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In Silico Drug Design of *Sembukan* (*Paederia scandens*) As Anti-Breast Cancer Agents

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Abstract: Cancer is a disease of excessive cell growth and is one of the cases of disease that has increased every year. cancer treatment therapy in the form of chemotherapy drugs has various side effects so that safer long-term treatment is needed, namely using herbal medicines such as *sembukan* plants (*Paederia scandens*). This research was conducted using experimental methods computationally through *in silico* methods as a potential prediction test as a reference for further studies. isolate compounds are carried out molecular tethering against progesterone, estrogen, HER2, and NF-κB receptors using PyRx 0.8 software. Then the isolated compounds were tested for the feasibility of chemical and pharmacokinetic properties and toxicity using the Lipinski Rules of Five data base and ADMETLab 3.0. Furthermore, visualization was carried out to see the bonding interaction between ligand and receptor protein using Biovia Discovery Studio 2024 software. Based on the results of molecular tethering compounds kaempferol 3-rutinoside-7-glucoside, cosmetin, quercetin 3-o-rutinoside-7-o-glucoside, daidzein and linarin have the potential as inhibitors respectively against progesterone, HER2, Nf-kB, estrogen and overall average receptors with each binding affinity value of -9. 6 kcal/mol, -9.8 kcal/mol, -9.8 kcal/mol, -10.8 kcal/mol, -8.9 kcal/mol and -9.0 kcal/mol respectively. The best physicochemical properties were obtained for daidzein and linarin compounds. Visualization data generated that Kaempferol 3-rutinoside-7-glucoside, Cosmetin, Quercetin 3-o-rutinoside-7-o-glucoside, daidzein and linarin compounds have similar interactions and amino acid residues with control drugs so that they are predicted to have similar pharmacological effects as breast anticancer.

Keywords: *in silico*, *Paederia scandens*, breast cancer

INTRODUCTION

Cancer is a disease caused by excessive and uncontrolled cell growth. Death cases in Indonesia due to cancer rank second to death cases from other diseases. The number of cancer cases in Indonesia in 2020 reached 396,914 cases with death data of 234,511 patients (Ferlay et al., 2021). Cancer cells can spread and cause cancer in other organs. Based on the place or organ affected, cancer is categorized into lung, rectal, cervical, blood, liver, mouth, stomach, eye and breast cancer.

Breast cancer cases rank first in women and third in men and women compared to other cancers based on Globocan data in 2022 (Bray et al., 2024). The data stated that the number of cases reached 68,858 (16.6%) of the total cancer cases in Indonesia with more than 22 thousand deaths (Ferlay et al., 2021). This disease is classified based on the type of receptor on cancer cells, namely Human Epidermal Growth Factor Receptor 2 (HER2) which is an activator of the cell division phase and hormonal receptors which include Estrogen Receptor (ER) and Progesterone Receptor (PR) which function as cell transcription factors (Putri & Noverial, 2023).

Synthesized drugs such as tamoxifen and trastuzumab are used to treat breast cancer but have significant side effects. Therefore, research for safer and more effective treatments, including herbal remedies, is needed. *Daun Sembukan* (Paederia scandens L.) is a plant used as medicine in several countries and has anticancer activity. Research shows that PS can induce cancer cell apoptosis and has cytotoxic activity on various cancer cell lines.
This study uses an *in silico* assay to predict the breast anticancer activity of PS compounds, as a first step before conducting in vitro or in vivo tests to minimize the risk of test weaknesses. The method used is molecular tethering with PyRx 0.8 software, which combines several functions for more valid analysis.

METHODS

The type of research to be carried out is a computational experimental study of *Sembukan* plant isolate compounds (Paederia scandens) against ER receptor (6VPF), HER2 (3PP0), progesterone receptor (1SQN) and Nf-kB (4KIK) breast cancer cells.

Receptor Protein Selection and Preparation

HER2, PR, ER and Nf-kB receptor proteins were searched for PDB IDs suitable for breast cancer through the Therapeutic Target Drug (TTD) website. Then a selection was made on the PDB ID to choose the best one. PDB IDs were selected including resolution, protein structure, and metric values through the RCSB PDB website. The smallest resolution of a maximum of 2 Å was selected, the protein structure did not have residues in the form of dotted lines, and the metric value tended towards blue. Next, a selection was made using the Ramachandran plot on the PDBsum website. Then identified by meeting the parameters of most favoured regions value > 90% and G-factor average > -0.05. The PDB ID with the best consideration value is then downloaded through the RCSB PDB website with the PDB file format. Binding site search was then conducted. The search process uses Biovia Discovery Studio 2024 to determine the grid box for molecular tethering. Then the preparation was carried out by removing water molecules, original ligands, and adding hydrogen atoms using Biovia Discovery Studio 2024 software.

Ligand Preparation

The ligands used consisted of 80 isolates of PS compounds obtained from the literature review study of Dutta et al (2023), comparator drugs namely trastuzumab and lapatinib (HER2 receptor), megestrol and tamoxifen (PR receptor), doxorubicin and paclitaxel (Nf-kB receptor), tamoxifen and toremifen (ER receptor) and native ligands for each ER, PR, HER2, and Nf-kB receptors. All ligand chemical structures were downloaded via the Pubchem website. If compounds were not found on the Pubchem search engine they were drawn manually using MarvinJS Chemaxon web.

Molecular docking

HER2

Opened PyRx software and entered the HER2 receptor protein (PDB ID: 3PP0). then entered the test ligand in the form of 80 Paederia scandens compounds, the original ligand, the drug trastuzumab and lapatinib in open babel. Then set the grid box 17.0, 16.5, and 26.6 for the X, Y and Z axes. Then click forward. The tethering process is ongoing until the indicator is 100% and the Binding affinity and Root Mean Square Deviation (RMSD) values are obtained.

