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Article

Exploring the Chemopreventive Potential of Soybean Phytochemicals Targeting BRCA1 Protein: A Molecular Docking Study

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Abstract. Breast cancer remains a significant cause of cancer-related mortality among women globally, highlighting the importance for preventive strategies targeting early molecular events. BRCA1 plays a critical role in maintaining genomic stability through DNA repair mechanisms. However, the potential of soybean phytochemicals to modulate BRCA1 activity at the molecular level, particularly through computational approaches, has not been extensively explored. This study aimed to evaluate the chemopreventive potential of soybean phytochemicals targeting the BRCA1 protein using an *in silico* approach. A total of 32 compounds were prepared and docked into the BRCA1 binding site using Autodock Tools 1.5.7, followed by interaction analysis and visualization, prediction of pharmacokinetic and toxicity profiles using SwissADME, pkCSM, and ProTox. The results showed that the top compounds exhibited binding energy ranging from -6.04 to -8.07 kcal/mol, which were lower than the reference compound. Interaction analysis revealed stable binding with key amino acid residues, including Met1775, Leu1839, and Lys1702 through hydrogen and hydrophobic interactions. Among the evaluated compounds, daidzin showed the most balanced profile in terms of binding affinity, interaction relevance, and favorable ADMET properties. This study provides a systematic *in silico* evaluation of soybean phytochemicals targeting BRCA1 and highlights their potential as candidates for breast cancer chemoprevention.

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1. Introduction

Breast cancer is still recognized as a leading factor contributing to both cancer-related morbidity and mortality among women worldwide. In 2022, the Global Cancer Observatory (GLOBOCAN) reported approximately that breast cancer affected around 2.3 million women globally, contributing to 11.7% of all cancer incidences. [1]. Among women in Indonesia, breast cancer ranks as the most frequently occurring malignancy with around 66,000 new cases and 22,500 deaths reported, making it leading the cause of both cancer incidence and mortality in the country [2]. These data highlight the urgent need for effective preventive strategies targeting the early stages of carcinogenesis.

The progression of breast cancer is a complex sequence of events that involves genetic mutations, oxidative stress, and DNA damage that ultimately lead to uncontrolled cell proliferation [3]. Among these, DNA damage is considered a critical initiating event, and failure in DNA repair mechanisms can result in genomic instability and tumor formation [4]. Therefore, prevention strategies targeting early molecular events such as DNA damage and mutation are essential stategies for decreasing the risk of breast cancer [5].

BRCA1 acts a tumor suppressor protein with a critical role in preserving genomic stability. It participates in DNA damage repair, particularly through homologous recombination for double-strand breaks as well as contributes to the regulation of cell cycle checkpoints and transcriptional processes [6]. Dysfunction or mutation of the BRCA1 impairs DNA repair mechanisms, leading to the accumulation of genetic mutations and initiation of carcinogenesis [7]. Thus, modulation of BRCA1 activity are considered as potential strategies in cancer prevention, especially in the early stages of carcinogenesis before tumor formation occurs.

Chemoprevention involves the application of natural or synthetic agents to prevent or delay carcinogenesis, or even reverse its progression. Numerous natural compounds, especially phytochemicals, have been shown to possess chemopreventive activities due to their antioxidant, anti-inflammatory, and antiproliferative effects. These substances may prevent cancer initiation by minimizing oxidative stress, protecting DNA from damage, and modulating molecular targets involved in DNA repair mechanisms and cell cycle regulation [8-9]

Soybean is recognized as a plant rich in various bioactive phytochemicals, including isoflavones (genistein, daidzein, and glycitein), flavonoids, saponins, and phenolic compounds [10-11]. Isoflavones in soybean have been widely reported to exhibit antioxidant, antiestrogenic, antiproliferative, and anticancer activities, particularly in hormone-related cancers such as breast cancer [12-13]. A number of previous studies have shown that soybean phytochemicals can modulate molecular pathways involved in cancer development, including oxidative stress, cell cycle regulation, apoptosis, and gene expression [10,13–16].

However, despite these findings, the interaction of soybean phytochemicals with BRCA1 at molecular levels remains limited, particularly in terms of systematic computational evaluation. This gap highlights the need for studies that spesifically investigate the binding behaviour, pharmacokinetic and toxicity properties of soybean phytochemicals targeting BRCA1.

Hence, this study aims to evaluate the binding affinity, pharmacokinetic and toxicity properties of soybean phytochemicals targeting BRCA1 using molecular docking and ADMET analysis. This study is expected to identify potential soybean-derived compounds that may act as BRCA1 modulators and contribute to the development of chemopreventive agents for breast cancer prevention.

2. Experimental Section

2.1. Materials

This research employed an *in silico* approach to assess the interaction between soybean (*Glycine max*) phytochemicals and BRCA1 through molecular docking and ADMET prediction. The study utilized the three-dimensional (3D) structure of the BRCA1 (PDB ID: 1T15) obtained from the Protein Data Bank (PDB). A total of 32 phytochemical compounds identified from soybean extract based on previous studies were used as ligands, while tamoxifen was used as a positive control dute to the absence of a native ligand in the selected protein structure [17]. The ligand structures were retrieved from the PubChem database in .sdf format, while those unavailable compounds in PubChem were manually constructed using ChemDraw.

The software used in this study included AutoDock Tools 1.5.7 for molecular docking preparation and simulation, ChemDraw for ligand construction, Chem3D for ligand optimization, and Discovery Studio Visualizer for interaction analysis and visualization. Drug-likeness and ADMET predictions were predicted using SwissADME, pkCSM, and ProTox 3.0 web servers [18–20].

