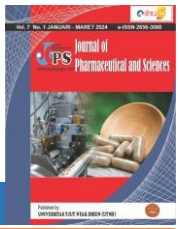
Journal of Pharmaceutical and Sciences
Electronic ISSN: 2656-3088 DOI: https://doi.org/10.36490/journal-jps.com
Homepage: https://journal-jps.com
ORIGINAL ARTICLE JPS. 2026, 9(1), 1091-1102



Cytotoxic activity test of citrus mistletoe (*Dendrophthoe glabrescens*) leaves on breast cancer lines: in silico study

Uji Aktivitas Sitotoksik Daun Benalu Jeruk (*Dendrophthoe glabrescens*) terhadap Garis Sel Kanker Payudara: Studi In Silico

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Abstract

This study aims investigate the potential of phytochemical compounds from citrus mistletoe leaves (*Dendrophthoe glabrescens*) leaves as anticancer candidates using an in silico approach. Phytocemical constituents identified by LC-MS and screened using Lipinski's Rule of Five. Followed by Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) prediction using ProTox-3.0. The docking protocol was validated with root mean square deviation (RMSD) values of 1.80 Å for epidermal growth factor receptor (EGFR) (PDB ID: 1M17) and 0.69 Å for estrogen receptor-α (ER-α) (PDB ID: 1A52). Tenylidone exhibited the strongest binding affinity toward EGFR (-8.12 kcal/mol), followed by quercetin (−7.48 kcal/mol) and kaempferol (−7.43 kcal/mol). For estrogen receptor alpha, fisetin showed the strongest affinity among the tested D. glabrescens compounds (−8.21 kcal/mol), followed by nomelidine (−8.16 kcal/mol) and tenylidone (−7.95 kcal/mol). Kaempferol showed the most favorable predicted acute toxicity profile among the leading compounds, with an estimated LD50 of 3919 mg/kg and toxicity class 5. Overall, tenylidone and fisetin were prioritized for epidermal growth factor receptor and estrogen receptor alpha, respectively, while kaempferol showed a favorable predicted safety profile.

Keywords: Breast cancer, in silico, Dendrophthoe glabrescens, anticancer, phytocemicals

Abstrak

Penelitian ini bertujuan untuk menyelidiki potensi senyawa fitokimia dari daun benalu jeruk (*Dendrophthoe glabrescens*) sebagai kandidat antikanker melalui pendekatan *in silico*. Senyawa fitokimia diidentifikasi menggunakan LC-MS dan disaring berdasarkan Aturan Lima Lipinski. Selanjutnya, dilakukan prediksi absorpsi, distribusi, metabolisme, ekskresi, dan toksisitas (ADMET) menggunakan ProTox-3.0. Protokol penambatan molekular divalidasi dengan nilai *root mean square deviation* (RMSD) sebesar 1,80 Å untuk reseptor faktor pertumbuhan epidermal (*epidermal growth factor receptor*/EGFR) (PDB ID: 1M17) dan 0,69 Å untuk reseptor estrogen-α (ER-α) (PDB ID: 1A52). Tenilidon menunjukkan afinitas pengikatan terkuat terhadap EGFR (-8,12 kkal/mol), diikuti oleh kuersetin (−7,48 kkal/mol) dan kaempferol (−7,43 kkal/mol). Untuk reseptor estrogen alfa, fisetin menunjukkan afinitas terkuat di antara senyawa *D. glabrescens* yang diuji (−8,21 kkal/mol), diikuti oleh nomelidin (−8,16 kkal/mol) dan tenilidon (−7,95 kkal/mol). Kaempferol menunjukkan profil toksisitas akut terbaik di antara senyawa unggulan, dengan perkiraan LD50 sebesar 3919 mg/kg dan kelas toksisitas 5. Secara keseluruhan, tenilidon dan fisetin diprioritaskan masing-masing untuk reseptor faktor pertumbuhan epidermal dan reseptor estrogen alfa, sedangkan kaempferol menunjukkan profil keamanan yang baik berdasarkan prediksi.

Kata kunci: Kanker payudara, in silico, Dendrophthoe glabrescens, antikanker, fitokimia

https://doi.org/10.36490/journal-jps.com.v9i1.1417

Article History:
Received: 06/10/2025,
Revised: 18/02/2026,
Accepted: 18/02/2026,
Available Online: 30/03/2026.

