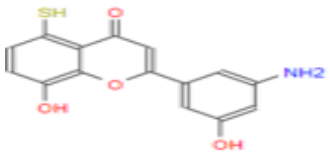
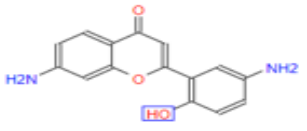


Figure 3: - Human Epidermal Growth Factor Receptor 2 (HER-2) with PDB ID:3PP0.

3.2) Docking analysis

Suganya et al (2014) demonstrated the docking of 19 different flavonoid original structures with Human Estrogen Receptor Alpha (HERα) and concluded that Chrysin and Equol have -11.01 kcal/mol and -10.83 kcal/mol of highest activation energy respectively. Hence, these two flavonoids, Chrysin and Equol were selected for docking with HERα. Similarly, Chandrika et al (2016) demonstrated the docking of 150 flavonoids with HER2 receptors of breast cancer and concluded that the two citric fruit flavonoids such as Hesperetin and Naringenin were the best-docked results with HER2. Therefore, all the 10 modified structures of four flavonoids such as Chrysin, Equol, Hesperetin, and Naringenin were successfully docked with two receptors of breast cancer, Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2).

Table -1: Docking results of Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2) with modified Chrysin flavonoid.

Sr. no.	Name (IUPAC)	Structure modified	Energy value (Kcal/mol) HERα	HER2
1.	5,7-dihydroxy-2-phenyl-4H-chromen-4-one		-6.2	-6.8
2.	2-(2-aminophenyl)-5-chloro-8-hydroxy-4H-chromen-4-one		-6.0	-6.3
3.	6-amino-2-(2-chloro-5-hydroxyphenyl)-4H-chromen-4-one		-5.0	-6.3
4.	2-(2-aminophenyl)-6-sulfanyl-4H-chromen-4-one		-5.7	-6.5
5.	5-amino-2-(3-amino-2-chlorophenyl)-6-chloro-4H-chromen-4-one		-6.0	-5.6
6.	2-(3-amino-5-hydroxyphenyl)-8-hydroxy-5-sulfanyl-4H-chromen-4-one		-5.7	-5.7
7.	7-amino-2-(5-amino-2-hydroxyphenyl)-4H-chromen-4-one		-5.9	-6.6

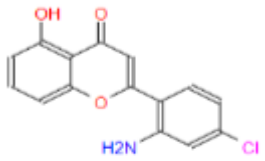
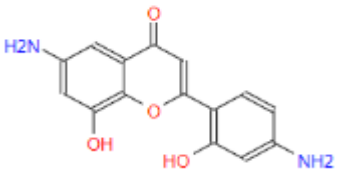
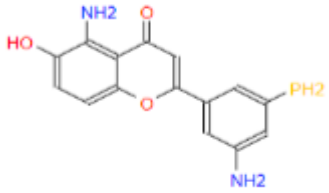
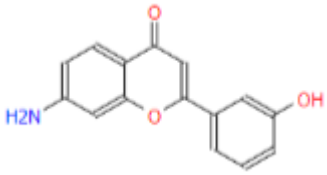
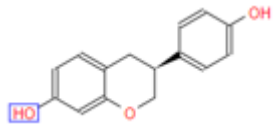
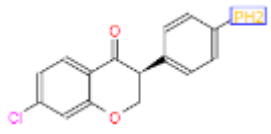
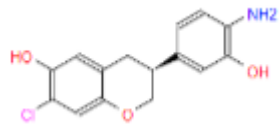
8.	2-(2-amino-4-chlorophenyl)-5-hydroxy-4H-chromen-4-one		-5.7	-6.7
9.	6-amino-2-(4-amino-2-hydroxyphenyl)-8-hydroxy-4H-chromen-4-one		-5.9	-5.4
10.	5-amino-2-(3-amino-5-phosphanylphenyl)-6-hydroxy-4H-chromen-4-one		-5.4	-6.4
11.	7-amino-2-(3-hydroxyphenyl)-4H-chromen-4-one		-5.3	-5.7

Table -2: Docking results of Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2) with modified Equol flavonoid.