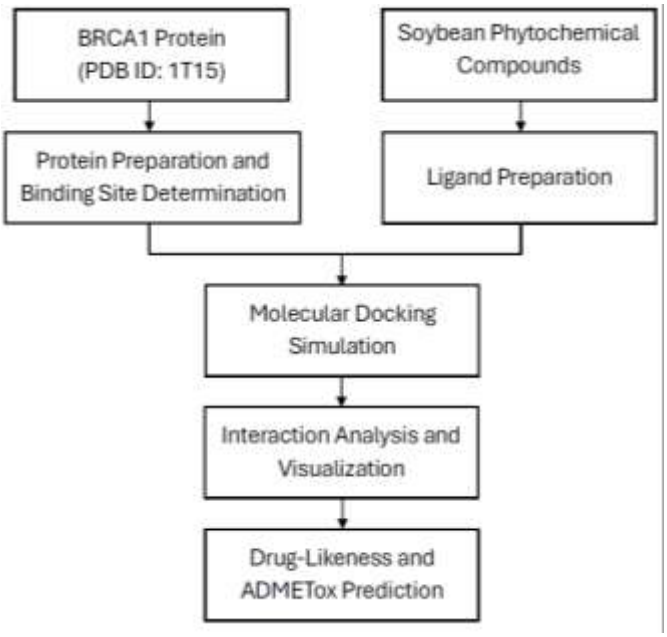


Figure 1. Flowchart of research

2.2. Methods

2.2.1. Protein and Ligand Preparation

The three-dimensional (3D) structure of the BRCA1 protein (PDB ID: 1T15) was obtained from the Protein Data Bank (PDB) [21]. Prior to docking, the protein was processed by removing water molecules, followed by the addition of polar hydrogen atoms, and assignment of Gasteiger charges using AutoDock Tools 1.5.7. The prepared protein structure was subsequently saved in .pdbqt format for molecular docking analysis. Since the selected BRCA1 structure used in this study did not contain a native ligand, tamoxifen was used as a positive control for ligand comparison.

The ligands used in this study consisted of 32 phytochemical compounds identified in soybean (*Glycine max*) extract based on phytochemical screening results reported in previous studies [17]. The three-dimensional structures of the ligands were obtained from the PubChem in .sdf format. For compounds not available in PubChem database, the chemical structures were manually drawn using ChemDraw and converted into 3D conformations. All ligand structures were subjected to energy minimization using the MM2 force field implemented in Chem3D to obtain energetically stable conformations and reduce steric strain. Subsequently, Gasteiger charges were assigned using AutoDock Tools 1.5.7, and the optimized ligands were saved in .pdbqt format for docking analysis.

2.2.2. Binding Site Determination and Docking Validation

The binding site was determined based on previously reported key amino acid residues obtained from literature and Protein Data Bank (PDB) data [21]. These critical amino acid residues are recognized for their significant involvement in ligand interaction and the biological function of BRCA1. To validate the reliability of the docking protocol, a redocking procedure was performed using the positive control ligand, tamoxifen, against the BRCA1 protein. The tamoxifen structure was extracted and separated from the protein complex, then re-docked into the predefined binding site using the same grid box coordinates and dimensions established during the binding site determination step. The accuracy of the docking protocol was evaluated by calculating the root-mean-square deviation (RMSD) between the redocked ligand pose and its reference conformation. An RMSD value of less than 2.0 Å is generally accepted as an indicator of a reliable and valid docking protocol, demonstrating the ability to reproduce the experimentally relevant binding pose. In this study, the obtained RMSD value met this criterion, confirming that the docking setup was appropriate for subsequent molecular docking simulations.

2.2.3. Molecular Docking Simulation

Molecular docking simulation was conducted using AutoDock Tools 1.5.7 to predict the binding affinity and interaction between ligands and the BRCA1 protein. The docking procedure employed the Lamarckian Genetic Algorithm (LGA) with parameters set to 50 runs, a population size of 150, and a maximum number of energy evaluations of 2.5×10^6. The grid box parameters were determined based on validated binding site coordinates. Each ligand was placed into the defined binding site of the BRCA1 protein to obtain binding energy values and potential binding poses. The most favorable docking outcome was identified based on the conformation exhibiting the lowest binding energy.

2.2.4. Interaction Analysis and Visualization

The interaction between the ligands and the BRCA1 protein were examined with Discovery Studio Visualizer. The analysis focused on identifying hydrogen bonds and hydrophobic interactions formed between the ligands and amino acid residues within the binding pocket. The docking outcomes were visualized in both two-dimensional (2D) and three-dimensional (3D) interaction diagrams to evaluate the binding mode and patterns of each ligand [22].

2.2.5. Drug-Likeness and ADMET Prediction

The drug-likeness properties of the ligands were assessed using Lipinski's Rule of Five that includes molecular weight, lipophilicity (LogP), hydrogen bond donors, and hydrogen bond acceptors. In addition, pharmacokinetic characteristics and toxicity profiles were estimated using online platforms, including SwissADME, pkCSM, and ProTox 3.0 [18–20]. These ADMET predictions encompassed several parameters related to absorption, distribution, metabolism, excretion, and toxicity, with particular emphasis on gastrointestinal absorption, blood–brain barrier penetration, cytochrome P450 enzyme inhibition (CYP1A2, CYP2C19, CYP2D6, CYP3A4), total clearance, and toxicity endpoints such as hepatotoxicity and hERG inhibition.

3. Results and Discussion

3.1. Protein and Ligand Preparation

An *in silico* docking approach was employed to evaluate the binding affinity between soybean phytochemicals and the BRCA1 protein. A total of 32 compounds were positioned within the protein's active site. The compounds selected based on the screening done in the previous study [17]. The protein structure used in this research (PDB ID: 1T15) was retrieved from Protein Data Bank (PDB) must fulfill several key requirements to guarantee the reliability and accuracy of molecular docking simulations. One of the primary criteria is the resolution of the protein structure, which should generally be lower than 2.75 Å. Resolution is a critical parameter that reflects the level of detail captured during the experimental determination of the protein structure, typically through X-ray crystallography. A lower resolution value indicates a higher-quality structure with more precise atomic positioning, which is essential for accurate prediction of ligand–protein interactions [23]. In addition to resolution, the selected protein structure is ideally free from mutations. However, in this study, a BRCA1 protein structure containing mutation was intentionally selected to better reflect the biological context of breast cancer. Alterations in the BRCA1 gene are closely related to the development and progression of breast cancer, mainly due to their impact on disrupting DNA repair processes [6]. Therefore, the use of a mutated BRCA1 structure is considered more relevant.

3.2. Binding Site Determination and Docking Validation

The selected BRCA1 structure does not contain a native ligand, as a result docking validation using RMSD-based redocking could not be performed. Therefore, an alternative validation strategy was applied by combining binding site determination based on previously reported key residues and the use of tamoxifen as a positive control ligand. The active site residues obtained from literature and Protein Data Bank (PDB) data [21]. These residues are known to contribute critically to ligand interaction and are linked to the biological function of BRCA1 in DNA repair mechanisms.

The docking simulation was focused on the binding pocket covering these key amino acid residues to ensure that the docking process occurred at the biologically relevant binding site [21]. The active site was defined using a grid box centered at (x, y, z) = (−6.399, 25.185, 37.804) with dimensions of 58 × 62 × 50 Å. Docking validation was performed by redocking tamoxifen into the predefined binding site, yielding an RMSD value of 0.77 Å, which is below the acceptable threshold of 2.0 Å. This result confirms the reliability of the docking protocol in reproducing a biologically relevant binding pose.