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Introduction

Cancer is a global health problem with 20 million cases in 2022 and its predicted to increase every year [1]. Breast cancer is the leading case in women with more than 2.3 million new cases with 665,684 deaths worldwide and its a contributor to cancer morbidity and mortality [1]. Estrogen receptor-α (ER-α) plays a central role in hormone-dependent proliferation in luminal A breast cancer, which represents approximately 70% of all breast cancer cases, making it a clinically relevant therapeutic target. In contrast, triple-negative breast cancer (TNBC), accounting for about 20% of cases, lacks hormone receptors and HER2 expression and frequently relies on epidermal growth factor receptor (EGFR) mediated signaling for tumor growth and metastasis, thereby providing a strong rationale for targeting EGFR [2]. Various cancer treatments have been carried out such as surgery, radiation, chemotherapy, and immunotherapy. However, conventional strategies needs improvement with best outcome especially chemotherapy due to low selectivity. Side effects and high treatment costs are still be considerations for treatment with these methods [3]. Therefore, this study was conducted with the aim of contributing to the WHO target of reducing breast cancer deaths by 2.5% per year with a comprehensive breast cancer management strategy [1].

Medicinal plants and natural compounds have potential as alternative and supportive therapies due to have diverse chemical contents and promising bioactivity [4]. Mistletoe is one type of plant that has potential in traditional medicine to treat various diseases such as cancer [5]. *Dendrophthoe pentandra* (DP) is one of the mistletoe species whose secondary metabolites have been analyzed. The n-hexane fraction of DP has cytotoxic activity with an IC50 of 39.57 µg/mL on T47D cells [6]. Another type of citrus mistletoe, DG has antioxidant activity with an IC50 value of 54.490 µg/mL [7]. Its chemical content consists of phenol, flavonoid, tannin, steroid, and saponin compounds. The n-hexane and ethanol fractions of DG have toxicity to *Artema salina* Leach larvae with IC50 values of 6.19 µg/mL and 9.93 µg/mL, respectively [8]. To date, no studies have investigated further about the compound constituent of DG using a molecular target-based approach to understand the potential of DG as an anticancer agent. Molecular docking represents an important, efficient and cost-effective computational energy for predicted the potential of compounds based on its interactions specifically with protein targets.

Materials and Methods

Materials

Molecular docking was conducted following the identification of phytochemical constituents present in citrus mistletoe (Dendrophthoe glabrescens) leaves. A total of eighteen ligand compounds were identified, including astragalin, cynaroside, diflufenzopyr, fisetin, kaempferol, kaempferol-7-O-glucoside, luteolin, luteolin-4-O-glucoside, morin, morin hydrate, nomelidine, oxazolidine-E, progabide, quercitrin, quercetin, tenylidone, tricetin, and viscidulin I. The compound was obtained from LC–MS analysis. 3D structures of all ligands were retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). These compounds were evaluated in silico against two protein targets, namely epidermal growth factor receptor (EGFR; PDB ID: 1M17) and estrogen receptor-α (ER-α; PDB ID: 1A52), both obtained from the Protein Data Bank (https://www.rcsb.org/) [9]. The co-crystallized ligand AQ4 [6,7-bis(2-methoxyethoxy)quinazoline-4-yl]-(3-

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ethinylphenyl)amine] ($C_{22}H_{23}N_3O_4$) for EGFR, estradiol ($C_{18}H_{24}O_2$) for ER-α, tamoxifen and erlotinib were used as reference compounds for comparative analysis.

Methods

ADMET (Adsorption, distribution, metabolism, excretion, and Toxicity) profile prediction of chemical structure the ligand compounds

The ligand compounds obtained from Dendrophthoe glabrescens were evaluated using the SwissADME web server (https://www.swissadme.ch/) in accordance with Lipinski's Rule of Five to assess their drug-likeness and potential suitability as drug candidates [10]. The toxicity of the three best-performing compounds for each receptor was predicted using ProTox-3.0 (https://tox.charite.de/) by evaluating several relevant toxicity parameters [11].

Proteins and native ligands preparation

The protein structures of EGFR and ER-α were prepared using Discovery Studio by removing co-crystallized ligands, ions, and water molecules, followed by the addition of hydrogen atoms. The prepared protein structures were saved in PDB format and subsequently energy-minimized using Swiss-PdbViewer. The native ligands associated with each receptor were extracted from the protein structures, and water molecules and ions were removed. Hydrogen atoms were added, and the ligand structures were energy-minimized using Avogadro prior to molecular docking analysis [12].