Sr. no.	Name (IUPAC)	Structure modified	Energy value (Kcal/mol)	
			HERα	HER2
1.	(3S)-3-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-7-ol		-6.3	-6.5
2.	(3S)-7-chloro-3-(4-phosphanylphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-5.5	-5.5
3.	(3S)-3-(4-amino-3-hydroxyphenyl)-7-chloro-3,4-dihydro-2H-1-benzopyran-6-ol		-5.3	-5.4

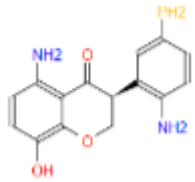
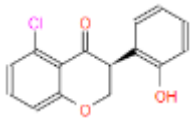
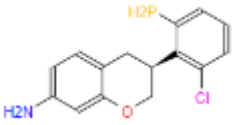
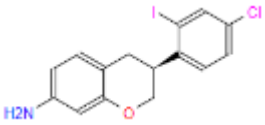
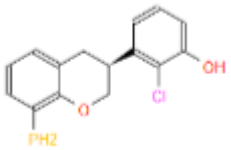
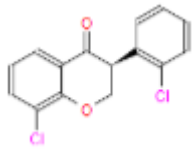
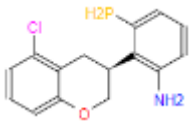
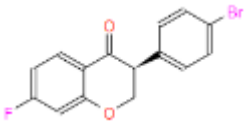
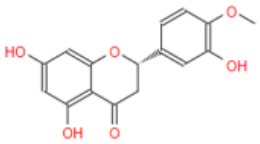
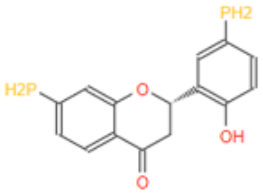
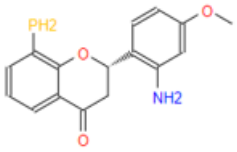
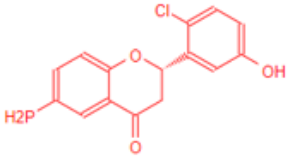
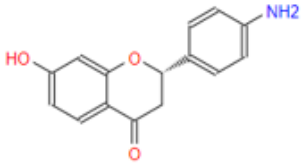
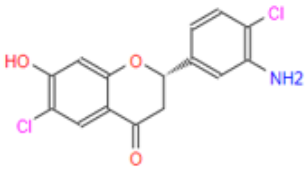
4.	(3S)-5-amino-3-(2-amino-5-phosphanylphenyl)-8-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one		-5.4	-5.3
5.	(3S)-5-chloro-3-(2-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-4.9	-6.5
6.	(3S)-3-(2-chloro-6-phosphanylphenyl)-3,4-dihydro-2H-1-benzopyran-7-amine		-4.2	-5.0
7.	(3S)-3-(4-chloro-2-iodophenyl)-3,4-dihydro-2H-1-benzopyran-7-amine		-5.3	-6.0
8.	2-chloro-3-[(3S)-8-phosphanyl-3,4-dihydro-2H-1-benzopyran-3-yl]phenol		-5.1	-4.8
9.	(3S)-8-chloro-3-(2-chlorophenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-5.2	-6.0
10.	2-[(3S)-5-chloro-3,4-dihydro-2H-1-benzopyran-3-yl]-3-phosphanylaniline		-5.1	-5.4
11.	(3S)-3-(4-bromophenyl)-7-fluoro-3,4-dihydro-2H-1-benzopyran-4-one		-5.6	-6.0

Table -3: Docking results of Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2) with modified Hesperetin flavonoid.

