EJMO

DOI: 10.14744/ejmo.2022.43656
EJMO 2022;6(2):142–149

Research Article

Structure-Based Molecular Docking Studies toward Exploring Phytoestrogen against Breast Cancer

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Abstract

Objectives: Breast cancer (BCa) remains the world's second biggest cause of cancer death. This occurs as a result of unregulated cell development and can be metastasized to other parts of the human. Estrogen receptor alpha is the renowned target that has piqued the interest of researchers to target BCa. FlexX molecular docking technique was used to predict the aspects of interaction, affinities energy, and orientation of natural compounds in the protein site. Phytoconstituents have a vital role in anticancer activities due to their important scaffolds, which may offer more effective and reduced costs and side effects than synthetic drugs. The present study aims to identify new anticancer agents from natural and dietary compounds with lesser adverse effects.

Methods: To accomplish this, we implemented with the help of molecular docking approaches using FlexX for predicting the features of bioactive phytocompounds from natural products and evaluating targeted binding affinity energy.

Results: Our results confirm that among various natural compounds, daidzein has the best docking score in the ten compounds compared with the standard drug cytarabine.

Conclusion: Our study suggests that daidzein is a potent ligand for ERα BCa among all and can be further investigated through in vitro and in vivo studies.

Keywords: Estrogen receptor, emodin, flexx docking, phytoconstituents, natural compounds

Cite This Article: *Lenin M, Ramakrishnan E, Sankaran M. Structure-Based Molecular Docking Studies toward Exploring Phytoestrogen against Breast Cancer. EJMO 2022;6(2):142–149.*

Breast cancer (BCa) is the second leading cause of cancer and the incidence is almost 1 in 8 women, requiring either therapy (chemotherapy, radiotherapy, and hormone therapy) or surgery or both. In 2022, 51 400 instances of ductal carcinoma in situ in the female breast and 97 920 cases of melanoma in situ will be diagnosed. [1] Malignant growth shows its nature in the human body through various pathways involving distinctive disease macromolecules, and inhibiting all macromolecules at once is extremely challenging for a single or combination of molecules. The estrogen receptor (ER) is an orphan nuclear hormone receptor, which is activated by the hormone 17β-estradiol (estrogen).[2] There are two forms of ER: ERα and ERβ. ERα is a ligand-activated transcription domain, which plays an important pivotal role in BCa, and the overexpression of ER in around 75% of BCa cases is reported after menopause. There are several distinct functional domains on ERα, such as C-terminal ligand-binding domain (LBD), DNA-binding domain, N-terminal domain (NTD), activation function-1 (located in NTD), activation function-2 (located in LBD), and the hinge region. The exact assessment of ER status is crucial for diagnosis and

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Submitted Date: March 02, 2022 **Accepted Date:** May 05, 2022 **Available Online Date:** June 06, 2022

treatment of BCa patients. Currently, three drugs that act as inhibitors or modulators of ERα are used in patients with BCa, which are tamoxifen, raloxifene, and toremifene.[2] Antiestrogens are also known as estrogen antagonists that block ERs and suppress cancer growth. The developed antiestrogens such as bazedoxifene, clomifene, cyclofenil, epimestrol, lasofoxifene, nafoxifene, ormeloxofene, raloxifene, tamoxifen, and toremifene have been used to block the estrogen signal.[3] In many cases, They may cause several adverse effects such as abnormal vaginal bleeding, chest pain, and shortness of breath, as well as having a low bioavailability.[4, 5] As a result, it is critical to find and develop better ERα inhibitors from natural sources to cure BCa without side effects. Natural compounds are being frequently investigated for use in modern medicine.[6] Natural compounds and their derivatives are currently being exploited to boost biological activity against BCa.[7] These compounds play a key role in the development of a variety of treatments against different types of malignancies. There are diverse bioactive phytochemicals such as chlorogenic acid, caffeic acid, mahanine, and kaemferol that exhibit a multitargeting potential to stimulate antiproliferation effects.[8–11] The anticancer effects of chlorogenic, caffeic, and Ferulic acids (phenolic acid groups) are selective estrogen receptor modulators in BCa cell line MCF-7 that mainly consist of ERα.[12] Naturally derived antiestrogens (NDAEs) have attracted a lot of attention due to their nontoxic nature and important role in the prevention and treatment options of BCa, as well as their various mechanisms of action.