3.3. Molecular Docking Analysis

The binding affinity of soybean phytochemicals toward the BRCA1 protein at the defined active site was evaluated through molecular docking simulations. The outcomes were reported as binding energy (kcal/mol), lower or more negative values reflecting higher binding affinity and more stable ligand–protein interactions [24]. The top 10 compounds with the lowest binding energy, along with tamoxifen as a positive control, are presented in Table 1.

Table 1. Binding energy of top-ranked soybean phytochemicals and tamoxifen against BRCA1 protein

Compound	Group	Compound Name	Binding Energy (kcal/mol)
Positive Control	Positive Control	Tamoxifen	-5.24
Ligand 1	Saponin	Curculigo saponin A	-8.07
Ligand 2	Flavonoid	Wogonin 7-O-glucuronide methyl ester	-7.31
Ligand 3	Flavonoid	Prunetin-4'-glucoside	-7.17
Ligand 4	Flavonoid	Acacetin-7-O-(6"-O-acetyl)-β-D-glucopyranoside	-6.64
Ligand 5	Flavonoid	5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside	-6.64
Ligand 6	Flavonoid	Daidzin	-6.62
Ligand 7	Flavonoid	Genistin	-6.57
Ligand 8	Saponin	3α,16α,21α,22α,28-Pentahydroxyolean-12-en-28-O-β-D-xylopyranoside	-6.49
Ligand 9	Saponin	Mubenoside A	-6.32
Ligand 10	Flavonoid	Kaempferol-3-O-rhamnoside	-6.04

The molecular docking results showed that all top-ranked soybean phytochemicals exhibited lower binding energy compared to tamoxifen, indicating their potential to have a stronger binding affinity toward the BRCA1 protein and to form a stable ligand and protein complex with BRCA1. Binding energy is commonly used as an indicator of the thermodynamic stability of ligand–protein interactions, where more negative values reflect stronger affinity and more favorable binding conformations [25-26]. This stability is governed by a combination of intermolecular forces, including hydrogen bonding, hydrophobic interactions, van der Waals forces, and electrostatic interactions within the binding pocket [27-28].

The relatively low binding energy observed in several compounds may be attributed to their structural characteristics. Flavonoid compounds contain multiple hydroxyl groups that enhance the hydrogen bond formation with polar amino acid residues, thereby increasing binding affinity [23]. In addition, the presence of aromatic rings contributed to hydrophobic interactions which are important to stabilizing ligand orientation within the BRCA1 binding site.

Among the tested compounds, Curculigo saponin A, Wogonin 7-O-glucuronide methyl ester, and Prunetin-4'-glucoside demonstrated the lowest binding energy, indicating that they may be considered as potential lead compounds for further investigation. Given the essential role of BRCA1 in DNA repair and genomic stability, strong interactions at the active site may influence its biological function and support the potential chemopreventive role of these compounds [21].

3.4. Interaction Analysis and Visualization

Interaction analysis was performed to assess the binding interaction of the highest-ranked soybean phytochemicals within the BRCA1 active site. This evaluation focused on identifying the types of interactions formed between ligands and amino acid residues, such as hydrogen bonding and hydrophobic contacts. The detailed results of interaction profile analyses are presented in Table 2.

Table 2. Interaction profiles of top-ranked soybean phytochemicals and tamoxifen with key amino acid residues at the BRCA1 binding site

Amino Acid	Binding Site	Positive Control	Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5	Ligand 6	Ligand 7	Ligand 8	Ligand 9	Ligand 10
Phe1622					HP							
Val1654				H (2.82Å)							H (2.64Å)	H (3.05Å)
Leu1679												H (2.63Å)
Pro1659								H (1.97Å)			H (2.70Å)	
Thr1733			H (2.30Å)							H (2.18Å)		
Arg1835			H (2.65Å)									
Thr1700				H (2.86Å)	H (2.21Å)	H (3.09Å)	H (2.62Å & 2.84Å)	H (2.21Å)	H (2.05Å)			
Phe1704	HP											
Met1775	HP	HP					HP			HP	HP	
Leu1839	HP	HP					HP					
Glu1836	H											
Asp1840	H											
Arg1699	H				H (2.06Å & 2.15Å)	HP, H (2.17Å & 1.85Å)	H (2.51Å)	H (2.86Å)	H (2.11Å)		HP, H (2.42Å)	
Glu1698	H	HP, H (2.06Å; 2.35Å; 3.03Å; 1.97Å)									H (2.60Å)	
Lys1702	H			HP, H (2.46Å; 2.60Å; 2.31Å; 2.41Å)	HP	H (2.85Å & 2.04Å)	HP, H (2.56Å)	HP, H (2.60Å)		H (2.37Å)	H (2.44Å; 2.31Å; 1.98Å)	HP, H (2.42Å; 1.75Å; 2.20Å; 2.21Å)
Leu1701	H			H (2.13Å)	H (2.05Å)	HP	H (1.91Å)	H (1.90Å)		HP	HP	H (2.61Å)
Asn1774	H				H (2.46Å & 2.99Å)	H (2.01Å)	H (2.77Å)	H (1.87Å; 3.08Å; 2.59Å)	H (1.66Å; 2.34Å; 2.99Å)	H (2.90Å & 3.09Å)		H (2.30Å)
Ile1680	H											
Gln1779	H											
Ser1655	H			H (2.69 & 2.43)	H (2.01Å)	H (2.70Å)		H (2.62Å)				
Leu1657	H		H (2.56Å & 3.04Å)	H (2.29)			H (1.66Å & 1.85Å)		H (2.20Å)		H (1.58Å & 2.74Å)	
Gly1656	H				H (1.93Å)		H (2.35Å)	H (1.90Å)				
Phe1704	H						HP			HP		

Amino Acid	Binding Site	Positive Control	Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5	Ligand 6	Ligand 7	Ligand 8	Ligand 9	Ligand 10
Val1741						HP						
Total Interaction	16	7	4	11	10	10	13	11	6	7	12	9

HP = Hydrophobic Bond
H = Hydrogen Bond

The results showed that several key residues, such as Met1775, Leu1839, Lys1702, Leu1701, Asn1744, and Leu1675 were consistently involved in ligand binding. These residues are known to have a significant role in the BRCA1 binding site [21]. This finding indicates that the docking simulations were successfully performed in a biologically relevant region. The consistent involvement of these residues across multiple ligands further supports the reliability of the docking protocol.