Sr. no.	Name (IUPAC)	Structure modified	Energy value (Kcal/mol)	
			HERα	HER2
1.	(2S)-5,7-dihydroxy-2-(3-hydroxy-4-methoxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-4.7	-5.9
2.	(2S)-2-(2-hydroxy-5-phosphanylphenyl)-7-phosphanyl-3,4-dihydro-2H-1-benzopyran-4-one		-5.2	-5.7
3.	(2S)-2-(2-amino-4-methoxyphenyl)-8-phosphanyl-3,4-dihydro-2H-1-benzopyran-4-one		-4.0	-5.1
4.	(2S)-2-(2-chloro-5-hydroxyphenyl)-6-phosphanyl-3,4-dihydro-2H-1-benzopyran-4-one		-5.4	-6.0
5.	(2S)-2-(2,4-diaminophenyl)-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one		-5.8	-5.4
6.	(2S)-2-(3-amino-4-chlorophenyl)-6-chloro-7-hydroxy-3,4-dihydro-2H-1-benzopyran-4-one		-5.8	-5.9

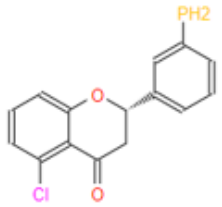
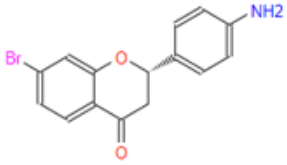
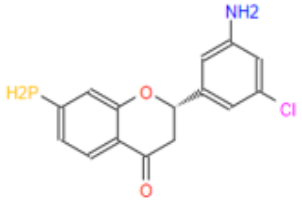
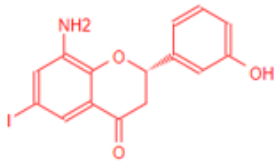
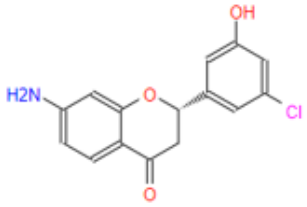
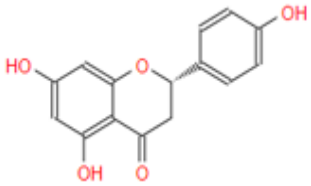
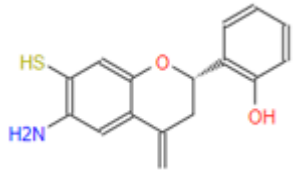
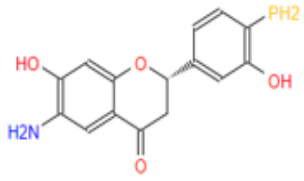
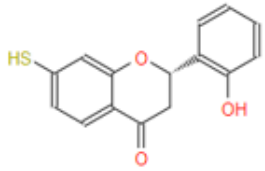
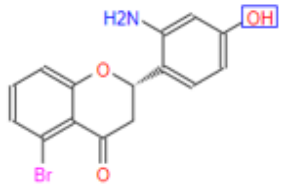
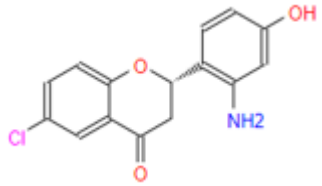
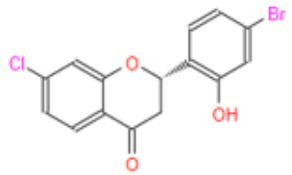
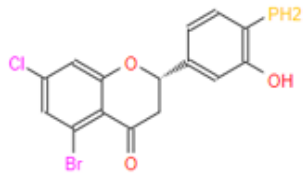
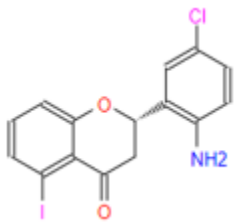
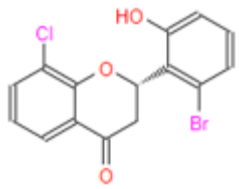
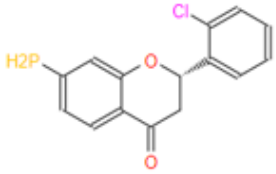
7.	(2S)-5-chloro-2-(3-phosphanylphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-5.0	-6.1
8.	(2S)-2-(4-aminophenyl)-7-bromo-3,4-dihydro-2H-1-benzopyran-4-one		-5.9	-4.7
9.	(2S)-2-(3-amino-5-chlorophenyl)-7-phosphanyl-3,4-dihydro-2H-1-benzopyran-4-one		-5.2	-6.1
10.	(2S)-8-amino-2-(3-hydroxyphenyl)-6-iodo-3,4-dihydro-2H-1-benzopyran-4-one		-6.3	-7.0
11.	(2S)-7-amino-2-(3-chloro-5-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-5.5	-6.4