PR

Opened PyRx software and entered the PR receptor protein (PDB ID: 1SQN). then entered the test ligand in the form of 80 Paederia scandens compounds, the original ligand, the drug magesterol and tamoxifene in open babel. Then set the grid box -2.4, 1.5, and 25.5 for the X, Y and Z axes. Then click forward. The tethering process is ongoing until the indicator is 100% and the Binding affinity and Root Mean Square Deviation (RMSD) values are obtained.

ER

Opened PyRx software and entered the ER receptor protein (PDB ID: 6VPF). then entered the test ligand in the form of 80 Paederia scandens compounds, the original ligand, the drug tamoxifene and toremifene in open babel. Then set the grid box 14.8, -11.8, and 21.5 for the X, Y and Z axes. Then click forward. The tethering process is ongoing until the indicator is 100% and the Binding affinity and Root Mean Square Deviation (RMSD) values are obtained.

NF-κB

Opened PyRx software and entered the NF-κB receptor protein (PDB ID: 4KIK). then entered the test ligand in the form of 80 Paederia scandens compounds, the original ligand, the drug doxorubicin and paclitaxel in open babel. Then set the grid box 48.3, 30.0, and 56.8 for the X, Y and Z axes. Then click forward. The tethering process is ongoing until the indicator is 100% and the Binding affinity and Root Mean Square Deviation (RMSD) values are obtained.

Selection of Most Potential Compounds

After molecular docking, 1 compound with the highest binding affinity value from each receptor was selected. Then 1 compound with the highest average binding affinity value in all receptors. The result obtained 5 compounds in total.

Analysis of Physicochemical Properties of Compounds

Pharmacokinetic and toxicity tests were performed using the ADMETlab 3.0 website. Open the ADMETlab 3.0

website in a browser. On the main page click the ADMETlab 3.0 box. Next, in the provide a SMILES string column, enter the Canonical SMILES formula. Then the results of absorption properties will be displayed which include solubility values, Caco2 permeability, intestinal absorption, distribution properties which include permeability values of the Blood Brain Barrier (BBB), Central Nerves System (CNS), and volume distribution (VDss), metabolic properties by substrates CYP2D6, CYP3A4, excretion properties of total clearance values, toxicity properties with AMES values, and hepatotoxicity. Furthermore, the feasibility test was carried out as an oral drug using the Lipinski Rules of Five. On the main web page click choose file > select compound file (SDF/PDB) > submit. Parameters of molecular weight (BM), hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), logarithm of octanol/water partition coefficient (Log P), and molar refractivity.

Visualization of Molecular Docking Results

The molecular docking results that meet the best criteria are then visualized using Biovia Discovery Studio 2024 software to see the bond interactions formed and determine the mechanism of compound actpivity against breast cancer receptors. Visualization of docking is done using Biovia Discovery Studio application. Select show 2D diagram to display 2D interactions that occur.

RESULT AND DISCUSSION

Receptor Protein Selection and Preparation

The results of the selection PDB ID receptors that caused breast cancer include PR (PDB ID: 1SQN), ER (PDB ID:6VPF), HER2 (PDB ID: 3PP0), and NF-κB (PDB ID: 4KIK). The PDB ID results selected each receptor to be used in the docking process along with its characteristics (Table 1).

Table 1. Characteristics of Protein Target

Receptors	PDB ID	Resolution	*most favoured regions*	*G-Factors*
ER	6VPF	1.60 Å	100%	0.35
PR	1SQN	1.45 Å	100%	0.10
HER2	3PP0	2.25 Å	100%	0.09
Nf-kB	4KIK	2.83 Å	100%	0.12

Molecular docking

Docking was performed between 80 compounds of Paederia scandens isolates with 4 breast cancer hormonal target proteins. The molecular docking results in the form of binding affinity values from the highest to each receptor are taken at RMSD value 0.0 (Table 2).

Table 2 Molecular Docking Results of Ligand with Target Protein

Ligand	Receptor			
	PR	ER	HER2	Nf-kB
10-O-Eferuloylmonotropein	-8.2	-7.4	-8.1	-6
2,5-Dihydroxybenzoic acid methyl ester	-5.9	-6.5	-6	-5.9
3-Hydroxy 4-methoxy benzaldehyde	-5.9	-6.7	-5.8	-5.3
6′-O-E-feruloylmonotropein	-8.1	-6.8	-7.5	-6.1
6-β-O-sinapoyl scandoside methyl ester	-8.4	-7.2	-8	-6.8
6β-O-β-D-Glucosylpaederosidic acid	-6.5	-7.5	-8.3	-7
Acacetin	-8.2	-9.3	-9.4	-7.6
Asperuloside	-7.3	-7.2	-7.9	-6.6
Asperulosidic acid	-7.9	-7.1	-8.4	-6.3
Astragalin	-7.3	-7.5	-9.2	-6.7
Caffeic acid	-6.7	-7.1	-6.9	-6.7
Cleomiscosin B	-8.4	-8.5	-9.4	-6.9
Cleomiscosin D	-6.8	-7.5	-9.4	-6.6