Indeed, with tremendous efforts in recent years, researchers provided several bioactive phytocompounds with a significant activity of ER blocking or estrogen stimulating effects. However, the increasing incidence of the drug-resistant nature of BCa necessitates the development of powerful NDAEs that can not only inhibit the tumour but also complete clinical trials. Natural compounds have a variety of promising effects in human cancer models. We investigated natural compounds such as daidzein,[13] emodin,[14] delphinidin,[15, 16] cyanidin,[16] apigenin,[17] cordycepin,[18, 19] ascorbigen,[20] biochanin A,[21] chrysin,[22] and demethoxycurcumin[23, 24] and compared them with the standard drug cytarabine using molecular docking analysis. The chemical structure of phytocompounds is depicted in Figure 1. Cytarabine (1-β-arabinofuranosylcytosine [ara-C]) is one of the most effective chemotherapeutic agents. Since the 1960s, it has been used to treat acute lymphocytic leukemia, acute myeloid leukemia, chronic myelogenous leukemia, and non-Hodgkin's lymphoma.[25] The target proteins and their key interactions were studied using a molecular docking technique.

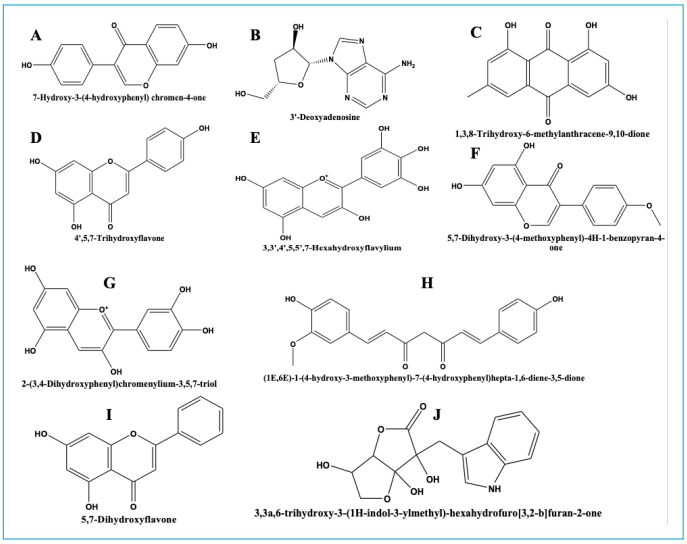

Figure 1. Structure of phytochemicals from different natural sources: **(a)** daidzein, **(b)** emodin, **(c)** delphinidin, **(d)** cyanidin, **(e)** apigenin, **(f)** cordycepin, **(g)** ascorbigen, **(h)** biochanin A, **(i)** chrysin, and **(j)** demethoxycurcumin.

FlexX is a fast and flexible docking tool that docks ligands into the active regions of proteins. It possesses excellent ligand flexibility by changing the conformations in the active site although protein is rigid. Our fascination with natural compounds aided in the identification of active molecules. Using FlexX docking software 2.3.2,[26] we screened ten natural compounds with the cocrystal structure of a human ER LBD in a complex with 4-hydroxytamoxifen (3ERT).

Methods

Selection of Ligands and Receptors

The ten natural compounds and the standard were considered for the study obtained from PubChem. The Protein Data Bank was used to obtain the X-ray crystal structure of the ER complex with 4-hydroxytamoxifen [PDB ID: 3ERT]. Prior to getting performed in docking studies, the protein structure was prepared.

Ligand Preparation

Daidzein, emodin, delphinidin, cyanidin, apigenin, cordycepin, ascorbigen, biochanin A, chrysin, demethoxycurcumin, and the standard cytarabine were redrawn in ACD-Chemsketch and their SMILES notations were obtained. The SMILES notation was submitted to "SMILES online converter" and "File generator of structure" and exported in SDF format. These natural compounds were also imported into the docking library of FlexX docking software 2.3.2 using an Incremental Construction Algorithm. In the scoring function, the default docking parameters were used.