Table -4: Docking results of Human Estrogen Receptor Alpha (HERα) and Human Epidermal Growth Factor Receptor 2 (HER-2) with modified Naringenin flavonoid.

Sr. no.	Name (IUPAC)	Structure modified	Energy value (Kcal/mol) HERα	HER2
1.	(2S)-5,7-dihydroxy-2-(4-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-6.2	-6.3

2.	(2S)-6-amino-2-(2-hydroxyphenyl)-7-sulfanyl-3,4-dihydro-2H-1-benzopyran-4-one		-5.7	-5.5
3.	(2S)-6-amino-7-hydroxy-2-(3-hydroxy-4-phosphanylphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-5.2	-5.7
4.	(2S)-2-(2-hydroxyphenyl)-7-sulfanyl-3,4-dihydro-2H-1-benzopyran-4-one		-5.3	-6.4
5.	(2S)-2-(2-amino-4-hydroxyphenyl)-5-bromo-3,4-dihydro-2H-1-benzopyran-4-one		-6.3	-6.3
6.	(2S)-2-(2-amino-4-hydroxyphenyl)-6-chloro-3,4-dihydro-2H-1-benzopyran-4-one		-5.6	-5.7
7.	(2S)-2-(4-bromo-2-hydroxyphenyl)-7-chloro-3,4-dihydro-2H-1-benzopyran-4-one		-5.3	-6.4
8.	(2S)-5-bromo-7-chloro-2-(3-hydroxy-4-phosphanylphenyl)-3,4-dihydro-2H-1-benzopyran-4-one		-5.5	-5.5

9.	(2S)-2-(2-amino-5-chlorophenyl)-5-iodo-3,4-dihydro-2H-1-benzopyran-4-one		-5.5	-6.2
10.	(2S)-2-(2-bromo-6-hydroxyphenyl)-8-chloro-3,4-dihydro-2H-1-benzopyran-4-one		-5.7	-5.8
11.	(2S)-2-(2-chlorophenyl)-7-phosphanyl-3,4-dihydro-2H-1-benzopyran-4-one		-5.1	-6.2

The activation energy for the original structures of Chrysin and Equol retrieved as -6.2 kcal/mol and -6.3 kcal/mol respectively with HERα and -6.8 kcal/mol and -6.5 kcal/mol with HER2 respectively. The activation energy of original structure of Hesperetin and Naringenin retrieved as -4.7 kcal/mole and -6.2 kcal/mole with HERα respectively and as -5.9 kcal/mole and -6.3 kcal/mole with HER2 respectively. The 10 modified structures of each flavonoid were docked with both HERα and HER2 receptors, and the results are shown in table 1,2,3 and 4 respectively.

