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Journal of Proteomics & Bioinformatics

Research Article

Docking Studies of Selected Flavonoids- Natural Healing Agent against Breast Cancer Using Virtual Screening Approach

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ABSTRACT

Breast cancer is the leading causes of disease among female individuals throughout the world causing the highest mortality rate in females, which occur due to uncontrolled cell division and can metastasize to future parts of the human. The Estrogen receptor in typical and diseased states is important for the improvement of applicable therapeutic approaches. Two major forms of ER exist ERα and ERβ, which are determined by discrete genes. Estrogens play a vital role in breast cancer growth with ERα being the mainly substantial interpreter of breast cancer prognosis. Now a day maximum of the drugs currently used for breast cancer treatment have several side effects and for that reason, we focused on natural compounds which do not exhibit any toxic effect against the normal human cell. Materials and Methodology: structure of the HER2 receptor was retrieved from a protein data bank and the structure of flavonoids compounds have been collected from PubChem databases. Molecular docking, Lipinski's rule, and Pharmacophore-based virtual screening methods were performed for those natural flavonoids compounds to evaluate and analyze the anti-breast cancer activity. Result: finally, five compounds that satisfy Lipinski's rule of five were reported and undergoes for the virtual screening process. The natural compound Daidzein shows the highest binding affinity with the HER2 receptor.

Keywords: Breast cancer; HER2; Docking; Lipinski's rule of five; Pharmacophore modeling

INTRODUCTION

Cancer can be a broad term. It describes the infection that consequences as soon as cell modifications purpose the out of control increase and subdivision of cells. Cancer is the second one main reason for mortality worldwide. Cancer is the fast-movable increase, at the same time as others purpose the cells to develop and divide at a slower rate. Certain forms of most cancers end growths known as tumors, while others, like malignant neoplastic disease, do not. Most of the frame's cells have precise capabilities and reduce lifespan. A mobile gets statistics to die in order that the frame will update it with a greater current cellular that features higher[1]. Cancerous cells lack the components that coach them to save you from dividing and dying. As a result, they increase inside the frame and vitamins that could nourish exclusive cells. Cancerous cells are a sort tumor, impair the system, and purpose exclusive modifications that save you the frame from functioning often. Cancerous cells might appear in a single area after which unfold to the frame through fluid nodes. These place unit clusters of immune cells located at some stage in the frame. Overall, the prevalence of most cancers has without a doubt increased; honestly inside the United States alone, shows 665,540 people suffered from most cancers, and 585,720 of them died because of this infection by 2014.17 Therefore, most cancers can be an enormous difficulty shifting the fitness of all human societies. Unfortunately, it's miles a selection infection on the tissue degree and this range can be a prime venture for its unique term, observed via way of means of efficaciousness of treatment.7, 12 Signs of breast, most cancers can also additionally encompass a lump in the breast, a extrade in breast shape, a scratch of the skin, and melted coming from the nipple, a newly-overturned nipple, or a purple or scaly plot of skin. In people with the close by unfold of the disease; there can be bone pain, swollen lymph nodes, shortness of breath, or yellow skin.19 the first essential cancers are lung cancers, abdomen cancers, liver cancers, and colon cancers. In

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Received date: July 20, 2021; **Accepted date:** October 18, 2021; **Published date:** October 29, 2021

Citation: KAVI PRABA A (2021) Docking Studies of Selected Flavonoids- Natural Healing Agent against Breast Cancer Using Virtual Screening Approach. J Proteomics Bioinform 14: p182.

2005, breast cancers caused 502,000 deaths in the global. (WHO) Among all girls in the global, breast cancers are the most common cancers (American most cancers society) In the United States, breast cancers are the most common cancers in girls, and the second most reason cancers death in girls (after lung most cancers). In 2007, breast cancers secured approximately 40,910 deaths (7% of most cancers deaths; nearly 2% of all deaths) in the U.S. (American Cancer Society) (American Cancer Society 18 September 2006). Women in United States have a 1 in eight fortuitous of having breast most cancers of their lives. (Cancer American Society 18 September).9 There are many human beings getting breast most cancers for the reason that 1970s. This is due to what number of human beings in the Western global live.11 due to the fact the breast is produced from equal tissues in men and females, breast cancers additionally happen in men, 11 [2-8].

The important stages are

Stage0: Is a pre-cancerous, either ductal carcinoma in situ (DCIS) or lobular carcinoma in situ (LCIS).

Stages1–3: spreads to breast or local lymph nodes.