Molecular Docking Studies

The structures of ERα and cocrystallized ligand (PDB ID: 3ERT) were obtained from Protein Data Bank. The FlexX 2.3.2 program was used to load the probable binding sites between the various ligands and the target protein. FlexX docking software is used to anticipate protein–ligand interactions.[26, 27] FlexX predicts the shape of a complex as well as an estimate of binding strength for a given protein and a ligand. FlexX docking software is used to run with the default docking program such as maximum allowed overlap volume of 2.5 Å3, clash factor of 0.6, full score contribution and threshold of 0.30, and no score contribution and threshold of 0.70.[28] The results were compared with the reference compound (cytarabine) obtained from the corresponding PDB ID. The docking scores and the 2D and 3D pose views were generated for further analysis of the interactions and binding affinities of the selected ten natural compounds.

Results and Discussion

Natural compounds have been found to preferentially suppress BCa in previous studies. The current study aimed to explore the ERα inhibition using bioactive natural compounds. Among the ten ligands, daidzein showed a superior docking score of -23.89 kcal/mol, followed by emodin, which had a score of -22.81 kcal/mol. Daidzein (7,4'-dihydroxyisoflavone) is a naturally occurring substance mainly found in soybeans and other legumes. It belongs to the isoflavone class of compounds.[13] Isoflavone belongs to flavonoid superfamily that ranks as one of the most estrogenic activities which is bound to Erα that potential to inhibit BCa cells is well documented.[13] According to the molecular size and structural characteristics, most of these compounds, such as isoflavones, polyphenols, flavonoids, have a chemical composition that mimics that of the human estrogen hormone, particularly 17-estradiol. In this study, we found that the active core pocket present in daidzein interacted with the target protein and amino acid residues to form polar H-bond and hydrophobic interactions. Amino acids Leu 391, Phe 404, Met 388, Leu 525, Leu 387, Met 421, Leu 384, Met 343, Leu 346, and Ile 424 of 3ERT are involved in hydrophobic interactions with daidzein, according to ligand–protein interactions. The polar hydrogen bond interaction also involves the amino acids Arg 394, Leu 346, and Ile 419. Emodin (3-methyl-1,6,8-trihydroxyanthraquinone) is obtained from the roots and rhizomes of *Rheum palmatum* L., as well as other plants such as Polygonum, Rhamnaceae, Leguminosae, and Liliaceae. Emodin may have antitumor activity by activating the AhR/CYP1A1 pathway, for its use in the treatment of BCa.[29] Emodin is structurally related to anthracycline and commonly present in Chinese herbs.[30] We examined the active pocket at which emodin bound to the target protein and found that it robustly interacted with the amino acid residues to form polar H-bond and hydrophobic interactions. Ligand–protein interactions revealed that amino acids Leu 391, Glu 353, Phe 404, Ala 350, Leu 349, Leu 387, Leu 345, Met 343, and Leu 525 of 3ERT involve in the hydrophobic interactions with the emodin. In addition, amino acids Leu 387, Arg 394, and Leu 346 are involved in the polar hydrogen bond interaction. The 3D representation of the best-docked pose view of daidzein, emodin, and delphinidin with ERα is shown in Figure 2.

Delphinidin showed the third most valuable docking score (-22.11 kcal/mol) with binding affinity energy value compared with control cytarabine. Delphinidin is the major bioactive component of an anthocyanidin monomer. Interaction between delphinidin and protein 3ERT to form H-bond and hydrophobic interactions participated in specific amino acid residues. The stability of the ligand–protein complex is aided by hydrophobic interactions from the docking result, such as Leu 525, Gly 521, Leu 384, Phe 404, Leu 387, Ala 350, Leu 391, Met 343, and Leu 346, and polar H-bond interaction including His 524, Gly 521, and Leu 346. Delphinidin which has six hydroxyl groups in its structure was able to inhibit apoptotic pathways.[31] Delphinidin especially induced programmed cell death and autophagy in HER-2 positive (MDA-MB-453 and BT474 cells) BCa cells through mTOR and AMPK signaling pathways.[31] Cyanidin and apigenin had the fourth and fifth docking score nearly delphinidin compound. Cyanidin and apigenin docking scores are, respectively, -21.60 and -20.27 kcal/mol). Hydrophobic interactions of cyanidin with protein produced amino acid residues such as Leu 346, Ala 350, Leu 387, Ile 424, Leu 384, Met 343, and Leu 52, and polar H-bond interactions produced Glu 353, Leu 346, Gly 521, and Glu 419. Apigenin interacted with protein to form amino acid residues Leu 391, Ala 350, Leu 346, Gly 521, Leu 384, Met 421, Leu 525, Ile 384, Met 388, and Met 343, and the polar H-bond interaction displayed amino acid residues Leu 346 and His 524. Apigenin reduces a variety of human carcinoma in cell lines and animal models by a variety of biological mechanisms, including cell cycle arrest, cell apoptosis and autophagy cell invasion and migration suppression, and immunological stimulation.[17] These docking score results indicate that apigenin is a potential cancer treatment reagent. Apigenin has the potential to be developed as a nutritional supplement or adjuvant chemotherapeutic drug.[17]