Ligand preparation and molecular docking

The ligand compounds including tamoxifen and erlotinib as standard were retrieved from the PubChem database in SDF format. Three-dimensional ligand structures were prepared using Discovery Studio by removing water molecules and adding hydrogen atoms, the structures were converted to PDB format. Energy minimization of the ligand structures was performed using Avogadro. Docking protocol validation was conducted by re-docking the native ligands into their respective receptor binding sites using AutoDock Tools version 4.2. The default parameters used in molecular docking included setting the X, Y, Z positions and grid box volume with number of points set to 10 and set to spacing 0,375 Å. The volume of the grid box used is 42x18x432 Å for EGFR and ER-α at 40x40x40 Å. Genetic algorithm parameters by default with number of run 10, population size 150 and maximum number of generations 27000. The docking procedure use Lamarckian genetic algorithm and was considered valid when the RMSD value was below 2 Å. Subsequently, molecular docking of the remaining ligand compounds was carried out using AutoDock Tools 4.2. Binding affinity values and RMSD results were obtained for each ligand–receptor complex, and the molecular interactions between ligands and receptor proteins were visualized using Discovery Studio [12].

Results and Discussion

The selection of EGFR and ER-α as molecular targets in this study is well justified. ER-α represents the dominant signaling pathway in approximately 75% of breast cancer cases, as its activation induces the transcription of oncogenic genes such as cyclin D1 and c-Myc, which directly contribute to tumor progression [9]. In parallel, overexpression of the epidermal growth factor receptor (EGFR) has been associated with enhanced breast cancer progression by promoting increased proliferation, survival, and resistance to apoptosis in cancer cells. Notably, both receptors regulate cancer cell growth through interconnected and overlapping signaling pathways [9]. Therefore, molecular docking of ligand compounds to these receptors enables the evaluation of structure-based interactions and provides insights into the suitability of the compounds as potential drug candidates.

Compound characteristic evaluation using lipinski's rule of five

Lipinski's Rule of Five defines several key criteria for assessing the drug-likeness of compounds, including a molecular weight of less than 500 Da, a logP value below 5, no more than 10 hydrogen bond acceptors, and no more than 5 hydrogen bond donors [13]. The Lipinski's Rule of Five analysis indicated that several identified compounds, namely astragalin, cynaroside, kaempferol-7-O-glucoside, luteolin, luteolin-4'-O-glucoside, and quercitrin, violated two of the assessed criteria (Figure 1). Multiple violations may indicate less favorable physicochemical characteristics, particularly those related to aqueous solubility, membrane

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permeability, and oral absorption. Therefore, compounds with two or more violations may have a greater risk of reduced oral bioavailability and membrane permeability. Nevertheless, the Rule of Five is intended as an early drug-likeness screening guideline rather than an absolute criterion for excluding biologically active compounds [13].

In this study, compounds with two Lipinski violations were not subjected to molecular docking to prioritize candidates with more favorable predicted drug-like properties and to minimize the inclusion of compounds with potential absorption-related limitations at the initial screening stage [14]. This exclusion does not necessarily indicate a lack of biological activity or therapeutic potential, as some bioactive compounds and clinically used drugs may fall outside the conventional Lipinski chemical space. From a physicochemical perspective, a high number of hydrogen bond donors and acceptors can increase molecular polarity and strengthen interactions with the aqueous environment [14]. During passive membrane permeation, these interactions must be disrupted as the compound moves from the aqueous phase into the lipophilic environment of the lipid bilayer [15]. Consequently, compounds with excessive hydrogen-bonding capacity may require greater desolvation and may exhibit reduced partitioning into biological membranes, which can negatively affect membrane permeability and, ultimately, oral absorption [13]. These considerations support the use of Lipinski criteria as an initial filter for selecting compounds with more favorable drug-like properties for subsequent molecular docking analysis.