Stage4: Are metastatic most cancers that have a much less beneficial diagnosis because it has unfolded beyond the breast and nearby lymph nodes.

In western countries, breast cancers are one of the second primary reasons for loss of life worldwide. In Asian countries, more than 60% of breast most cancers instances are Analysis as Androgen receptor alpha high quality (ERα) cancers. 1 in everyday mammary gland development, ERα performs a great function in breast cancers development. Breast cancers diagnostic techniques with the most high-quality expected value (88%) with estrogen are progesterone hormone receptors in a stepwise manner.14

The hyper manufacturing of Androgen is one of the leading reasons for the improvement of breast cancer. It was described that estrogen receptor is a receptor of nuclear and productively activated by binding of 17β- estradiol ligand and additionally defined as estrogen nodes.19, 20 naturally, the human populace includes ERα and ERβ estrogen Sense organ, of those receptors, ERα is especially expressed in the mammary gland and uterus. In women, estrogen receptors performing a crucial position in apoptosis, inflammation, homeostasis, differentiation, metabolism, maturation, and proliferation in breast cancer.5

The receptor, ERα is widely known to take part in immune surveillance; resistance to apoptosis, metastasis, and molecular increase.8 The hyperactivity of estrogen hormone might also additionally doubtlessly result in the multiplication of the ERα in the mammalian cells which results in the renovation and increase of varieties of breast cancers, and additionally holds diverse molecular goals for the research of most cancer drugs. The presence of the ERα receptor indicates that digital screening can be used as a powerful device to pick out and display screen the capacity compounds from numerous herbal sources.2,6,16 Many techniques containing poor image-primarily based totally screening, molecular docking, and well-known Pharmacophore speculation had been used for the identity of ligands towards ERα receptor.13 About 50% of patients identified with most cancers for each progesterone and ER-a receptor respond to numerous treatments, including, Tamoxifen, that is especially designed to disrupt the feature of ERα

ER-co regulatory proteins are very tightly regulated proteins below herbal situations with the absence of expression became decide in cancer.18 the estrogen receptor can bind with DNA. In humans, alpha and beta have been estrogen receptors became pronounced, and plenty of research absorbed in this receptor.15 Estrogen is an essential steroid hormone, which controls differentiation, improvement, and characteristic of the precise organ. The Hellenic mechanism of ERs indicates the binding of estrogen to its receptor in the nucleus. ERs bind, especially with androgen Receptor Elements (EREs) and EREs, are specifically represented in the Advocate of particular goal genes.16 EREs bind with ERs efficiently stimulates conformational modifications in the ligand-binding area of the receptors [9-11].

The tablets now used for breast cancer are Tamoxifen, Raloxifene, and Toremifene. These tablets were interfering with estrogen manufacturing which reasons such a lot of aspect consequences such as uterine most cancers, blood clots, etc., and the aspect impact of those tablets make a want for important for brand new stepped forward tablets. The opportunity approach of producing a brand-new drug may be carried out through a conventional approach through the use of the herbal compounds from 20 flavonoids that have an excessive anti-oxidant interest which does now no longer have any aspect consequences to a human everyday cell. The following compounds used were, Achillicin, Caffeic acid, Caffeine, Curcumin, Ferulic acid, L-theanine, Omega 3 fatty acid, Rosemarie acid, S- allyl, Alliin, Genistein, Daidzein, Glycerin, Equol, Myricetin, Biochannin, Hesperetin, Quercetin, Kaempferol, Isorhamnetin, having high binding affinity for breast cancer receptor which lead to breast cancer treatment by molecular docking method.

In the field of molecular modeling, docking is a technique that predicts the well-liked orientation of one molecule to a second when bounce to one another to create a stable complicated .11 knowledge of well-liked orientation successively is also want to predict the strength of association or binding affinity between two molecules using, as an example, rating functions. Molecular docking is one of the often-used strategies in structure-based drug style, (figure1) because of its capability to predict the binding-conformation of small-molecule ligands to the suitable target binding website. Characterization of the binding behavior plays a very important role in the rational design of drugs, similarly on elucidating basic organic chemistry process.10, 15 in this study, the best outcome drug is taken to further process by Lipinski rule for molecular properties and drug-likeness of the compound and virtual screening method Pharmacophore modeling was examined.