Cordycepin showed the sixth docking score (-19.93 kcal/mol) with binding affinity energy value compared with control cytarabine. Cordycepin, the active component in *Cordyceps sinensis*, has been shown to have significant

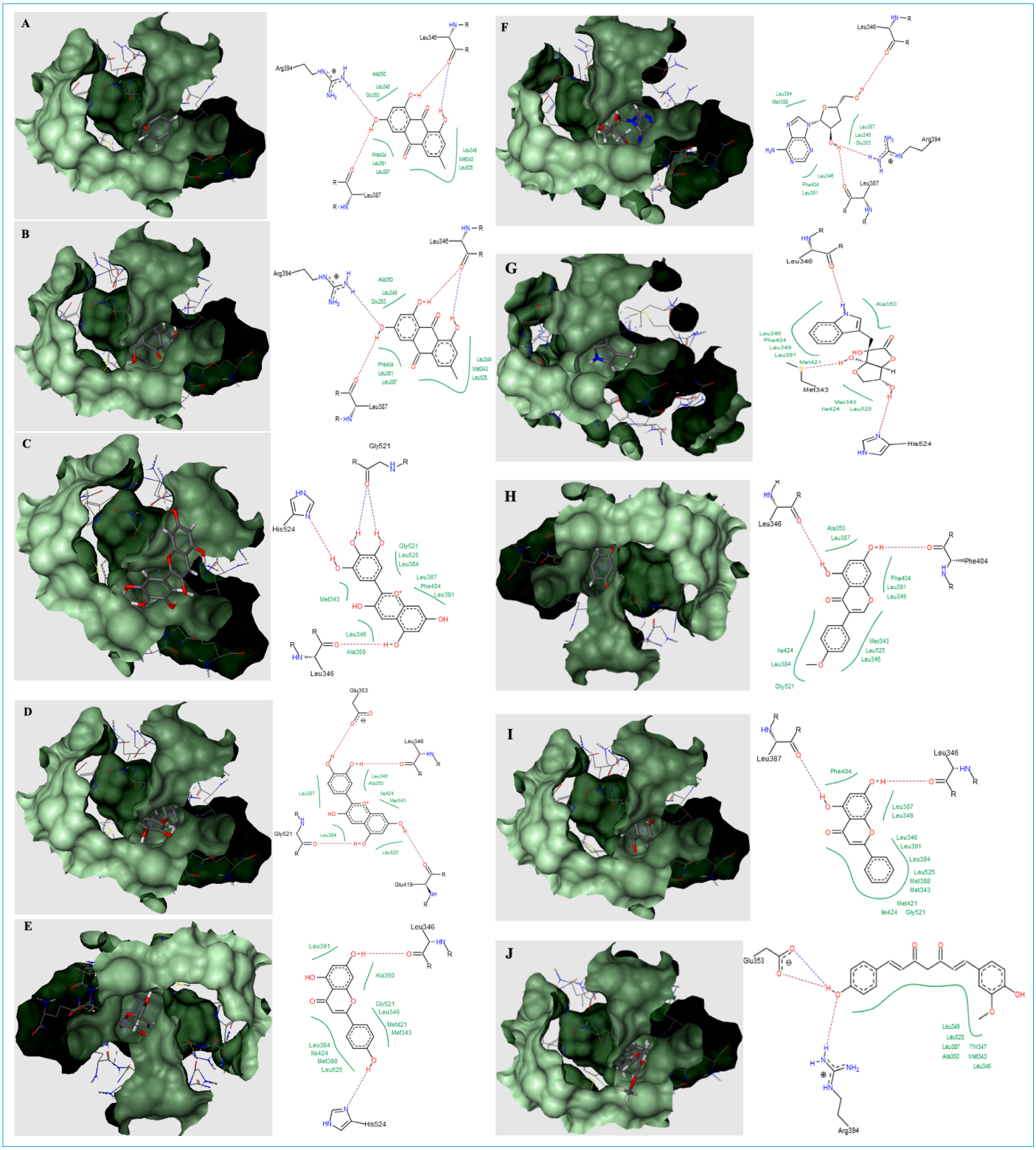

Figure 2. Three-dimensional representation and best pose view indicating the interaction of the top three ligands: **(a)** daidzein, **(b)** emodin, and **(c)** delphinidin docked in the ERα protein. Three-dimensional structure and pose view of phytocompounds with their active pocket: **(d)** cyanidin, **(e)** apigenin, and **(f)** cordycepin. Pose view of phytochemicals with their active pockets: **(g)** ascorbigen, **(h)** biochanin A, **(i)** chrysin, and **(j)** demethoxycurcumin.

anticancer, antioxidant, and anti-inflammatory activities. The PI3K and eNOS inhibitors suppressed all of cordycepin's anti-inflammatory and antiapoptotic activities, suggesting that the PI3K/Akt/eNOS signallng pathway may play a role in its antiatherosclerotic properties.[29] Cordycepin is a pharmacologically active substance obtained

from the fungus *Cordyceps militaris*. It is also known as 3-deoxyadenosine and has a structure identical to adenosine but lacks the ribose moiety's 3'-hydroxyl group. It has inhibitory effects on the PI3K/AKT/mTOR signaling pathway while also activating AMPK.[30] The docking plot shows the amino acid residue interactions of Leu 384, Met 388, Leu 346, Phe 404, Leu 391, Leu 387, Leu 349, and Glu 353. The contact involved different kinds of polar hydrogen and hydrophobic bondings and had side and back chain contacts with cordycepin. They function by interacting with cell surface receptors like adenosine receptors.