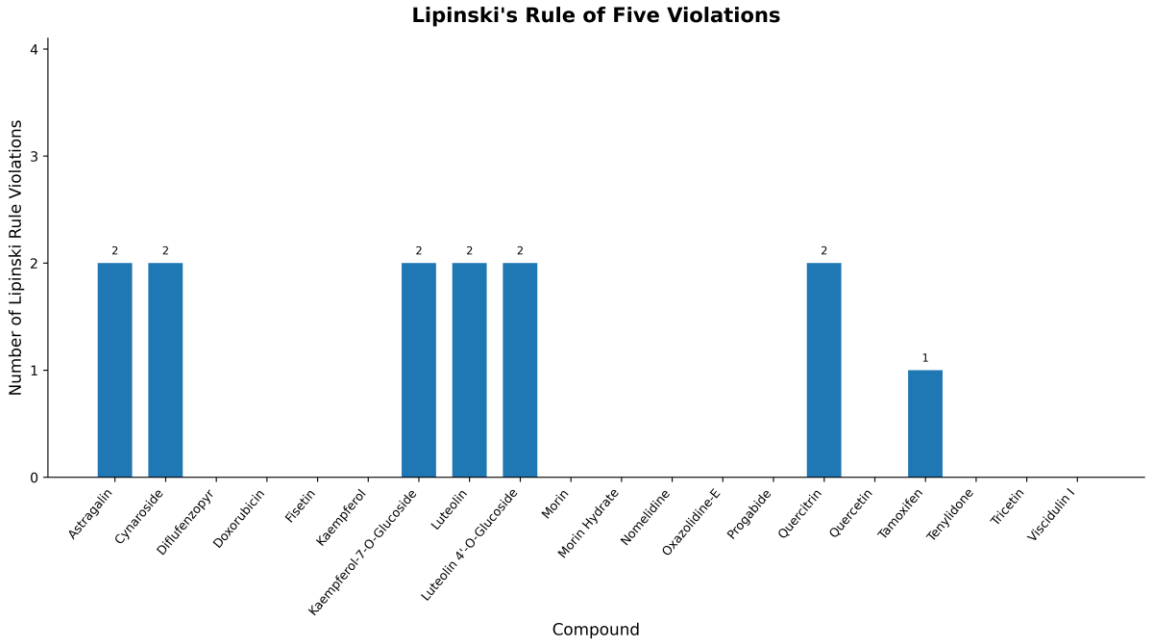

Figure 1. Lipinsi Rule's Violation on the drug candidate compound

Validation method

The validation process represents the initial step to ensure that the docking protocol and software employed are capable of accurately reproducing the binding pose of the native ligand within the active site of the target enzyme or receptor, as defined by the reference co-crystallized complex. This accuracy is indicated by a RMSD value of less than 2 Å, which is considered an acceptable threshold for docking validation [16,17]. Binding affinity energy is a key parameter used to estimate the strength of interaction between a ligand and a protein, where more negative binding affinity values indicate a more stable and energetically favorable ligand–protein complex[13].

Determination of the appropriate grid box coordinates (x, y, z) is a critical step in the docking validation process. The grid box defines the search space around the active site of the protein where ligand–receptor interactions are evaluated. An excessively large grid box may result in inaccurate scoring, whereas an overly small grid box can lead to sampling failure if the correct ligand orientation falls outside the defined boundaries [13]. In this study, grid box optimization was performed and the optimal grid box dimensions along with the corresponding RMSD values (1,80 Å and 0,69 Å) has meet the requirement (Figure 2). Molecular docking of other ligands was conducted using the validated coordinates and grid box volumes.

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In this study, the native ligand used for comparison in the EGFR binding site was AQ4, which exhibited a binding affinity of −6.55 kcal/mol and formed a hydrogen bond interaction with the amino acid residue Met769. Among the tested ligand compounds, three showed the most promising binding affinities toward the epidermal growth factor receptor (EGFR), namely tenylidone (−8.12 kcal/mol), quercetin (−7.48 kcal/mol), and kaempferol (−7.43 kcal/mol). Notably, all three compounds exhibited more favorable predicted binding affinities than erlotinib (-6.57 kcal/mol). This comparative result suggest favorable interactions with EGFR. However, the lower docking scores should not be interpreted as evidence of superior pharmacological efficacy compared with erlotinib. The three ligand compounds showed involvement of Met769, with additional interactions involving Lys721, Thr766, Gln767, Asp831, and Thr830 (Table 1). The stability of ligand–protein complexes is not determined solely by the number of hydrogen bonds but is also influenced by hydrophobic interactions, van der Waals forces, and π-mediated interactions [18,19].