The results of docking were analysed and were outlined that among all the 10 modified structures of each flavonoid, (2S)-8-amino-2-(3-hydroxyphenyl)-6-iodo-3,4dihydro-2H-1benzopyran-4-one is the best modified structure of Hesperetin flavonoid and 2(S)-2-(2 amino-4-hydroxyphenyl)-5-bromo-3,4-dihydro-2H-1-benzopyran-4-oneis best modified structure of Naringenin flavonoid, as both exhibits the same highest activation energy of -6.3 Kcal/molwith HERα receptor, which is greater than their original structure activation energy (-4.7 Kcal/mol and -6.2 Kcal/molrepectively), therefore these two modified structure of Hesperetin and Naringenin flavonoid is best suited to inhibit the activity of HERα receptor. Similarly,2-(2-amoniphenyl)-5chloro-8-hydroxy-4H-chromen-4-one which is the best modified structure of Chrysin flavonoidexhibits the activation energy of -6.0 Kcal/mol with HERα receptor, but is less than the original structure activation energy of Chrysin flavonoid (-6.2 Kcal/mol). Hence, there no significant difference of activation energy between the modified and original structure of Chrysin flavonoid, to possess inhibitory activity of HERα receptor. None of the modified structures of Equol flavonoid exhibited the highest activation energy than the original structure, so the original structure with an activation energy of -6.3 Kcal/mol is best suited to inhibit the activity of HERα receptor.

Similarly, (2S)-8-amino-2-(3-hydroxyphenyl)-6-iodo-3,4dihydro-2H-1benzopyran-4-one which is best-modified structure of Hesperetin flavonoid exhibits the activation energy of -7.0 Kcal/mol, with HER2 receptor, that is greater than the activation energy of it's original structure (-5.9 Kcal/mol). So, this best-modified structure shows good interaction with HER2 receptor and can be used to inhibit the activity of HER2 receptor. 2-(2-amino-4-chlorophenyl)-5-hydroxy-4H-chromen-4-one is the best-modified structure of Chrysin flavonoid and (3S)-5-chloro-3-(2-hydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-4-one is the best-modified structure of Equol flavonoid that exhibits the activation energy of -6.7 Kcal/mol and -6.5 Kcal/mol repectively, which is same as their original structure activation energy with HER2 receptor. Hence, these two modified structures of Chrysin and Equolflavonoid that can be used to show inhibitory activity with HER2 receptor but will not be

significant as compared to the original structure of both. The best-modified structure Naringenin flavonoids are(2S)-2-(2-hydroxyphrnyl)-7-sulfanyl-3,4-dihydro-2H-1-benzopyran-4-one and (2S)-2-(4-bromo-2-hydroxyphenyl)-7-chloro-3,4-dihydro-2H-1-benzopyran-4-one that have a same activation energy of -6.4 Kcal/mol, which is same as the activation energy of original structure of Naringenin flavonoid with HER2 receptor. Hence, these two modified structure Naringenin flavonoid can be used to show inhibitory activity with HER2 receptor but will not be significant as compared to original structure.

4. CONCLUSION:

There is a need for new drugs that have biological activity. In this learning, the best modified flavonoid of Chrysin, Equol, Hesperetin, and Naringenin was found to be effective in binding to the HERα and HER2 receptors of breast cancer cells. The best modified structures of Naringenin, Chrysin and Equol flavonoid did not show a significant difference in their structure activation energy. The best modified form of hesperitin is (2S)-8-amino-2-(3-hydroxyphenyl)-6-iodo-3,4-dihydro-2H-1benzopyran-4-one, which has an interaction energy of -6.3 kcal/mol and -7.0 kcal/mol, respectively, with the HERα and HER2 receptors of breast cancer. This is the only modified flavonoid with a higher interaction energy between its original and modified structures. Hence, it was concluded that this is the potent modified drug of Hesperetin flavonoid against breast cancer receptors called HERα and HER2.Further investigations are needed to determine the dosage of security and safety levels with clinical trials.

ACKNOWLEDGEMENT

We express our gratitude to Prashant Singh Parihar, for his interest in this paper. He explained the solutions to our problems. Without his help, it was a matter of acute impossibility to propel in this endeavor. His enthusiasm, knowledge, and exacting attention to detail have been an inspiration and kept our work on track. It is a matter of profound privilege, and pleasure to pay our sincere and heartfelt thanks to him.

REFERENCES

[1] Singhal, G., Roy, A., &Bharadvaja, N. (2017). In-silico study on plant determined flavonoids compounds for the synthetic medications against breast cancer growth. *Journal of Ayurvedic and Herbal Medicine*, *3*(3), 116-121.