Figure1: Molecular Docking

MATERIALS AND METHODOLOGY

- Before starting the Docking (Auto Dock) processes following files are
- Protein in 3D format
- Ligand in 3D format
- Active site informationCentroid information (x, y, z-axis) Duplicate copy of the active site Amino acid information of the binding site

PROTEIN PREPARATION

The 3-D crystal structure of HER2 with PDB: 2IOG in complex with the ligand N-[(1R-(4- HYDROXYPHENYL)-1-METHYLPROPYL]-2-[2-PHENYL-6-(2-PIPERIDIN-1-YLETHOXY) 1H- INDOL-3-YL] ACETAMIDE was retrieved from protein data bank. 3 The complexes bound to the receptor molecule, all the heteroatom's, and the non-essential water molecules were removed, and finally, hydrogen atoms were merged to the target receptor molecule using Pymol.

LIGAND PREPARATION

20 flavonoids were collected from the PubChem database which shows inhibitory effects towards breast cancer. The 3-D structure of the flavonoids was downloaded in SDF format using an openable database the SDF format is converted into PDB format which future used for docking studies.

ACTIVE SITE IDENTIFICATION OF HER2

The catalytic site of the human estrogen receptor was obtained from the protein databank along with area and volume of binding pocket was given literature review of 2IOG receptor.4

DOCKING STUDIES USING AUTO DOCK

The docking analysis of HER2 with 20 flavonoids was carried out by auto dock database which is the most frequently accessible software.

Steps involved in Docking Process

- Pre-processing of a Protein PDB file
- Preparing the ligand for the Auto dock
- Preparing the macromolecule (Protein)
- Identification or searching the search space
- Preparing the Grid parameter file
- Generating the Grid
- Preparing the Auto Dock Parameter file
- Starting Auto Dock
- Analysis of docking results

Step-I: Pre-processing of a Protein PDB file

PDB files have problems like missing atoms, more than one molecule, chain breaks, etc. this needs to be corrected before going to docking setup. After opening Auto Dock tools, in the left panel, you find all molecules panel. Place the pointer and Right-click on it. It will open a popup as Read molecule, click on it and using file browser load the PDB file.

Step-2: Preparing the ligand for the Auto dock

For ligand, preparation click on Ligand panel input open.

It opens the file browser and selects the ligand with the file option as mol2.

Step-3: Preparing the macromolecule (Protein)

This will open the select molecule window where the protein PDB file name is provided, it is the protein that has been processed already, choose the protein PDB.

Step-4: Grid generation steps are given below

- Identification or searching the search space
- Preparing the Grid parameter file
- Generating the Grid

Step -5: Docking steps are given below

- Preparing the docking parameter file
- Running Auto Dock

Preparation Docking Parameter files (.Dpf)

This .Dpf file describes the docking center, the number of torsions, where to start the ligand, and which docking algorithm to use. Based on the parameters available in the Genetic Algorithm changes has to be made in the number of energy evaluations as short/Medium/Long.

Running Auto Dock

Under the Run, tab clicks Run Auto Dock.

Provide auto dock program path by using the browse button and ligand docking parameter file.

LIPINSKI'S RULE OF FIVE

Lipinski's rule five is done by using Molinspiration server molecular property and drug-likeness of the compounds was examined. Lipinski's rules of five undergo certain criteria:

- Not more than 5 hydrogen bond donors
- Not more than 10 hydrogen bond acceptors
- Molecular weight must be below 500
- Partition coefficient log P must be less than 5

PHARMACOPHORE MODELLING

A Pharmacophore version is the ensemble of common steric and digital functions which are vital to make certain the best

molecular interactions with a selected organic target and to trigger (or block) its biological response. It may be used to symbolize and signify molecules on a schematic 2D or 3-D stage through figuring out the vital residences of molecular recognition. Every form of atom or organization in a compound may be decreased to a Pharmacophore feature (or Pharmacophore fingerprints). These molecular styles might be categorized through numerous chemical residences, consisting of hydrogen bond donors or acceptors, aromatic, cationic, etc., which may be used to investigate the similarity amongst a library of small molecules and pick out the key contributing functions to the organic function [12].

RESULT AND DISCUSSION

Molecular Docking

Molecular docking was performed for HER2+ve receptor (breast cancer) and plant secondary metabolites compounds such as flavonoids. 20 plant-based ligands were docked with HER2 +ve receptor and binding energy was examined. These ligands were obtained from plants that have high anti-oxidant properties such as, Tealeaf, Garlic, Flaxseed, Turmeric, Black cohosh, Achillea, Echinacea, Soya bean, Fennel seed, Clover, Grapefruit, Cherries, Moringa leaves. Plant flavonoids compound such as Achillicin, Caffeic acid, Caffein, Ferulic acid, L-theanine, omega3 fatty acid, Rosemaric acid, S-allyl, Alliin, Geneistein, Daidzein, Glycetein, Equol, Myricetin, Biochanin, Hesperetin, Quercetin, Kaempferol, and Isorhamnetin [13].