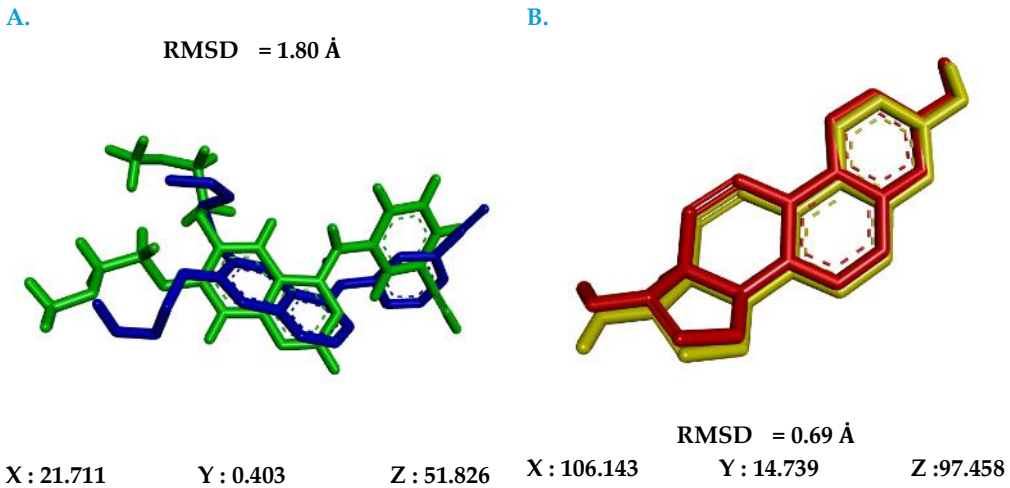

Figure 2. Validation of the grid box for the molecular docking method: A)1M17, re-dock ligand (blue) and native ligand (green); B) 15A2, re-docked ligan (red) and native ligand (yellow).

Table 1. Binding affinity values and interactions of ligand amino acid residues with protein receptors.

No	Compound	EGFR		ER-α	
		a*	b*	a	b
1	Diflufenzopyr	-6.38	2 : MET769, THR830	-6.91	2 : LYS529, ASP351
2	Fisetin	-7.27	5 : LYS721, ASP831, THR766, GLN767, MET769	**-8.21**	**3 : GLY521, GLU353, ARG394**
3	Erlotinib	-6,57	3 : **MET769, GLN767**	**-**	**-**
4	Kaempferol	**-7.43**	**6 : PRO770, MET769, GLN767, THR766, ASP831, LYS721**	-7.18	5 : GLY521, HIS524, LEU387, ARG394, GLU363
5	Morin	-7.04	7 : LYS721, ASP831, THR766, GLN767, MET769, PRO770	-7.36	1 : LEU346
6	Morin Hydrate	-7.26	6 : PRO770, MET769, GLN767, THR766, LYS721	-7.37	2 : ARG394, LEU346
7	**Nativeligand**	**-6.55**	**1 : MET769**	**-9.76**	**1 : GLU363**
8	Nomelidine	-6.78	1 : ASP831	**-8.16**	**1 : GLU363**
9	Oxazolidine-E	-4.05	2 : THR766, LYS721	-4.41	1 : ARG394
10	Progabide	-6.22	2 : MET769, GLN767	-7.77	3 : HIS524, LEU346, GLU353
11	Quercetin	**-7.48**	**5 : LYS721, ASP831, THR766, GLN767, MET769**	-7.79	3 : GLU363, ARG394, GLY521
12	Tamoxifen	**-**	**-**	-10.08	**1 : GLU363**
13	Tenylidone	**-8.12**	**2 : THR830, MET769**	**-7.95**	**2 : THR347, PHE404**
14	Tricetin	-6.46	5 : GLU738, LYS721, ASP831, MET769, CYS773	-7.73	4 : GLY521(2), ARG394, LEU346
15	Viscidulin I	-6.93	5 : LYS721, ASP831, THR766, GLN767, MET769	-6.42	1 : LEU346

* a = binding affinity, b = the number and type of amino acid residues that form hydrogen bonds with the ligand

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All three compounds exhibited nonpolar contacts with residues surrounding the binding pocket, including Leu694, Val702, Ala719, and Leu820, accompanied by π-alkyl and/or π-sigma interactions that may contribute to maintaining the orientation of the ligand aromatic rings within the binding pocket. The contribution of these nonpolar interactions may explain the relatively strong binding affinity of tenylidone (−8.12 kcal/mol) despite forming only two hydrogen bonds. This finding is consistent with previous molecular modeling studies of EGFR, which demonstrated that van der waals forces and alkyl interactions involving hydrophobic residues surrounding the ATP-binding pocket can contribute substantially to ligand–EGFR complex stabilization [20]. Thus, the docking results suggest that ligand affinity is influenced not only by individual polar interactions but also by the overall spatial complementarity and combined contribution of polar and nonpolar interactions within the binding pocket.