Ligand	Receptor			
	PR	ER	HER2	Nf-kB
Compound 26	-7.8	-7.1	-7.9	-5.9
Compound 29	-7.7	-7.1	-7.3	-6
Compound 30	-8.1	-7.8	-9.1	-7.3
Compound 31	-7.5	-8.5	-9.3	-7.7
Compound 32	-7.5	-6.9	-8.3	-7.4
Compound 33	-7.7	-7.7	-9.2	-6.6
Compound 35	-6.7	-6.9	-7.6	-5.8
Compound 36	-7.9	-7.4	-8.1	-6.1
Compound 37	-6.7	-7.4	-7.7	-5.6
Compound 38	-8.8	-8.2	-9.1	-7.3
Compound 39	-7.1	-7.4	-9.1	-6.4
Compound 40	-6.6	-8.4	-8.9	-6.4
Compound 41	-1.7	-1.5	-1.9	-1.7
Compound 42	-7	-6.3	-6.9	-7.2
Compound 43	-7.4	-7.4	-7.9	-5.5
Compound 45	-6	-7	-9.1	-5.6
Compound 46	-7.9	-8	-9.3	-6.7
Compound 47	-5.8	-8	-8.6	-7.4
Cosmetin	-8.7	-9.8	-10.1	-7
Coumarinic acid	-6.2	-6.9	-6.3	-5.6
Cynaroside	-8.9	-7.8	-10.3	-7.7
Daidzein	-7.8	-9.3	-9.2	-8.9
Daphylloside	-6.5	-6.8	-8.2	-6.1
Deacetyl asperulosidic acid	-7.8	-6.9	-7.4	-6.1
Deacetyl asperulosidic acid methyl ester	-7.8	-7	-7.8	-5.8
Deacetylasperuloside	-8.2	-7.4	-8.3	-6.8
Dimer of methyl paederosidate	-7.4	-6.6	-8	-6.4
Dimer of paederoside, Paederoscandoside	-7.6	-7.9	-9	-7.6
Dimer of paederosidic acid	-7.2	-6.1	-7.7	-6.2
Dimeric iridoid glucoside	-7.8	-7.7	-8.9	-6.6
Diosmetin	-8.3	-9.8	-9.7	-6.6
Ethyl paederosidate	-7.9	-7.2	-7.5	-6
Fraxidin	-7.1	-7.1	-6.9	-6.7
Geniposide	-7.6	-7.3	-7.8	-5.9
Geniposidic acid	-7.9	-7.2	-7.8	-6.6
Guaiaverin	-7.3	-7.7	-9.1	-6.6
Hyperoside	-7.6	-8.5	-10.4	-6.5
Iridoid glucoside	-8.2	-6.8	-8	-6.4
Isolariciresinol	-6.8	-8.9	-8.2	-6.3
Isoquercitrin	-7.6	-7.6	-9.4	-8.1
Isorhamnetin-3-O-glucoside	-7.4	-8	-8.7	-7
Isoscopoletin	-6.9	-7.4	-7.2	-6.6
Isovitexin	-8	-7.4	-10	-6.5
Kaempferol 3-rutinoside-7-glucoside	-9.6	-7.6	-9	-7.6
Kaempferol-3-rutinoside	-8.5	-7.7	-10	-6.9

Ligand	Receptor			
	PR	ER	HER2	Nf-kB
Linarin	-9	-9.4	-9.6	-8.2
Myricitrin	-8.5	-7.7	-10.4	-7.2
Narcissin	-8.9	-8.1	-9.1	-7.3
Paederinin	-7.9	-7	-8.7	-6.8
Paederoscandoside	-6.9	-7.2	-8.7	-6.6
Paederoside B	-6.6	-8.2	-8.7	-7
Paederosidic acid methyl ester	-6.4	-7	-8.2	-5.8
Paederoxepane A	-6.7	-7.3	-7	-6
Paederoxepane B	-7.1	-7	-7.7	-7
p-Hydroxyl-benzoic acid	-6	-6.4	-5.8	-5.8
Populnin	-7.7	-9	-9.1	-7.9
Procyanidin B2	-7.8	-7.7	-9.5	-7.2
Protocatechualdehyde	-5.8	-6.2	-5.7	-5.8
Quercetin 3-o-rutinoside-7-o-glucoside	-8.7	-8.1	-10.8	-7.9
Quercimeritrin	-8.6	-7.9	-10.4	-7.6
Quercitrin	-8.5	-7.9	-9.6	-7
Saprosmoside D	-7	-7.3	-8.8	-6.4
Saprosmoside E	-7.8	-6.8	-9.1	-6.9
Saprosmoside F	-7.5	-7.3	-8.6	-7.3
Scandoside	-8	-7.4	-7.3	-6.1
Scandoside methyl ester	-7.9	-6.9	-7.6	-5.8
Transferulic acid	-7	-6.8	-6.6	-5.5
Native ligand	-9.1	-10.7	-9.2	-6.4
Megesterol	-8.2			
Tamoxifen	-6.1			
Lapatinib		-10		
Trastuzumab		-7.7		
Paclitaxel			-14.3	
Doxorubicin			-9.6	
Tamoxifen				-8.6
Toremifene				-5.8

Binding affinity or binding free energy is the strength of interaction between ligand and receptor. The Vina program performs tethering through command operations according to formats and gradient optimization algorithms to find the best conformation of the ligand and receptor which further considers the interactions between atoms and calculates the binding free energy (ΔG-bind) based on the resulting configuration (Trott & Olson, 2016). The binding free energy value describes the stability of the bonding interaction between the ligand and receptor at the binding site.

A ΔG value < 0 indicates the reaction is spontaneous towards the product. Conversely, a ΔG value > 0 indicates that the reaction does not take place towards the product but towards the reactants or it can be considered that no reaction occurs. The smaller the ΔG value, the stronger and more stable the bond formed between the ligand and the receptor (Xiao1 et al., 2019). Thus, the free energy value of binding can be used as a reference for determining the potential activity of the compound against the test receptor.