Table1: Binding energy value of 20 flavonids compound

Compound	Runs	Binding energy
Achillicin	27	-5.27
Alliin	6	-3.93
Biocahanin	10	-8.18
Caffeic acid	15	-7.27
Caffein	27	-5.27
Daidzein	48	-8.03
Equol	21	-8.05
Ferulic acid	29	-6.6
Geneistein	13	-7.78
Glycetein	48	-7.78
Hesperetein	9	-7.68
Isorhamnetein	35	-6.99
Kaempferol	46	-7.44
L-theanine	7	-4.86
Myricetein	46	-7.37
Omega 3 fatty acid	21	-6.21
Querectein	9	-7.69
Rosemaric acid	38	-6.72
S- allyl	21	-4.25

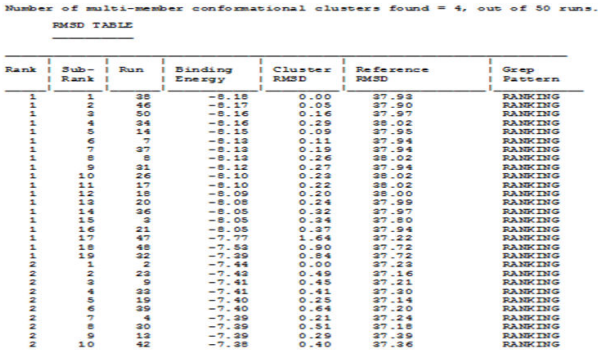

Figure2: Shows the binding energy of Biochannin compound

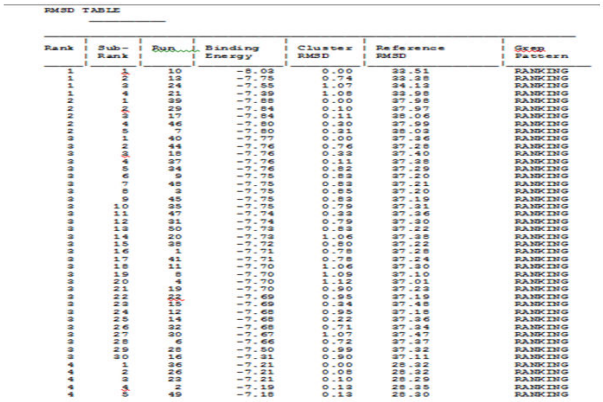

Figure3: Shows the binding energy of Daidzein compound

From the above result several plant compound have been docked but plant compound Daidzein from soyabean leaves show highest energy -8.03. And plant compound, Equol from soyabean leaves shows the highest binding energy -8.05, Hespertein from clover leaves shows the highest binding energy -8.18.

LIPINSKI'S RULE OF FIVE

Molinspiration is a software tool which is necessary for drug desings. It is based on LIPINSKI'S RULE OF FIVE for determining the molecular property, structure, and drug likeness of the compounds. Our selected 20 flavonids compound was undergone for examining the drug likeness property.

Table2: Shows the drug likeness of our selected compound

Molecules	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
Achillicin	-0.03	0.02	-0.48	0.34	0	0.33
Caffeic acid	-0.48	-0.23	-0.81	-0.1	-0.79	-0.09
Caffeine	-0.53	-0.98	-1.07	-2.1	-1.23	-0.22
Curcumin	-0.06	-0.2	-0.26	0.12	-0.14	0.08
Ferulic acid	-0.47	-0.3	-0.72	0.14	-0.81	-0.12
l-theanine	-0.17	0.12	-0.99	-1.07	0.03	0.13
Omega 3 fatty acid	0.34	0.18	-0.09	0.37	0.21	0.34
Rosemaric acid	0.17	-0.08	-0.18	0.57	0 .15	0.24
s-allyl	-0.98	-0.46	-1.87	1.5	-0.4	-0.25
Alliin	-0.58	-0.38	-1.42	-1.01	-0.3	0.07
Equol	-0.02	0.02	-0.05	0.4	-0.29	0.24
Geneistein	-0.22	-0.54	-0.6	0.23	-0.68	0.13
Daidzein	-0.3	-0.64	-0.2	0.04	-0.83	0.02
Glycetein	-0.24	-0.66	-0.08	0.07	-0.77	0.01
Mycertein	-0.06	-0.18	0.28	0.32	-0.2	0.3
Biochannin	-0.23	-0.59	-0.7	0.23	-0.66	0.07
Hesperetin	0.04	-0.26	-0.2	0.38	-0.13	0.16
Quercetin	-0.06	-0.19	0.28	0.36	-0.25	0.28
Kaempferol	-0.1	-0.21	0.21	0.32	-0.27	0.26
Isorhamnetin	-0.1	-0.26	0.25	0.28	-0.3	0.22