[2] Gross, J. and Yee, D., 2002. How does the estrogen receptor work? *Breast Cancer Research*, 4(2).

[3] Rapin N, Lund O, Bernaschi M, Castiglione F. Computational Immunology Meets Bioinformatics: The Use of Prediction Tools for Molecular Binding in the Simulation of the Immune System. PLoS ONE. 2010;5(4):e9862.

[4] Forli S, Huey R, Pique M, Sanner M, Goodsell D, Olson A. Computational protein–ligand docking and virtual drug screening with the AutoDock suite. Nature Protocols. 2016;11(5):905-919.

[5] Gupta A, Shridhar K, Dhillon P. A review of breast cancer awareness among women in India: Cancer literate or awareness deficit. European Journal of Cancer. 2015;51(14):2058-2066.

[6] Torre L, Islami F, Siegel R, Ward E, Jemal A. Global Cancer in Women: Burden and Trends. Cancer Epidemiology Biomarkers & Prevention. 2017;26(4):444-457.

[7] Debeb, Y.G.; Berihu, B.A. Review on the role of estrogen receptors in breast cancer. *Int. J. Pharma Sci. Res. (IJPSR)* 2015, *6*, 1100–1103.

[8] ZHENG Y, SHAO X, HUANG Y, SHI L, CHEN B, WANG X et al. Role of estrogen receptor in breast cancer cell gene expression. Molecular Medicine Reports. 2016;13(5):4046-4050.

[9] Siersbæk R, Kumar S, Carroll J. Signaling pathways and steroid receptors modulating estrogen receptor α function in breast cancer. Genes & Development. 2018;32(17-18):1141-1154.

[10] Berchuck A, Kamel A, Whitaker R, Kerns B, Olt G, Kinney R, Soper JT, Dodge R, Clarke-Pearson DL, Marks P, et al: Overexpression of HER2/neu is associated with poor survival in advanced epithelial ovarian cancer. Cancer Res 1990;50:4087–4091.

[11] Slamon D, Clark G, Wong S, Levin W, Ullrich A, McGuire W. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science. 1987;235(4785):177-182.

[12] Slamon D, Godolphin W, Jones L, Holt J, Wong S, Keith D et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244(4905):707-712.

[13] Zhang X, Silva E, Gersenhson D, Hung MC: Amplification and re-arrangement of c-erbBprotooncogenes in cancer of human female genital tract. Oncogene 1989;4:985–989.

[14] ZHENG Y, SHAO X, HUANG Y, SHI L, CHEN B, WANG X et al. Role of estrogen receptor in breast cancer cell gene expression. Molecular Medicine Reports. 2016;13(5):4046-4050.

[15] Slamon D, Godolphin W, Jones L, Holt J, Wong S, Keith D et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244(4905):707-712.

[16] Slamon D, Godolphin W, Jones L, Holt J, Wong S, Keith D et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science. 1989;244(4905):707-712.

[17] Hynes N. The biology of erbB-2/nue/HER-2 and its role in cancer. Biochimica et BiophysicaActa (BBA) - Reviews on Cancer. 1994;1198(2-3):165-184.

[18] Hung M, Schechter A, Chevray P, Stern D, Weinberg R. Molecular cloning of the neu gene: absence of gross structural alteration in oncogenic alleles. Proceedings of the National Academy of Sciences. 1986;83(2):261-264.

[19] Chandrika B, Steephan M, Kumar T, Sabu A, Haridas M. Hesperetin and Naringenin sensitize HER2 positive cancer cells to death by serving as HER2 Tyrosine Kinase inhibitors. Life Sciences. 2016;160:47-56.

[20] Lv Q, Meng Z, Yu Y, Jiang F, Guan D, Liang C et al. Molecular Mechanisms and Translational Therapies for Human Epidermal Receptor 2 Positive Breast Cancer. International Journal of Molecular Sciences. 2016;17(12):2095.