Hydrogen bonds and hydrophobic interactions were identified as the dominant types of interactions. Hydrogen bonds were frequently observed with polar residues such as Glu1836, Asp1840, Arg1699, Lys1702, and Ser1655, contributing to binding specificity and stability. These interactions occur when hydrogen atoms covalently bound to electronegative donor atoms interact with electronegative acceptors, forming highly directional non-covalent interactions that are essential for accurate molecular recognition. In protein–ligand systems, hydrogen bonding plays a crucial role in stabilizing binding conformations and ensuring selective interaction with key amino acid residues [26],[28]. Meanwhile, hydrophobic interactions with residues such as Met1775, Leu1839, Leu1701, and Phe1704 were also commonly observed. These interactions contribute to the stabilization of ligand orientation within the hydrophobic regions of the binding pocket by minimizing unfavorable interactions with the aqueous environment. Hydrophobic contacts are particularly important in maintaining the structural integrity of the ligand–protein complex, as they promote tighter packing and reduce conformational flexibility [28].

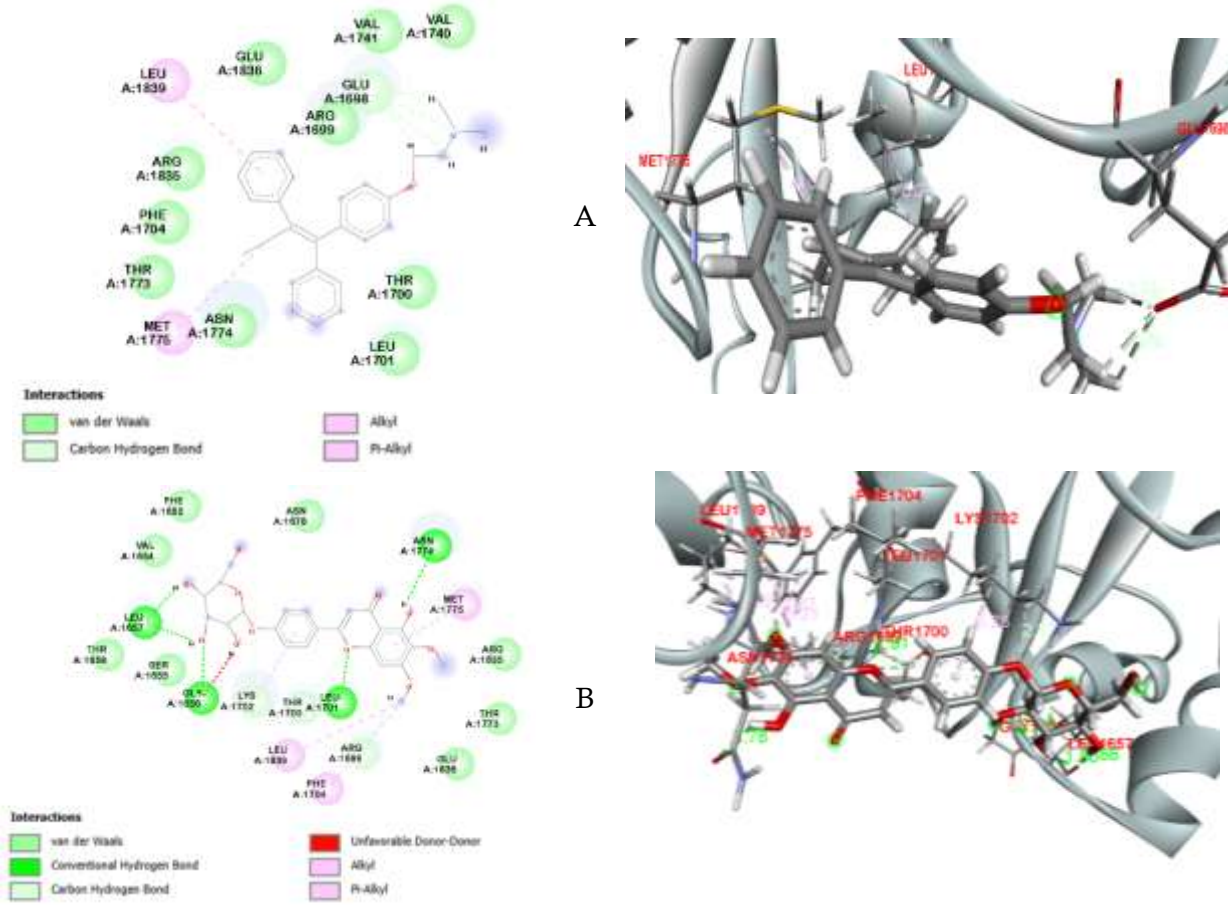
From a structure–activity relationship (SAR) perspective, the observed interaction patterns can be explained by the molecular features of the compounds. The presence of multiple hydroxyl (–OH) groups in flavonoid structures facilitates hydrogen bond formation with polar amino acid residues, thereby increasing binding affinity. Meanwhile, aromatic rings and non-polar moieties promote hydrophobic interactions, which are crucial for maintaining ligand stability within the binding pocket [29]. These combined interactions contribute to the lower binding energy observed in several compounds. The hydrogen bond distances observed in this study were generally within the range of 1.6–3.1 Å, indicating moderate to strong interactions. Shorter bond distances (<2.5 Å) were associated with stronger interactions and contributed significantly to the stability of the ligand–protein complex. Overall, the interaction analysis demonstrates that the selected soybean phytochemicals can form stable and specific interactions with key residues in the BRCA1 binding site [30-31].

The interaction profiles of the selected phytochemicals also showed similarities with the positive control, particularly in terms of shared key residues such as Met1775 and Leu1839, suggesting that these compounds occupy the same binding region. Notably, several phytochemicals formed additional interactions with surrounding residues, which may explain their lower binding energy observed in docking simulations.

Among the evaluated compounds, 5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside, Mubenoside A, and Daidzin exhibited the highest number of total interactions, with 13, 12, and 11 interactions with BRCA1 protein. However, the total number of interactions alone does not necessarily reflect the relevance or effectiveness of ligand binding. A more critical factor is whether these interactions occur within the biologically relevant key amino acid residues contributing to an essential function in the BRCA1 binding site which used for ligand recognition and stabilization [21]. When considering binding site relevance, 5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside

showed the highest number of interactions with key residues (11 interactions), followed by Mubenoside A (10 interactions), and both Daidzin and Wogonin 7-O-glucuronide methyl ester (9 interactions). This indicates that interaction relevance within the binding site is more critical than the total number of contacts in determining biological significance.

Therefore, for a more focused visualization purposes, those four representative compounds were selected based on an integrated consideration of binding affinity and interaction relevance within the BRCA1 active site. The 2D and 3D interaction diagrams are illustrated in Figures 2.