Selection of Most Potential Compounds

Based on the docking results that have been done, the compounds with the highest bond affinity values are obtained as follows in Table 3

Table 3. Highest Binding Affinity of Each Receptor

Receptors	Ligand	*Binding affinity* (kkal/mol)	RMSD
PR	*Kaempferol 3-rutinoside-7-glucoside* (K)	-9.6	0
	Megesterol	-8.2	0
HER2	*Cosmetin* (C)	-9.8	0
	Trastuzumab	-7.7	0
NF-kB	*Quercetin 3-o-rutinoside-7-oglucoside* (Q)	-10.8	0
	Doxorubicin	-9.6	0
ER	*Daidzein* (D)	-8.9	0
	Tamoxifen	-8.6	0
Rata-rata	*Linarin* (L)	-9.05	0

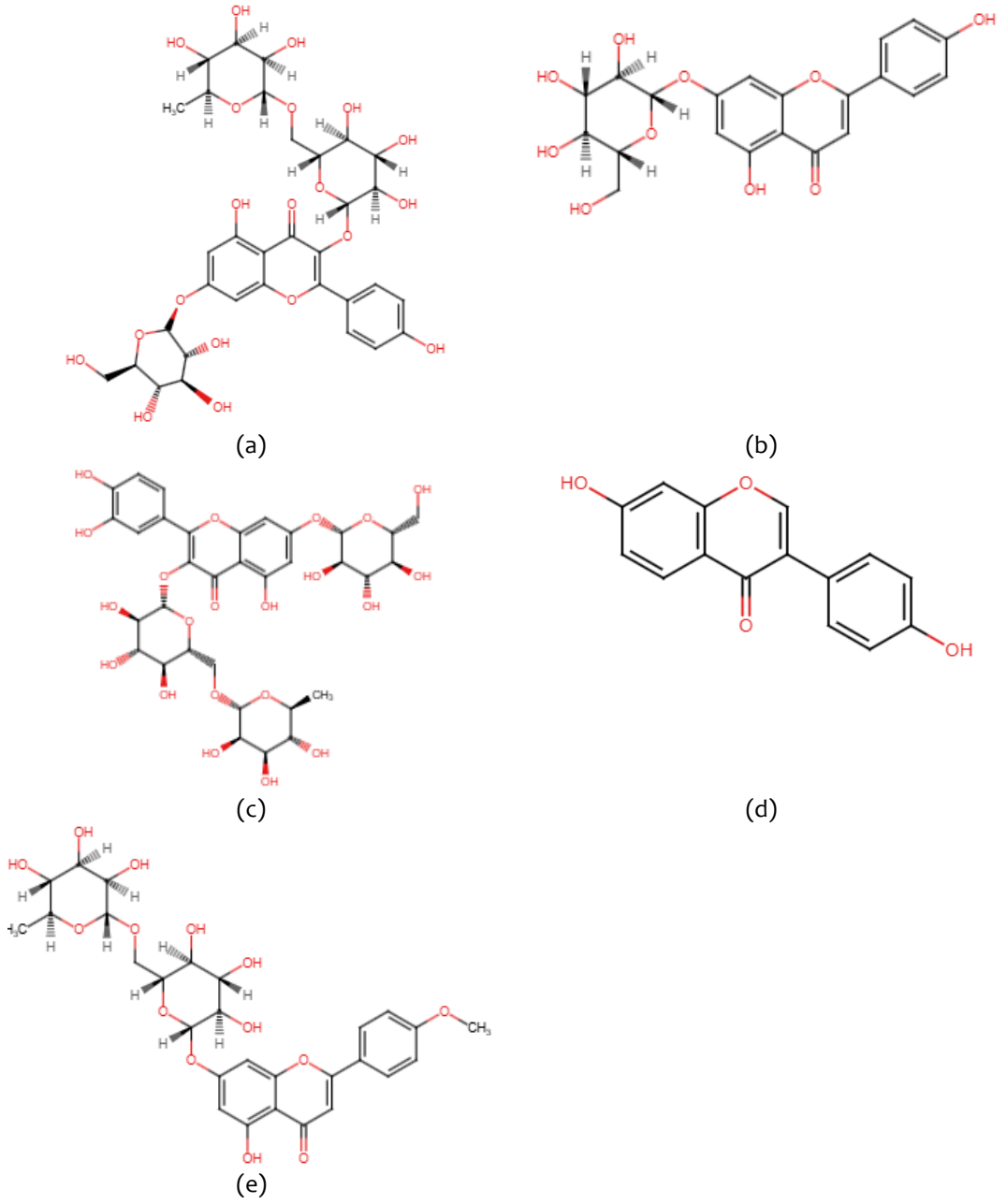

Figure 1 Structur Compounds (a) *Kaempferol 3-rutinoside-7-glucoside* (b) *Cosmetin* (c) *Quercetin 3-o-rutinoside-7-o-glucoside* (d) *Daidzein* (e) *Linarin.*

All of these binding affinity values are stronger than the binding affinity of breast cancer comparator drugs at each receptor, here are namely megesterol -8.2 kcal/mol to the progesterone receptor, trastuzumab -7.7 kcal/mol to the HER2 receptor, doxorubicin -9.6 kcal/mol to the Nf-kB receptor, and tamoxifen -8.6 kcal/mol to the estrogen receptor.

Based on the analysis of the compound structure, it was found that all compounds belonged to the flavonoid group with glycosides except for the Daidzein compound which is an isoflavone without glycosides. The structure of flavonoid compounds has an aromatic ring that produces interactions with aromatic residues on the test receptor through strong bonds, namely π-π stacking. This bond occurs due to the overlapping of the π orbitals of the two aromatic rings which induces a force of attraction between the π electrons. In a study conducted by Ummah et al (2024) flavonoid compounds from pomegranate peel extract have a π-π stacking mechanism that results in a bond affinity between flavonoid compounds and estrogen receptors that is stronger than the drug tamoxifen in breast cancer. This interaction occurs in the ketone group as the center of interaction on the active site of the receptor through the hydrogen bonds formed. This hydrogen bond is mediated by hydroxyl groups that act as donor or acceptor polar groups on the active side of the estrogen receptor and play a role in the aggregation process of most biological systems from protein forms to nucleic acids (Fabbrizzi, 2022).