[21] Bryant H, Schultz N, Thomas H, Parker K, Flower D, Lopez E et al. Specific killing of BRCA2-deficient tumours with inhibitors of poly(ADP-ribose) polymerase. Nature. 2005;434(7035):913-917.

[22] Manni A, Pearson OH. Antioestrogens in tumour therapy. Clin Oncol 1982; 1:65-75.

[23] KLIJN, J.G.M. (1984). Long-term LHRH-agonist treatment in metastatic breast cancer as a single treatment and in combination with other additive endocrine treatments. Med. Oncol. & Tumor. Pharmacother., 1, 123

[24] Fleming C, Heneghan H, O'Brien D, McCartan D, McDermott E, Prichard R. Meta-analysis of the cumulative risk of endometrial malignancy and systematic review of endometrial surveillance in extended tamoxifen therapy. British Journal of Surgery. 2018;105(9):1098-1106.

[25] Stemmler H, Mengele K, Schmitt M, Harbeck N, Laessig D, Herrmann K et al. Intrathecal trastuzumab (Herceptin) and methotrexate for meningeal carcinomatosis in HER2-overexpressing metastatic breast cancer: a case report. Anti-Cancer Drugs. 2008;19(8):832-836.

[26] Evan G. A Matter of Life and Cell Death. Science. 1998;281(5381):1317-1322.

[27] Hanahan D, Weinberg R. Hallmarks of Cancer: The Next Generation. Cell. 2011;144(5):646-674.

[28] Fulda S, Debatin K. Extrinsic versus intrinsic apoptosis pathways in anticancer chemotherapy. Oncogene. 2006;25(34):4798-4811.

[29] Monsuez J, Charniot J, Vignat N, Artigou J. Cardiac side-effects of cancer chemotherapy. International Journal of Cardiology. 2010;144(1):3-15.

[30] Rivera E, Cianfrocca M. Overview of neuropathy associated with taxanes for the treatment of metastatic breast cancer. Cancer Chemotherapy and Pharmacology. 2015;75(4):659-670.

[31] KAWAII S, TOMONO Y, KATASE E, OGAWA K, YANO M. Antiproliferative Activity of Flavonoids on Several Cancer Cell Lines. Bioscience, Biotechnology, and Biochemistry. 1999;63(5):896-899.

[32] Pouget C, Lauthier F, Simon A, Fagnere C, Basly J, Delage C et al. Flavonoids: structural requirements for antiproliferative activity on breast cancer cells. Bioorganic & Medicinal Chemistry Letters. 2001;11(24):3095-3097.

[33] Havsteen B. The biochemistry and medical significance of the flavonoids. Pharmacology & Therapeutics. 2002;96(2-3):67-202.

[34] Wang T, Li Q, Bi K. Bioactive flavonoids in medicinal plants: Structure, activity and biological fate. Asian Journal of Pharmaceutical Sciences. 2018;13(1):12-23.

[35] Mishra A, Sharma A, Kumar S, Saxena A, Pandey A. Bauhinia variegataLeaf Extracts Exhibit Considerable Antibacterial, Antioxidant, and Anticancer Activities. BioMed Research International. 2013;2013:1-10.

[36] Wu D, Kong Y, Han C, Chen J, Hu L, Jiang H et al. d-Alanine:d-alanine ligase as a new target for the flavonoids quercetin and apigenin. International Journal of Antimicrobial Agents. 2008;32(5):421-426.

[37] Wang H, Xia Y, Yang Z, Morris Natschke S, Lee K. Recent Advances in the Discovery and Development of Flavonoids and their Analogues as Antitumor and Anti-HIV Agents. Advances in Experimental Medicine and Biology. 1998;:191-225.

[38] Alcaraz M, Ferrándiz M. Modification of arachidonic metabolism by flavonoids. Journal of Ethnopharmacology. 1987;21(3):209-229.