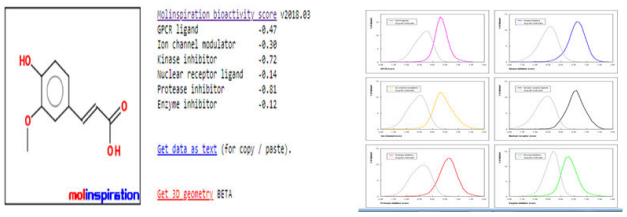

Figure4: Structure and drug likeness of ferulic acid compound.white colour line shows the drug common ability value. Pink, blue, yellow, grey, black,green shows the drug likness of our compound.

From the above result among 20 flavonoids compound, caffeic acid, caffeine compounds(tea leaf),biochanin compound (clover), glycetein compound from (soyabean) Daidzein compound(soyabean levaes) satisfiy the LIPINSKI'S RULE OF FIVE which is safe and acceptable as an oral drug for human consumption.

PHARMACOPHORE MODELLING

It is a virtual screening effective tool for identifying active compounds or lead molecules. The molecules which passed from Lipinski's rule of five, further goes for next process called virtual screening method. Plant compounds such as Biochannin, Caffeic acid, Caffeine, Daidzein and Hesperetin were screened by ZINC PHARMER software.

Table3: Shows the least energy value of our screened molecules

COMPOUND	NAME	RMSD	MASS	RBnds
Biochanin	ZINC69169012	0.03	336	6
Caffeic acid	ZINC04261891	0.728	439	9
Caffeine	ZINC77264418	0.839	378	5
Daidzein	ZINC06041520	0.006	432	10
Hesperetin	ZINC81099724	0.738	332	7

From the above top 5 virtuval screened molelcues, Daidzein compound satisfy the screen method with the least energy value .

CONCLUSION

The investigation of the present work concludes that the docking studies carried out on HER2 corroborate the findings that the most suitable drug-like properties are possessed by the compound. Other than chemical compounds, the natural

compound has no side effects. However, this provides evidence of how natural compounds from plants can be sources of a potential anti-cancer agent. The pre-clinical studies will pay the way for a potential anti-cancer compound. The study aimed at finding the compatible natural lead molecule from plant and it shows that the compound is druggable based on Lipinski's rule and also it undergoes virtual screening based on Pharmacophore modelling study studies are also positive, adding an advantage for the compounds to be druggable. With the docking studies, the compound that is docked with the target has been found. All the 20 natural flavonoids compound**,** The following compounds used were, Achillicin, Caffeic acid, Caffeine, Curcumin, Ferulic acid, L-theanine, Omega 3 fatty acid, Rosemarie acid, S- allyl, Alliin, Geneistein, Daidzein, Glycerin, Equol, Myricetein, Biochannin, Hesperetin, Quercetin, Kaempferol, Isorhamnetin, having high binding affinity for breast cancer receptor which lead to breast cancer treatment by molecular docking method. Among 20 natural compounds **Biochannin, Daidzein** shows the highest binding energy values as**-8.16 and -8.05**.

Biochannin and Daidzein compound shows the highest binding energy value. However other compounds also undergo Lipinski's rule five by which our selected flavonoids follow Lipinski's criteria. From the above result among 20 flavonoids compound, **Caffeic acid, caffeine compounds** (tea leaf), **biochannin compound** (clover), **glycetein compound** from(soybean) **Daidzein compound** (soybean leaves) satisfy the LIPINSKI'S RULE OF FIVE which is safe and acceptable as an oral drug for human consumption.

The compound Caffeic acid, caffeine, biochannin, glycetein, and daidzein compound undergo virtual screening-based Pharmacophore modelling. From the above top 5 virtual screened molecules, **the Daidzein compound** satisfies the screen method with the least energy value. The RMSD, MASS, and hydrogen bond interaction outcome denote that the complex is highly constant through the simulation period. From this work, we conclude that our selected flavonoids compounds, **Daidzein compound** (soybean leaves) has the capability for the treatment of HER2 positive breast cancer, with no side effect. Further, this work will be continued on breast cancer cell line study in-vitro and then in vivo studies [14-20].

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