In addition to interactions on the active site of the bond, in estrogen receptors ketone groups also influence the stability of the ligand-receptor complex through hydrophobic interactions in van der waals bonds. Hydrophobic interactions play an important role in compounds with a significant hydrophobic portion. These bonds are responsible for chemical and biological phenomena in aqueous solutions such as protein folding, micelle formation and stability, biological membranes, and macromolecular complexes (Sun, 2022). Van der Waals bonding occurs when two atoms are close to each other and form a nonspecific bond with its function to keep the ligand in a stable complex conformational position at the binding site (Tantardini et al., 2020). Glycoside groups in flavonoid glycoside group compounds play a role in increasing polarity, making the bond formed at the receptor stronger (Ummah et al., 2024). The flavonoid group with the presence of glycoside groups in this tethering produces the strongest and most bond affinity values as evidenced by 4 of the top 5 compounds are flavonoid glycoside groups.

Kaempferol 3-rutinoside-7-glucoside is one of the flavonoid glycoside class compounds. This compound forms the strongest bond of interaction with progesterone receptors. The structure of kaempferol has a hydroxy functional group at position C4' which is able to induce the mechanism of death-associated protein kinase 1 (DAPK1), a form of serine or threonine kinase in the Calmodulin dependent protein kinase (CaMK) family that plays a role in tumour inhibition, mediation of apoptosis, and autophagy activity. This compound has glycoside groups in the form of rutinoside and glucoside, both of which play a role in solubility and bioavailability in the body (Fadlan et al., 2022).

Another flavonoid glycoside group is Cosmetin. This compound has apigenin which binds to a glucose group at position 7-OH. Hydroxyl and glucoside groups at the 7-OH position play a role in increasing solubility and bioavailability so that it is easier to interact with apoptotic target proteins. This compound can increase the expression of apoptotic proteins such as Bax and decrease anti-apoptotic proteins Bcl-2 and Bcl-xL. Furthermore, it induces the release of cytochrome c from the mitochondria to the cytoplasm which results in the activation of the caspase cascade (caspase-9, -3, and -7) triggering cell apoptosis (Amalina et al., 2021). The glycoside structure of this compound affects the penetration of cancer cells and inhibits proliferation. The mechanism of proliferation inhibition occurs through modulation of cyclic protein expression and kinases that cause cell cycle arrest in the G1 or G2/M phase.

The next flavonoid glycoside class compound is quercetin 3-o-rutinoside-7-o-glucoside. This compound has hydroxyl groups in the quercetin flavonoid structure in positions 3', 4', 5, 7 which play a role in antioxidant activity and cellular signaling. The monosaccharide structure at position C7 increases the binding affinity to target proteins. The planar formation of quercetin can inhibit LDH-A through interaction with lactate dehydrogenase-A (LDH-A) enzyme in cancer and interfere with the glycolysis metabolism of cancer cells. The sugar cluster also increases the selectivity of the PI3K/Akt signaling pathway which is hyperactive in cancer cells (Komalasari et al., 2024).

Linarin is a class of flavonoid glycoside compounds. This compound has a conjugated diketone system that plays a role in increasing interactions with apoptosis regulator proteins and COX-2 enzymes. The 4'-OCH3 methoxy group affects lipophilicity and the ability to penetrate cell membranes including cancer cells. The hydroxyl and methoxy substitution pattern forms interactions with apoptotic and proliferative enzymes such as topoisomerase, and kinase. This compound induces the apoptotic process through the activation of caspase-3 and caspase-9. This compound is also able to inhibit cancer cell proliferation through cell cycle arrest (G0/G1 phase) (Syaqila et al., 2024).

Furthermore, flavonoid group compounds without glycosides are Daidzein. This compound has a double hydroxyl group that is responsible for the process of forming bonds with target proteins. Structurally, Daidzein

compounds are isoflavones which have a 3-phenyl-chromone group that can bind to estrogen receptor beta (Erβ) in anticancer mechanisms (Akyuni et al., 2023).

Analysis of Physicochemical Properties of Compounds

Based on the results of the test of physicochemical properties of compounds using Lipinski's rule of five, it is found that compounds with mass parameters for oral drugs that meet are Cosmetin and Daidzein compounds. The molar refractivity that meets is the compound Kaempferol 3-rutinoside-7-glucoside, Cosmetin and Daidzein. The lipophilicity properties met were Kaempferol 3-rutinoside-7-glucoside, Cosmetin, Quercetin 3-o-rutinoside-7-o-glucoside, Linarin and Daidzein. The amount of HBA and HBD that met the requirements was only Daidzein. Chemical physical properties test results based on Lipinski's rule (Table 4).

Table 4. Chemical Physical Properties of Compounds.

	Lipinski's Rule of Five				
Compounds	***Mass***	***HBD***	***HBA***	***Log P***	***Refractivity***
K	726	0	20	-0.6	125
C	432	6	10	-0.4	103
Q	732	0	21	-22	137
L	592	7	14	-0.9	139
D	254	2	4	2.7	69

In addition to physicochemical properties, drug delivery in the body is also strongly influenced by the stages of absorption, distribution, metabolism, excretion, and toxicity (ADMET). Where these stages of the process differ depending on the body's acceptance of each individual and the nature of the drug compound. The results of the ADMET properties test through ADMETlab 3.0 (Table 5).