[31] Figure 2 depicts a 3D depiction of cyanidin, apigenin, and cordycepin and receptor-interacting pose view with 3ERT. Ascorbigen is a glucosinolate that is found primarily in *Brassica* vegetables. It is made up of glucobrassicin as a precursor. Enzymatic hydrolysis of indoles containing glucobrassicin produces indole-3-carbinol that combines with L-ascorbic acid to produce ascorbigen.[32, 34] It has hydrophobic interactions with Met 343, Leu 346, Met 421, Leu 525, Leu 391, Leu 387, and Ala 350, and polar H-bond interactions with Arg 394 and Glu 353. The results of natural compounds against the ERα protein target docking score are presented in Table 1. Biochanin A and chrysin docking scores displayed more than -19 kcal/mol. Biochanin A interacted with amino acid residues Leu 387, Ala 350, Leu 391, Phe 404, Leu 349, Met 343, Leu 525, Ile 424, Leu 346, Gly 521, and Leu 384, and polar H-bond interactions with Leu 346 and Phe 404. Chrysin interacted with protein 3ERT to find amino acid residues including Leu 387, Ile 424, Gly 521, Leu 349, Phe 404, Leu 346, Leu 391, Leu 384, Leu 525, Met 388, Met 343, and Met 421, and polar H-bond interactions with Leu 387, and Leu 346. Biochanin A (5,7-dihydroxy-4'-methoxy-isoflavone) is an isoflavone found in red clover, alfalfa, cabbage, and a variety of other herbal items. Biochanin A is a chemoprotective agent that can be used as an alternative therapy for a variety of hormone imbalances.[21] Chrysin (5,7-dihydroxyflavone) is a polyphenolic flavone found in