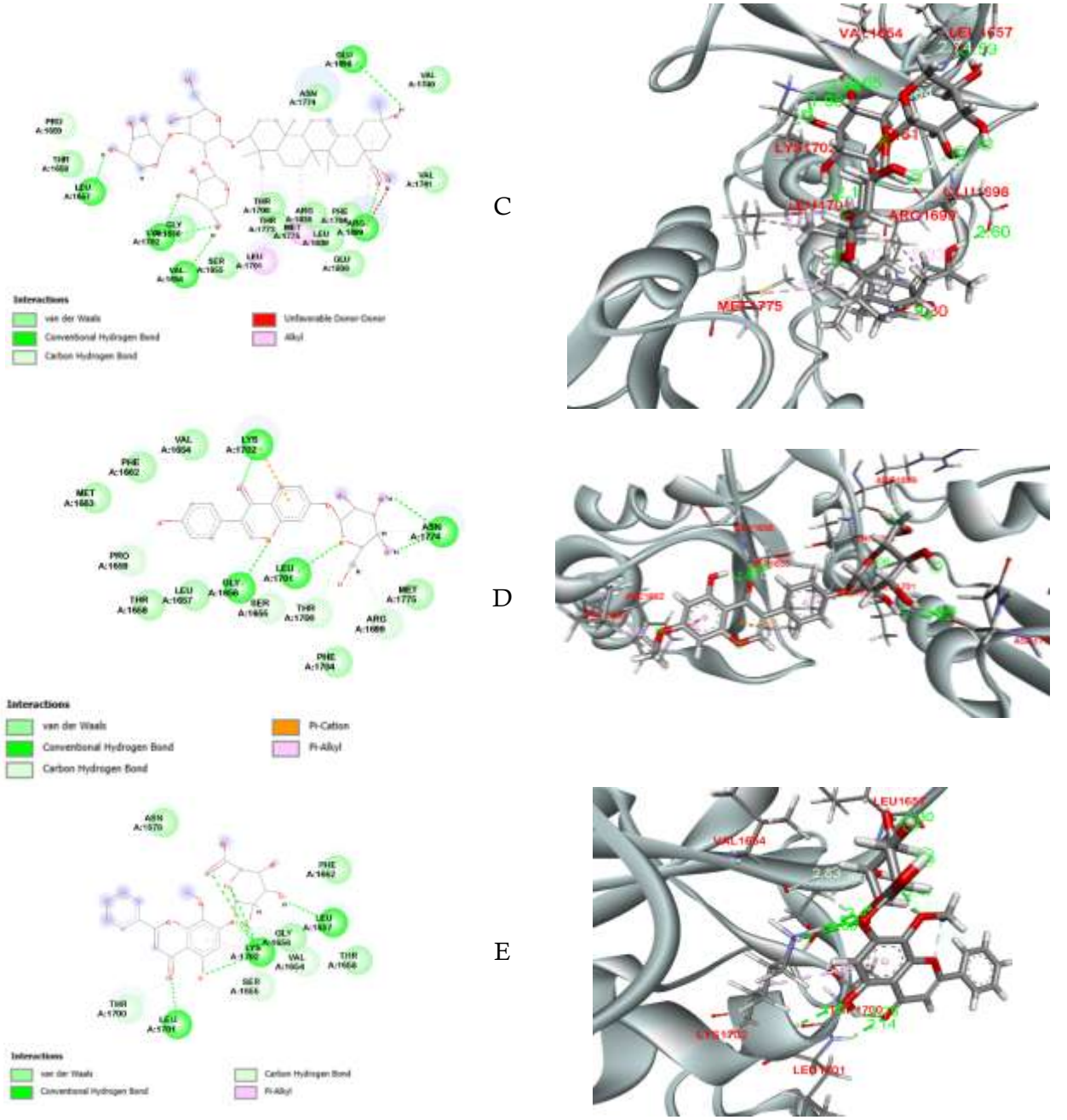


Figure 2. 2D and 3D Visualization for A) Positive Control; B) Ligand 5 (5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside); C) Ligand 9 (Mubenoside A); D) Ligand 6 (Daidzin); E) Ligand 2 (Wogonin7-O-glucuronide methyl ester)

The visualization results of the four selected ligands indicate that all compounds bind within the BRCA1 active site at positions consistent with key amino acid residues reported in the Protein Data Bank, particularly Lys1702, Leu1701, and Leu1657. These residues are known to play an important role in ligand recognition and stabilization within the binding pocket.

In addition to interactions with these key residues, each ligand also forms additional contacts within the binding site, further strengthening the overall ligand–protein interaction. These interactions include both hydrogen bonds and hydrophobic contacts. Hydrogen bonding, primarily involving polar

residues such as Lys1702, contributes to binding specificity and directional stability of the ligand within the active site. This type of interaction plays a crucial role in maintaining the correct orientation of the ligand, which is essential for effective binding.

Meanwhile, hydrophobic interactions with non-polar residues such as Leu1701 and Leu1657 enhance the stability of the ligand within the hydrophobic core of the binding pocket. These interactions reduce the exposure of non-polar regions to the aqueous environment, thereby increasing the overall thermodynamic stability of the ligand–protein complex. Collectively, the combination of hydrogen bonding and hydrophobic interactions supports the formation of stable and specific ligand–protein complexes, which may contribute to the favorable binding affinity observed in the docking results.

3.5. Drug-likeness and ADMET Analysis

Although 5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside demonstrated the highest level of interaction within the binding site, its relatively large molecular structure and potential limitations in pharmacokinetic properties should be taken into consideration. Mubenoside A also exhibited strong interaction patterns. However, the multiple violations of Lipinski's Rule of Five may reduce its suitability as a drug candidate.Further assessment of the selected soybean phytochemicals was carried out to characterize their pharmacokinetic profiles and potential safety concerns using drug-likeness and ADMET analyses. A concise synthesis of the observed results is provided in Table 3.