Table 5. ADMET of Compounds

Parameters	***K***	***C***	**Q**	**L**	***D***
Absorption					
Solubility	-2.8	-2.5	-2.8	-0.1	-3.8
Caco2 permeability (log Papp in 10-6 cm/s)	-0.6	0.33	-0.7	1.3	0.8
Intestinal absorption (% Absorbed)	0	37	0	100	92
Distribution					
BBB permeability (log BB)	-2.3	-1.4	-2.5	0.3	-0.2
CNS permeability (log PS)	-6.8	-4	-7.1	-2.8	-2
VDss (human) (log L/kg)	-0.3	0.3	-0.22	0.27	-0.2
Metabolism					
CYP2D6 substrate	no	no	no	no	no
CYP3A4 substrate	no	no	no	no	no
CYP2D6 inhibitor	no	no	no	no	no
CYP3A4 inhibitor	no	no	no	no	no
Excretion					
Total Clearance (log ml/min/kg)	-0.09	0.72	-0.2	0.9	0.17
Toxicity					
AMES	no	no	no	no	no
Hepatotoxicity	no	no	no	no	no

Based on the ADMETlab 3.0 test, the compound that fulfils all parameters is the Linarin compound. Kaempferol 3-rutinoside-7-glucoside and Quercetin 3-o-rutinoside-7-o-glucoside compounds have low absorption properties due to mass weight of more than 500 Daltons. Thus, the compound is difficult to penetrate the cell membrane to be absorbed. Cosmetin compounds also have absorption properties that do not meet the requirements. This is possible because the amount of HBD is too high. As a result, the compound is more bound to aqueous solutions while the cell membrane is a lipid bilayer membrane. Daidzein compounds meet all Lipinski parameters but have poor absorption properties possible because there are parameters that are not calculated in

Lipinski, namely polar surface area (PSA) which is the total surface area of polar atomic molecules such as oxygen, nitrogen, and hydrogen that are bound. PSA values >140 Å² tend to have hydrophilic properties. This makes it difficult for molecules to penetrate cell membranes and causes poor absorption properties (Amalina et al., 2021).

Visualization of Molecular Docking Results

Progesterone receptor

Based on the results of bond visualization using Biovia Discovery Studio, data obtained in the form of interactions and types of bonds that occur between Kaempferol 3-rutinoside-7-glucoside compounds against amino acid residues in progesterone receptors (Figure 2). The interaction between the progesterone receptor protein and the Kaempferol 3-rutinoside-7-glucoside compound has similar types and amino acid residues with the comparative drug tamoxifen including alkyl bonds to the Arg766 amino acid, pi-sigma bonds to the Val698 residue, pi-cation bonds to the Arg766 residue, and hydrogen bonds to the Gln815 residue (Table 6).

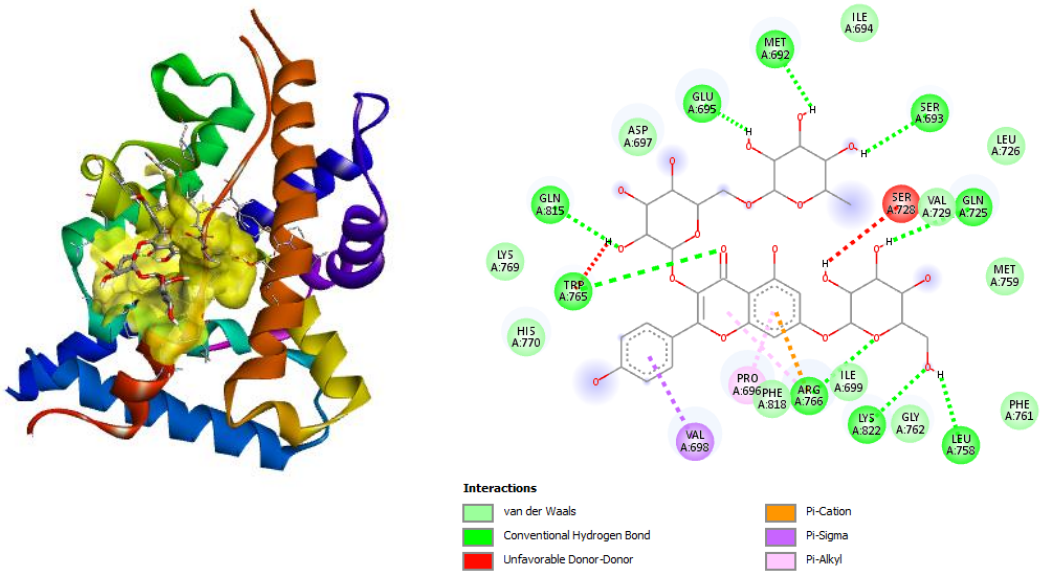

Figure 2. 2D and 3D Visualization of the Interaction Between PR and Kaempferol 3-rutinoside-7-glucoside

Table 6. Interactions Formed Between PR and Ligand

Compounds	Type of Bond	
Native ligand	Alkyl	Pro698, Arg766
	Pi-Alkyl	Trp765, Lys769, His770
Megesterol	H-Bond	Gln747
Tamoxifen	Alkyl	**Pro696, Arg766,**
	Pi-Sigma	**Val698**
	Pi-cation	Glu695, Arg**766**
	Hydrogen	**Gln815**
(K)	Alkyl	**Pro696, Arg766**
	Pi-Sigma	**Val698**
	Pi-Cation	**Arg766**
	Hydrogen	Met692, Ser693, Gln725, Leu758, Lys822, Arg766, Trp765, **Gln815**, Glu695

Estrogen Receptor

Based on the results of bond visualization using Biovia Discovery Studio, data obtained in the form of interactions and types of bonds that occur between Daidzein compounds to amino acid residues in estrogen receptors (Figure 3). The similarity of bond types and amino acid residues between Daidzein compounds and tamoxifen comparison drugs is obtained, namely pi-alkyl bonds on amino acid residues Leu346, Ala350 and Leu87 (Table 7).