Table 1. Molecular interactions of natural compounds with ERα (3ERT) protein

S. No.	Ligands	Compound ID	Binding affinity energy (kcal/mol)	Nature of interaction	Interacting residues
1	Daidzein	5281708	-23.89	Hydrophobic interaction	Leu 391, Phe 404, Met 388, Leu 525, Leu 387, Met 421, Leu 384, Met 343, Leu 346, Ile 424
				Polar H-bond interaction	Arg 394, Leu 387, Glu 419
2	Emodin	3220	-22.81	Hydrophobic interaction	Leu 391, Glu 353, Phe 404, Ala 350, Leu 349, Leu 387, Leu 345, Met 343, Leu 525
				Polar H-bond interaction	Leu 387, Arg 394, Leu 346
3	Delphinidin	68245	-22.11	Hydrophobic interaction	Leu 525, Gly 521, Leu 384, Phe 404, Leu 387, Ala 350, Leu 391, Met 343, Leu 346
				Polar H-bond interaction	His 524, Gly 521, Leu 346
4	Cyanidin	128861	-21.60	Hydrophobic interaction	Leu 346, Ala 350, Leu 387, Ile 424, Leu 384, Met 343, Leu 525
				Polar H-bond interaction	Glu 353, Leu 346, Gly 521, Glu 419
5	Apigenin	5280443	-20.27	Hydrophobic interaction	Leu 391, Ala 350, Leu 346, Gly 521, Leu 384, Met 421, Leu 525, Ile 384, Met 388, Met 343
				Polar H-bond interaction	Leu 346, His 524
6	Cordycepin	6303	-19.93	Hydrophobic interaction	Leu 384, Met 388, Leu 346, Phe 404, Leu 391, Leu 387, Leu 349, Glu 353
				Polar H-bond interaction	Leu 387, Arg 394, Leu 346
7	Ascorbigen	3081416	-19.88	Hydrophobic interaction	Met 343, Leu 346, Met 421, Leu 525, Leu 391, Leu 349, Ala 350, Ile 424, Phe 404
				Polar H-bond interaction	Arg 394, Glu 353, Met 343
8	Biochanin A	5280373	-19.84	Hydrophobic interaction	Leu 387, Ala 350, Leu 391, Phe 404, Leu 349, Met 343, Leu 525, Ile 424, Leu 346, Gly 521, Leu 384
				Polar H-bond interaction	Leu 346, Phe 404
9	Chrysin	5281607	-18.76	Hydrophobic interaction	Leu 387, Ile 424, Gly 521, Leu 349, Phe 404, Leu 346, Leu 391, Leu 384, Leu 525, Met 388,
				Polar H-bond interaction	Met 343, Met 421, Leu 387, Leu 346
10	Demethoxy curcumin	5469424	-14.57	Hydrophobic interaction	Leu 349, Leu 525, Leu 387, Ala 350, Thr 347, Met 343, Leu 345
				Polar H-bond interaction	Glu 353, Arg 394

high concentrations in honey and propolis. Chrysin inhibits the aromatase enzyme, and it can be used to prevent and treat hormone-dependent BCa as well as adjuvant therapy for estrogen-dependent disorders.[22]

Demethoxycurcumin had the docking scores and binding energy values mentioned in Table 1. Demethoxycurcumin, a derivative of curcumin obtained from the rhizome of the *Curcuma longa* plant, is one such remedy that has been used in Southeast Asia.[23] Figure 2 depicts a 3D depiction of phytochemicals with their active pockets. Moreover, the molecular docking result of 3ERT against natural compounds revealed compound daidzein has a better docking score as compared with standard (cytarabine: -16.96) (Table 2). Cytarabine, an anticancer medicine, is commonly used to treat hematological malignancies; however, it has limited action against solid tumors, which necessitates continuous infusion, resulting in high dose cytarabine toxicity. However, it shows a lower binding affinity than the standard drug cytarabine. The results of natural compounds' drug-likeness score and biological activity score according to Molinspiration Cheminformatics software are presented in Tables 3 and 4. Figure 3 depicts a 3D depiction of cytarabine and receptor-interacting pose view with 3ERT. In this docking analysis, daidzein has a higher docking score than those of the other ligand molecules. Furthermore, it shows better binding energy for the target protein (ERα) than the other compounds do. The bioactive natural compound of daidzein comes under the group of isoflavones.