Table 3. Drug-likeness and ADMET profiles of top-ranked soybean phytochemical compounds based on *in silico* prediction

Parameters		Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5	Ligand 6	Ligand 7	Ligand 8	Ligand 9	Ligand 10
Drug-likeness											
MW (g/mol)		636.89	460.39	446.4	488.44	476.43	416.38	432.38	622.83	885.04	432.38
Hydrogen Bond Acceptor		9	11	10	11	11	9	10	9	17	10
Hydrogen Bond Donor		6	5	5	4	5	5	6	7	10	6
LogP		3.21	0.49	0.79	1.31	0.96	0.63	0.42	2.6	0.53	0.6
Pharmacokinetics and Toxicities (ADMET)											
Absorption	**GI Abs**	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
	Water solubility (log mol/L)	-4.118	-2.924	-3.079	-4.292	-3.024	-2.784	-2.759	-3.532	-2.993	-2.969
Distribution	**VDss (log L/kg)**	-1.216	-0.061	-0.376	-0.419	-0.289	-0.166	0.274	0.044	-0.685	1.15
	Fraction unbound	0.198	0.231	0.138	0.072	0.163	0.19	0.211	0.277	0.486	0.087
	BBB permeability	-1.074	-1.443	-1.48	-1.924	-1.689	-1.232	-1.417	-1.081	-1.904	-1.265
Metabolism	**CYP1A2 inhibitor**	No	No	No	No	No	No	No	No	No	No
	CYP2C19 inhibitor	No	No	No	No	No	No	No	No	No	No
	CYP2D6 inhibitor	No	No	No	No	No	No	No	No	No	No
	CYP3A4 inhibitor	No	No	Yes	Yes	Yes	No	No	No	Yes	No
Excretion	**Total clearance (log ml/min/kg)**	0.334	0.128	0.205	0.914	0.554	0.104	0.096	0.09	0.054	0.431

Parameters		Ligand 1	Ligand 2	Ligand 3	Ligand 4	Ligand 5	Ligand 6	Ligand 7	Ligand 8	Ligand 9	Ligand 10
	Renal OCT2 substrate	No	No	No	No	No	No	No	No	No	No
Toxicities	**Hepatotoxicity**	No	No	No	No	No	No	No	No	No	No
	hERG I inhibitor	No	No	No	No	No	No	No	No	No	No
	hERG II inhibitor	No	No	No	Yes	Yes	Yes	No	Yes	No	Yes

Evaluation of the compounds' drug-like properties according to Lipinski's Rule of Five revealed that most of the selected soybean phytochemicals exhibited acceptable physicochemical properties. However, three compounds, namely ligand 1 (Curculigo saponin A), ligand 8 (3α,16α,21α,22α,28-Pentahydroxyolean-12-en-28-O-β-D-xylopyranoside), and ligand 9 (Mubenoside A), showed violations of Lipinski's criteria.

Ligand 1 and ligand 8 violated the molecular weight criterion (>500 g/mol), while ligand 9 exhibited multiple violations, including molecular weight, logP, hydrogen bond acceptors and donors. These findings are critical because molecular size and polarity strongly influence membrane permeability. Compounds with high molecular weight generally exhibit reduced passive diffusion across biological membranes, thereby limiting oral absorption and bioavailability. In addition, a high number of hydroxyl (–OH) groups, commonly found in flavonoid glycosides and saponins, increases hydrogen bonding capacity. While this enhances binding interactions at the target site, it simultaneously increases molecular polarity and reduces lipophilicity, which may hinder membrane permeability [32].

The observed violations in these compounds can be attributed to their structural characteristics as natural products. Compounds such as saponins and triterpenoids typically possess large and complex molecular structures with multiple hydroxyl groups and glycosidic moieties. These structural features contribute to increased molecular weight and a higher number of hydrogen bond donors and acceptors, which often lead to deviations from Lipinski's criteria. In contrast, ligand 3 (Prunetin-4'-glucoside) and ligand 6 (Daidzin) demonstrated the most favorable drug-likeness profiles, as they did not exhibit any violations of Lipinski's Rule of Five These findings suggest that these compounds exhibit more favorable and well-balanced physicochemical properties, which may support better oral bioavailability and membrane permeability compared to other compounds in this study.

Overall, while several compounds showed strong binding affinity toward the BRCA1 protein, their drug-likeness profiles indicate that not all of them are equally suitable as oral drug candidates. Compounds with no or fewer Lipinski violations, such as Prunetin-4'-glucoside and Daidzin, may represent more promising candidates for further development, particularly when considering both binding affinity and pharmacokinetic properties.

The pharmacokinetic properties of the selected compounds were further evaluated using ADMET prediction tools. The absorption analysis revealed that all evaluated compounds were estimated to have low gastrointestinal (GI) absorption. This may be attributed to their relatively high molecular weight and polar nature, which can limit passive diffusion across intestinal membranes. In addition, variations in water solubility were observed, suggesting differences in dissolution and absorption potential among the compounds. Similar findings have been reported in natural product-based compounds, where high polarity and molecular size were associated with low gastrointestinal absorption [33].

In terms of distribution, most compounds demonstrated low blood–brain barrier (BBB) permeability, indicating a low likelihood of central nervous system penetration. This property may be advantageous in reducing potential central nervous system-related side effects. The fraction unbound

values suggest that a moderate proportion of the compounds remains free in plasma and is available for interaction with target proteins [34].

The metabolism prediction indicated that most compounds were not predicted to inhibit cytochrome P450 enzymes (CYP1A2, CYP2C19, and CYP2D6), indicating a minimal potential of metabolism-related drug–drug interactions. However, several compounds such as Prunetin-4'-glucoside, Acacetin-7-O-(6"-O-acetyl)-β-D-glucopyranoside, 5-Hydroxy-6,7-dimethoxyflavone-4'-O-β-D-glucoside, and Mubenoside A predicted to inhibit CYP3A4, which is an important enzyme involved in drug metabolism. This may affect metabolic stability and should be considered in further studies.

The total clearance values varied among the compounds, indicating differences in elimination rates. Compounds with higher clearance values are expected to be eliminated more rapidly, which may influence their duration of action. On the other hand, no compounds showed substrate activity toward renal OCT2, indicating limited involvement of this transporter in their excretion.

Toxicity prediction showed that most compounds were non-hepatotoxic and did not inhibit hERG I, indicating a low risk of hepatotoxicity and cardiotoxicity. However, several compounds were predicted to inhibit hERG II, which may be associated with potential cardiac risks and needs further investigation.

Overall, although several compounds demonstrated strong binding affinity and favorable interaction profiles, their pharmacokinetic limitations highlight the importance of integrating docking results with drug-likeness and ADMET properties. Therefore, a comprehensive evaluation combining these parameters is required to identify the most promising lead compound.

3.6. Integrated Analysis and Lead Selection

To identify the most promising candidate, an integrated analysis combining molecular docking results, interaction profiles, structure–activity relationship (SAR), drug-likeness, and ADMET properties was performed. Although several compounds, such as Curculigo saponin A and Wogonin 7-O-glucuronide methyl ester, exhibited lower binding energy in docking simulations, these compounds were not considered optimal candidates due to limitations in their pharmacokinetic profiles and physicochemical properties. In particular, larger molecules with high molecular weight and excessive hydrogen bond donors or acceptors tend to exhibit reduced membrane permeability and poor oral bioavailability, which may limit their therapeutic potential.