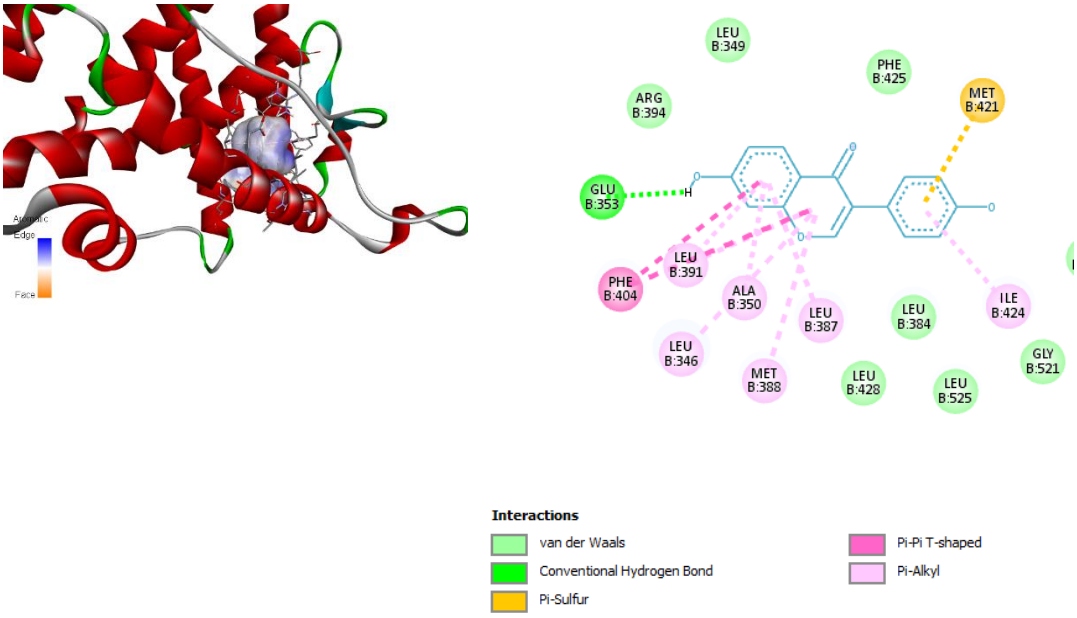

Figure 3. 2D and 3D Visualization of Interaction Between ER and Daidzein Ligand

Table 7. Interactions Formed Between ER and Ligand

Compounds	Type of Bond	
Native ligand	Alkyl	Ile326, Arg394, Leu403
Tamoxifen	Pi-Alkyl	**Leu346, Ala350, Leu387**, Met421, Ile424, Leu525
	Hydrogen	Val533
	Van der waals	Thr347, Ala350
Toremifen	Alkyl	**Leu346, Ala350**, Met388
	Pi-Alkyl	Leu346, Ala350
	Pi-Sulphur	Met343
	Pi-Sigma	Leu525
(D)	Pi-Alkyl	**Leu346**, Ala**350**, Leu**387**, Met388, Leu391, Ile424
	Pi-Sulphur	Met421
	Pi-pi T-Shape	Phe404
	Hydrogen	Glu353

Human Epidermal Receptor 2 (HER2)

Based on the results of bond visualization using Biovia Discovery Studio, data obtained in the form of interactions and types of bonds that occur between Cosmetin compounds to amino acid residues in the HER2 receptor (Figure 4). There is a similarity in the type of bond and amino acid residue between Cosmetin compound and the comparative drug lapatinib, namely alkyl bonds on amino acid residues Ala751, Lys753, Leu852 bonds (Table 8).

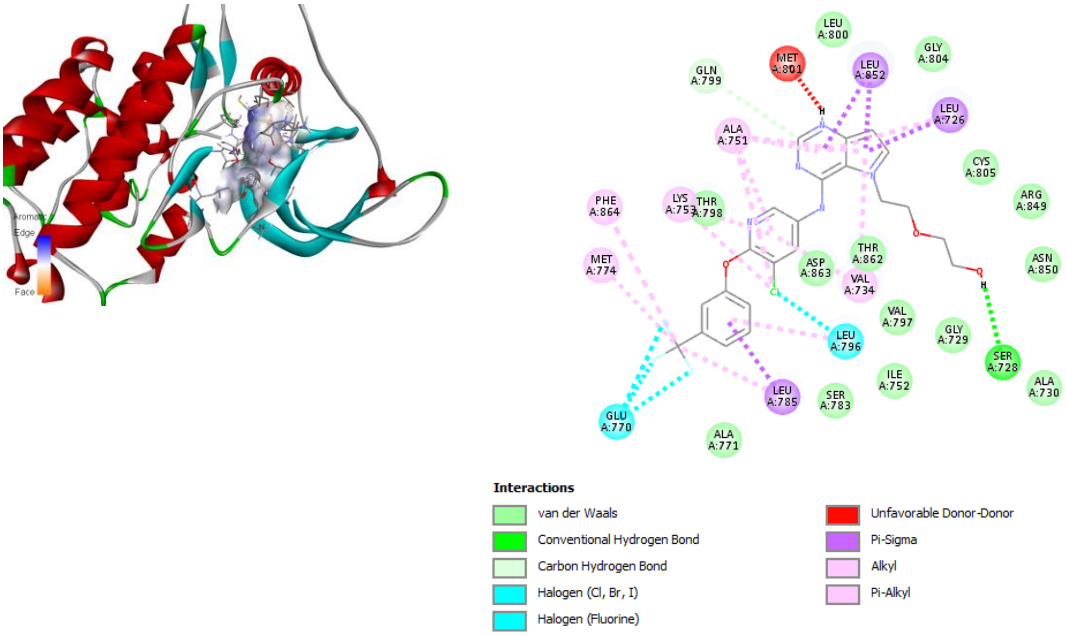

Figure 4. 2D and 3D Visualization of Interaction Between HER2 and Cosmetin Ligand.