[39] Cancer Chemoprevention by Flavonoids, Dietary Polyphenols and Terpenoids. Biointerface Research in Applied Chemistry. 2020;11(1):8502-8537.

[40] Moghadam E, Ang H, Asnaf S, Zabolian A, Saleki H, Yavari M et al. Broad-Spectrum Preclinical Antitumor Activity of Chrysin: Current Trends and Future Perspectives. Biomolecules. 2020;10(10):1374.

[41] Yadav S, Singh J. Synthesis and preliminary biological evaluation for the anticancer activity of organochalcogen (S/se) tethered chrysin-based organometallic RuII(η6-p-cymene) complexes. Journal of Biomolecular Structure and Dynamics. 2018;37(13):3337-3353.

[42] Zhang W, Chen S, Liu X, Bing-Lin, Liu X, Zhou Y. Study on antitumor activities of the chrysin-chromene-spirooxindole on Lewis lung carcinoma C57BL/6 mice in vivo. Bioorganic & Medicinal Chemistry Letters. 2020;30(17):127410.

[43] Hughes LA, Arts IC, Ambergen T, Brants HA, Dagnelie PC, Goldbohm RA. Higher dietary flavone, flavonol, and catechin intakes are associated with less of an increase in BMI over time in women: a longitudinal analysis from the Netherlands Cohort Study. Am J ClinNutr. 2008; 88:1341-1352.

[44] Erdogdu Y, Unsalan O, Gulluoglu. Vibrational analysis of flavone. Turk J Phys. 2009; 33:249-259.

[45] Morris G, Huey R, Olson A. Using AutoDock for Ligand-Receptor Docking. Current Protocols in Bioinformatics. 2008;24(1).

[46] Lipinski C, Lombardo F, Dominy B, Feeney P. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings 1PII of original article: S0169-409X(96)00423-1. The article was originally published in Advanced Drug Delivery Reviews 23 (1997) 3–25. 1. Advanced Drug Delivery Reviews. 2001;46(1-3):3-26.

[47] Chandrika B, Steephan M, Kumar T, Sabu A, Haridas M. Hesperetin and Naringenin sensitize HER2 positive cancer cells to death by serving as HER2 Tyrosine Kinase inhibitors. Life Sciences. 2016;160:47-56.

[48] Suganya J, Radha M, Naorem D, Nishandhini M. In Silico Docking Studies of Selected Flavonoids - Natural Healing Agents against Breast Cancer. Asian Pacific Journal of Cancer Prevention. 2014;15(19):8155-8159.

[49] Hui C, Qi X, Qianyong Z, Xiaoli P, Jundong Z, Mantian M. Flavonoids, Flavonoid Subclasses and Breast Cancer Risk: A Meta-Analysis of Epidemiologic Studies. PLoS ONE. 2013;8(1):e54318.

[50] Verbeek R, Plomp A, van Tol E, van Noort J. The flavones luteolin and apigenin inhibit in vitro antigen-specific proliferation and interferon-gamma production by murine and human autoimmune T cells. Biochemical Pharmacology. 2004;68(4):621-629.

[51] Wang H, Zhou Y, Liu X, Zhang W, Chen S, Liu X et al. Regioselective synthesis and evaluation of 2-amino 3-cyano chromene-chrysin hybrids as potential anticancer agents. Bioorganic & Medicinal Chemistry Letters. 2020;30(9):127087.

[52] Prakash S, Elavarasan N, Subashini K, Kanaga S, Dhandapani R, Sivanandam M et al. Isolation of hesperetin - A flavonoid from Cordiasebestena flower extract through antioxidant assay guided method and its antibacterial, anticancer effect on cervical cancer via in vitro and in silico molecular docking studies. Journal of Molecular Structure. 2020; 1207:127751.

[53] Sandeep, G., Nagasree, K. P., Hanisha, M., & Kumar, M. M. K. AUDocker LE: A GUI for virtual screening with AUTODOCK Vina. BMC Research Notes. 2011; 4(1), 445.