From an SAR perspective, the presence of hydroxyl (–OH) groups in flavonoid glycosides played a critical role in enhancing binding affinity through hydrogen bond formation with key residues such as Lys1702 and Asn1744. However, excessive polarity associated with multiple hydroxyl groups and glycosidic moieties can negatively affect lipophilicity (LogP) and membrane permeability. This highlights the importance of achieving a balance between polarity and hydrophobicity to optimize both binding interaction and pharmacokinetic behavior.

Among the evaluated compounds, Daidzin demonstrated a well-balanced profile across all evaluated parameters. Although its binding energy was not the lowest, Daidzin consistently interacted with key amino acid residues within the BRCA1 binding site, indicating biologically relevant binding. In addition, Daidzin showed no violations of Lipinski's Rule of Five, suggesting favorable molecular weight, hydrogen bonding capacity, and lipophilicity. Its moderate polarity and acceptable LogP value support better membrane permeability compared to larger and more complex compounds such as saponins.

Furthermore, ADMET analysis revealed that Daidzin exhibited a relatively favorable pharmacokinetic profile, including acceptable absorption characteristics, low blood–brain barrier permeability (reducing potential central nervous system side effects), minimal predicted inhibition of major cytochrome P450 enzymes, and low toxicity risk. In contrast, several other high-affinity

compounds showed potential issues such as CYP3A4 inhibition or poor drug-likeness, which may limit their development.

Taken together, these findings indicate that Daidzin represents the most promising lead compound due to its balanced performance in binding affinity, interaction specificity, physicochemical properties, and pharmacokinetic profile. Rather than selecting compounds solely based on docking scores, this integrated approach highlights that optimal candidates for further development should exhibit a combination of adequate target binding and favorable drug-like characteristics.

Isoflavone such as daidzin have been previously reported to exhibit anticancer and chemopreventive activities, particularly in hormone-related cancers such as breast cancer. Isoflavones such as daidzin have been reported to exhibit anticancer activity in breast cancer through modulation of key oncogenic pathways, including PI3K/Akt signaling, and suppression of oncogenes such as KRAS, CCND1, and MDM2. Computational studies have also demonstrated its ability to form stable interactions with cancer-related proteins [35]. In the present study, the binding of daidzin to key residues within the BRCA1 active site suggests a potential additional mechanism involving modulation of DNA repair pathways, supporting its chemopreventive potential.

4. Conclusion

This study demonstrated that several soybean phytochemicals exhibit strong binding affinity toward the BRCA1 protein, with interaction patterns occurring at biologically relevant binding sites and involving key amino acid residues. The analyzed compounds showed stronger binding affinity, as indicated by lower binding energy values, when compared to tamoxifen, a standard chemopreventive agent for breast cancer. This indicating stronger binding affinity and potentially more stable ligand-protein interaction compared to tamoxifen. Although some compounds showed a higher number of interactions, their drug-likeness profiles were limited by Lipinski's rule violations.

Among the evaluated compounds, daidzin exhibited the most optimal overall profile, characterized by strong binding affinity, relevant interactions with essentials amino acid residues, and favorable drug-likeness without any violations. This compound may serve as promising candidates for chemopreventive strategies targeting BRCA1, although further experimental validation is required.

References

[1] Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R. L., Soerjomataram, I., & Jemal, A. (2024). Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*, *74*(3), 229-263.

[2] Ferlay J, Ervik M, Lam F, Laversanne. (2025). Global Cancer Observatory: Cancer Today (Indonesia) [Internet]. Global Cancer Observatory: Cancer Today. Lyon, France: International Agency for Research on Cancer.;[cited 2025 Feb 14]. Available from: https://gco.iarc.who.int/today

[3] Nindrea, R. D., Aryandono, T., & Lazuardi, L. (2017). Breast cancer risk from modifiable and non-modifiable risk factors among women in Southeast Asia: a meta-analysis. *Asian Pacific journal of cancer prevention: APJCP*, *18*(12), 3201.

[4] Koya AI, Ibrahim SA. Carcinogenesis. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 [cited 2025 Sep 30]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK604463/ PubMed PMID: 38917272.

[5] Manna, E. D. F., Serrano, D., Aurilio, G., Bonanni, B., & Lazzeroni, M. (2023). Chemoprevention and lifestyle modifications for risk reduction in sporadic and hereditary breast cancer. In *Healthcare* (Vol. 11, No. 16, p. 2360). MDPI.

[6] Arun, B., Couch, F. J., Abraham, J., Tung, N., & Fasching, P. A. (2024). BRCA-mutated breast cancer: the unmet need, challenges and therapeutic benefits of genetic testing. *British journal of cancer*, *131*(9), 1400-1414.

[7] Zattarin, E., Taglialatela, I., Lobefaro, R., Leporati, R., Fuca, G., Ligorio, F., ... & Vernieri, C. (2023). Breast cancers arising in subjects with germline BRCA1 or BRCA2 mutations: Different biological and clinical entities with potentially diverse therapeutic opportunities. *Critical Reviews in Oncology/Hematology*, *190*, 104109.

[8] Swetha, M., Keerthana, C. K., Rayginia, T. P., & Anto, R. J. (2022). Cancer chemoprevention: A strategic approach using phytochemicals. *Frontiers in pharmacology*, *12*, 809308.

[9] Ren, J., Yan, G., Yang, L., Kong, L., Guan, Y., Sun, H., ... & Wang, X. (2025). Cancer chemoprevention: signaling pathways and strategic approaches. *Signal Transduction and Targeted Therapy*, *10*(1), 113.

[10] Kusmardi, K., Wiyarta, E., Rusdi, N. K., Maulana, A. M., Estuningtyas, A., & Sunaryo, H. (2021). The potential of lunasin extract for the prevention of breast cancer progression by upregulating E-Cadherin and inhibiting ICAM-1. *F1000Research*, *10*, 902.

[11] Swallah, M. S., Yang, X., Li, J., Korese, J. K., Wang, S., Fan, H., ... & Huang, Q. (2023). The pros and cons of soybean bioactive compounds: An overview. *Food Reviews International*, *39*(8), 5104-5131.

[12] Kang, J. H., Dong, Z., & Shin, S. H. (2023). Benefits of soybean in the era of precision medicine: a review of clinical evidence. *Journal of Microbiology and Biotechnology*, *33*(12), 1552.