Table 8. Interactions Formed Between HER2 and Ligand

Compounds	Type of Bond	
Native ligand	Halogen	Glu770, Leu796
	Pi-Alkyl	Leu726, Val734, Ala751, Lys753, Met774, Leu785, Leu796, Phe864
		Leu726, Leu785, Leu852
	Pi-Sigma	Ser728, Met801
	Hydrogen	Gln799
	Van der waals	
Trastuzumab	Pi-Alkyl	Val734, Ala751, Cys805
	Pi-Sigma	Val734, Leu852
	Hydrogen	Ala751, Leu796, Thr862
Lapatinib	Alkyl	**Ala751**, Lys753, Leu807, Arg849 Phe864
	Pi-Sulphur	**Leu726**, Val734, Leu**852**
	Pi-Sigma	Ser783, Arg849, Asp863
	Hydrogen	Cys804
	Van der waals	
(C)	Alkyl	Leu726, Val734, Ala**751**, Lys753, Met774, Leu785, Phe864
		Glu770, Leu796
	Halogen	**Leu726**, Leu785, Leu**852**
	Pi-Sigma	Ser728
	Hydrogen	Gln799
	Van der waals	Met801

NF-κB Receptor

Based on the results of bond visualization using Biovia Discovery Studio, data obtained in the form of interactions and types of bonds that occur between Quercetin 3-o-rutinoside-7-o-glucoside compounds against amino acid residues in the Nf-kB receptor (Figure 5). The similarity of bond types and amino acid residues between the Quercetin 3-o-rutinoside-7-o-glucoside compound and the comparison drug doxorubicin is obtained, namely hydrogen bonds on the amino acid residue Leu21 (Table 9).

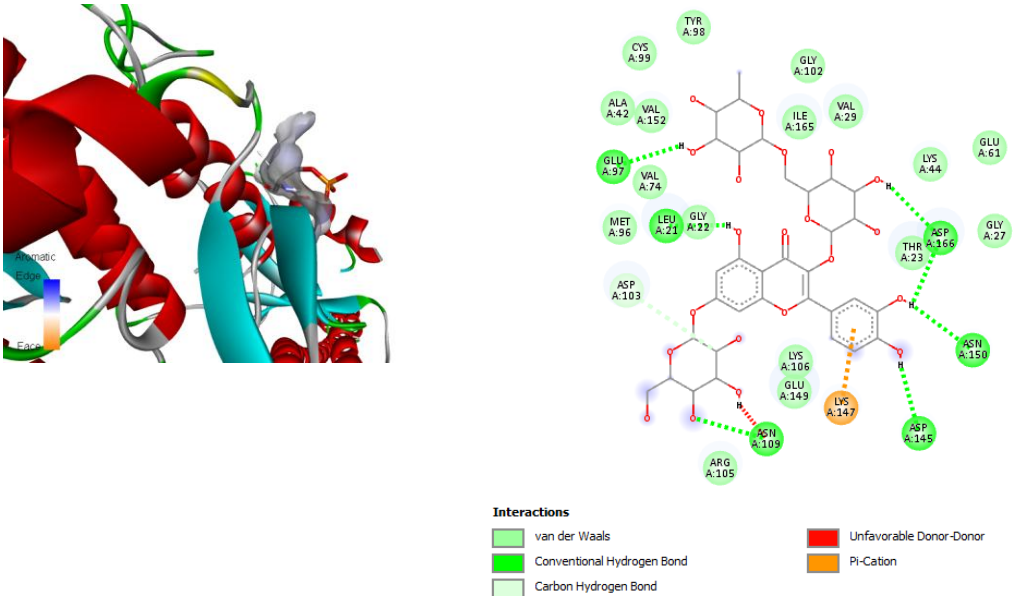

Figure 5. 2D and 3D Visualization of Interaction Between Nf-kB and Quercetin 3-o-rutinoside-7-o-glucoside Ligand

Table 9. Interactions Formed Between Nf-kB and Ligand

Compounds	Type of Bond	
Native ligand	Halogen	Glu97, Cys99
	Pi-Alkyl	Leu21, Val29, Ala42, Tyr98, Cys99, Val152, Ile165
	Hydrogen	Lys147, Glu149, Asn150, **Asp166**
Doxorubicin	Alkyl	Ala42, Lys106, Cys99, Arg105, Lys106, Val152, Ile165
	Pi-Sigma	Val29, Ile165
	Hydrogen	**Leu21**
Paclitaxel	Alkyl	Leu21, Ala42, Tyr98, Val152
	Pi-Sigma	Val29, Ile165
	Hydrogen	Lys44, Asp103
	Van der waals	Cys99
(Q)	Pi-Cation	Lys147
	Hydrogen	**Leu21**, Glu97, Asn109, Asp145, Asn159, **Asp166**
	Van der waals	Asp103

The similarity of bonds and amino acid residues between Kaempferol 3-rutinoside-7-glucoside, Cosmetin, Quercetin 3-o-rutinoside-7-o-glucoside, Daidzein and the comparator drug may indicate a similar potential interaction at the target receptor and may lead to a similar mechanism of action. Thus, it can be said that those compounds can be used as a candidate breast anticancer agent.

CONCLUSION

Bioactive compounds in *sembukan* plants (Paederia scandens) that have the highest potential as breast anticancer are compounds of Kaempferol 3-rutinoside-7-glucoside, Cosmetin, Quercetin 3-o-rutinoside-7-o-glucoside, Daidzein and Linarin respectively against progesterone, HER2, Nf-kB, estrogen and overall average receptors with each binding affinity value of -9. 6 kcal/mol, -9.8 kcal/mol, -9.8 kcal/mol, -10.8 kcal/mol, -8.9 kcal/mol and -9.0 kcal/mol respectively. Daidzein and Linarin compounds have the most high-potential physicochemical properties. The high potential of Daidzein compounds is indicated by fulfilling all Lipinski rules of five criteria. In the ADMET test, the compound with the highest potential by fulfilling all ADMET parameters is the Linarin compound. Further studies are needed in the development of modifications to the physicochemical properties and ADMET of potential compounds in Paederia scandens to improve their therapeutic effects.

CONFLICT OF INTEREST

We declare that we don't have any conflict of interest.

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