Table 2. Molecular interactions of a standard compound with ERα (3ERT) protein

S.No.	Compounds	Binding affinity energy (kcal/mol)	Nature of interaction	Interacting residues
1	Cytarabine	-16.96	Hydrophobic interaction	Leu 391, Met 388, Leu 428, Phe 404, Glu 353, Leu 349, Leu 387, Leu 346
			Polar H-bond interaction	Leu 387, Glu 353, Arg 394

Table 3. Drug likeness score for natural compounds

S.No.	Compound	miLogP	TPSA	n, atoms	n, ON	n, OHNH	n, violation	n, rotb.	Volume	MW
1	Daidzein	2.56	70.67	19	4	2	0	1	216.03	254.24
2	Emodin	3.01	94.83	20	5	3	0	0	223.19	270.24
3	Delphinidin	-1.04	132.54	22	7	6	1	1	242.83	303.25
4	Cyanidin	-0.75	112.31	21	6	5	0	1	234.81	287.25
5	Apigenin	2.46	90.89	20	5	3	0	1	224.05	270.24
6	Cordycepin	-0.90	119.32	18	8	4	0	2	210.49	251.25
7	Ascorbigen	-1.38	112.01	22	7	4	0	2	252.61	305.29
8	Biochanin A	2.80	79.90	21	5	2	0	2	241.58	284.27
9	Chrysin	2.94	70.67	19	4	2	0	1	216.03	254.24
10	Demethoxycurcumin	2.48	83.83	25	5	2	0	7	306.64	338.36

Table 4. Bioactivity score of the compounds according to Molinspiration Cheminformatics software

S.No.	Compound	GPCR ligand	Ion channel modulator	Kinase inhibitor	Nuclear receptor ligand	Protease inhibitor	Enzyme inhibitor
1	Daidzein	-0.30	-0.64	-0.20	0.04	-0.83	0.02
2	Emodin	-0.14	-0.14	0.07	0.17	-0.21	0.21
3	Delphinidin	-0.12	-0.09	0.05	0.07	-0.24	0.04
4	Cyanidin	-0.13	-0.09	0.02	0.09	-0.30	0.01
5	Apigenin	-0.07	-0.09	0.18	0.34	-0.25	0.26
6	Cordycepin	0.83	0.41	0.76	-1.65	-0.20	1.30
7	Ascorbigen	0.52	0.27	0.20	0.40	0.27	0.59
8	Biochanin A	-0.23	-0.59	-0.07	0.23	-0.66	0.07
9	Chrysin	-0.11	-0.08	0.15	0.30	-0.30	0.26
10	Demethoxycurcumin	-0.04	-0.20	-0.26	0.18	-0.14	0.10

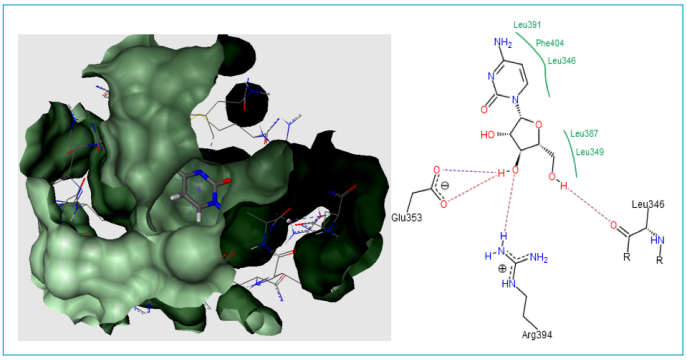

Figure 3. Pose view of the reference compound (cytarabine) with its active pockets.

Conclusion

The analysis of molecular interactions and docking scores of the natural compounds with anti-BCa targets imply that they can bind to multiple targets involved in the BCa mechanism. The results of the present study demonstrated that binding affinity energy calculated the excellent dock score for the daidzein (-23.89 kcal/mol) when docked with ERα. It is concluded that daidzein may act as a novel anticancer agent for treating BCa and other types of cancer. In addition, in vitro and in vivo experimental validation will be carried out in the near future.

Acknowledgments

The authors are thankful to the Vice-Chancellor, Annamalai University & Director, IASST for giving us the facility to carry out this work. Thanks are attributable to Bioinformatics Infrastructure Facility, IASST.

Disclosures

Peer-review: Externally peer-reviewed.

Conflict of Interest: The authors confirm that this article content has no conflict of interest.

Funding: Mrs. V.L. Maruthanila thank Annamalai University for University Research Studentship for the year 2021-2022. Dr. R.Elancheran thanks DST-PURSE phase II for the financial support.

Authorship Contributions: Concept – M.L.; Design – M.L., E.R.; Supervision – M.S.; Materials – M.L., E.R.; Data collection &/or processing – M.L., E.R.; Analysis and/or interpretation – M.L., E.R.; Literature search – E.R.; Writing – M.L.; Critical review – M.L., E.R., M.S.

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