[13] Maulana, A. M., Kusmardi, K., Purwaningsih, E. H., Hestiantoro, A., & Mahmud, T. (2024). Inhibitory Mechanisms of Soybean Extract on the Development of Breast Cancer Through Modulation of Cellular Immune Response.

[14] Evita, L., Kusmardi, K., & Rusdi, N. K. (2025). Soybean Extract Rich in Lunasin Enhances p21 Expression in DMBA-Induced Breast Cancer Rat: A Potential Adjuvant Therapy: unasin enhances p21 in breast cancer. *Archives of Breast Cancer*, *12*(2), 203-210.

[15] Kumar, V., & Chauhan, S. S. (2021). Daidzein induces intrinsic pathway of apoptosis along with ER α/β ratio alteration and ROS production. *Asian Pacific journal of cancer prevention: APJCP*, *22*(2), 603.

[16] Alshehri, M. M., Sharifi-Rad, J., Herrera-Bravo, J., Jara, E. L., Salazar, L. A., Kregiel, D., ... & Cho, W. C. (2021). Therapeutic potential of isoflavones with an emphasis on daidzein. *Oxidative medicine and cellular longevity*, *2021*(1), 6331630.

[17] Maulana AMuh. Ekstrak Kedelai Menghambat Patogenesis Kanker Payudara Tikus yang Diinduksi DMBA: Kajian Klinis, Respons Imun, Histopatologik, Ekspresi Protein Ki-67, dan VEGF [Dissertation]. [Jakarta]: Universitas Indonesia.

[18] Daina, A., Michielin, O., & Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Scientific reports*, *7*(1), 42717.

[19] Pires, D. E., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of medicinal chemistry*, *58*(9), 4066-4072.

[20] Banerjee, P., Kemmler, E., Dunkel, M., & Preissner, R. (2024). ProTox 3.0: a webserver for the prediction of toxicity of chemicals. *Nucleic acids research*, *52*(W1), W513-W520.

[21] Clapperton, J. A., Manke, I. A., Lowery, D. M., Ho, T., Haire, L. F., Yaffe, M. B., & Smerdon, S. J. (2004). Structure and mechanism of BRCA1 BRCT domain recognition of phosphorylated BACH1 with implications for cancer. *Nature structural & molecular biology*, *11*(6), 512-518.

[22] Arsianti, A., Akbar, M. K., & Erlina, L. (2025). Arctigenin and biochanin A impact on MDA-MB-231 breast cancer cells: In silico and in vitro analysis. *Journal of Pharmacy & Pharmacognosy Research*, *13*(2), 606-620.
[23] de Azevedo Jr, W. F. (Ed.). (2019). *Docking screens for drug discovery*. New York: Humana Press.
[24] Puspita Sari M, Inggrarsih R, Hidayat R, Maritska Z, Triwani. (2024).Molecular Docking On Bioactive Compounds Of Genistein, Quercetin And Resveratrol To Brca1, Erα, And Egfr Receptors In Breast Cancer. Vol. 5.Sep;5(3):7695–703.
[25] García-Ortegón, M., Simm, G. N., Tripp, A. J., Hernández-Lobato, J. M., Bender, A., & Bacallado, S. (2022). DOCKSTRING: easy molecular docking yields better benchmarks for ligand design. *Journal of chemical information and modeling*, *62*(15), 3486-3502.
[26] Rahma, R., & Estuningtyas, A. (2024). Molecular Docking of Active Compounds from The Ethanol Extract of Phaleria macrocarpa Fruit with Iron Transporters DMT1 and ZIP14. *EKSAKTA: Berkala Ilmiah Bidang MIPA*, *25*(02), 231-246.
[27] Jin, J., Chen, B., Zhan, X., Zhou, Z., Liu, H., & Dong, Y. (2021). Network pharmacology and molecular docking study on the mechanism of colorectal cancer treatment using Xiao-Chai-Hu-Tang. *PLoS One*, *16*(6), e0252508.
[28] Fariska, A. B., Erlina, L., Arsianti, A., & Tedjo, A. (2025). In silico evaluation of natural compounds as dual inhibitors of exotoxin A and LasB (elastase) virulence proteins in Pseudomonas aeruginosa. *Eksakta: Berkala Ilmiah Bidang MIPA*, *26*(04), 480-499.
[29] Millan-Casarrubias, E. J., García-Tejeda, Y. V., González-De la Rosa, C. H., Ruiz-Mazón, L., Hernández-Rodríguez, Y. M., & Cigarroa-Mayorga, O. E. (2025). Molecular Docking and pharmacological in silico evaluation of camptothecin and related ligands as promising HER2-targeted therapies for breast cancer. *Current issues in molecular biology*, *47*(3), 193.
[30] Putri, T. Z. A. D., Findrayani, R. P., Isrul, M., & Lolok, N. (2024). Studi Molecular Docking Senyawa Kimia dari Herba Putri Malu (Mimosa pudica) Terhadap Inhibisi Enzim A-Glukosidase Sebagai Antidiabetes Melitus. *Jurnal Pharmacia Mandala Waluya*, *3*(4), 225-233.
[31] Abdulkadir, W. S., Puana, F., Taupik, M., Tungadi, R., Hutuba, A. H., Djuwarno, E. N., ... & Hiola, F. (2024). In Silico Analysis of Isoflavone Compounds in Soybean (Glycine max L) as Anti-Breast Cancer Agents Targeting Estrogen Receptor Alpha. *Tropical Journal of Phytochemistry and Pharmaceutical Sciences*, *3*(7), 375-379.
[32] Jayaraman, S., Veeraraghavan, V., Sreekandan, R. N., Mohan, S. K., Suga, S. S. D., Kamaraj, D., ... & Koora, S. (2020). Molecular docking analysis of the BRCA1 protein with compounds from Justica adhatoda L. *Bioinformation*, *16*(11), 888.
[33] Nasim, N., Sandeep, I. S., & Mohanty, S. (2022). Plant-derived natural products for drug discovery: current approaches and prospects. *The Nucleus*, *65*(3), 399-411.
[34] Shakil, M. A. K., Khaliphaa, A. B. R., Rakhib, S. A., Ahmeda, S., Siddiquea, A. B., & Akter, T. (2023). In-silico drug design of some bioactive compounds against BRCA1 for treatment of cancer.
[35] Uddin, M. N., Wang, J., Bhuiyan, M. H. R., Rashid, M. M., Al Mamun, M. Z. U., Syed, A., & Roney, M. (2025). Exploring the anti-cancer potential of daidzin in breast cancer: Integrated bioinformatics and computational insights on oncogene inhibition. *Computational Biology and Chemistry*, *119*, 108590.