The similar binding locations and overlapping interacting residues observed between the three compounds and the native ligand suggest that these compounds may adopt a similar binding mode within the EGFR ATP-binding pocket. In particular, the involvement of Met769 and Thr766 places these interactions within the hinge region of EGFR, which plays an important role in the recognition of ATP-site kinase inhibitors [21]. The observed binding poses therefore suggest that tenylidone, quercetin, and kaempferol may inhibit EGFR kinase activity by occupying a binding pocket that overlaps with the ATP-binding site of the native ligand. However, the in silico experiment results could not conclusively establish a competitive inhibitory mechanism, as docking scores and predicted binding poses provide structural predictions rather than direct evidence of enzymatic inhibition. Therefore, the findings should be interpreted as supporting a potential ATP-competitive binding mode, which requires further experimental validation using biochemical approaches such as enzyme kinetic analysis or an ATP-competition assay [22].

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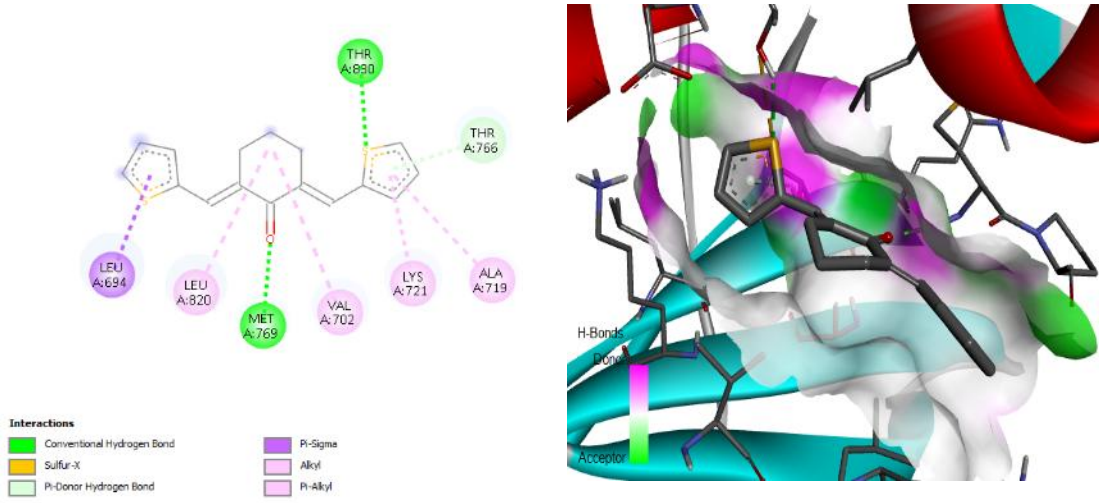

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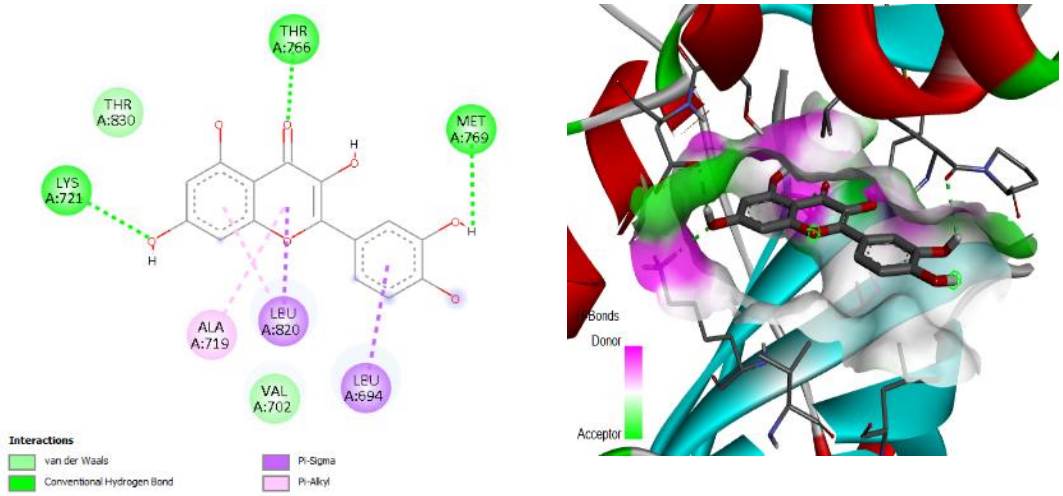

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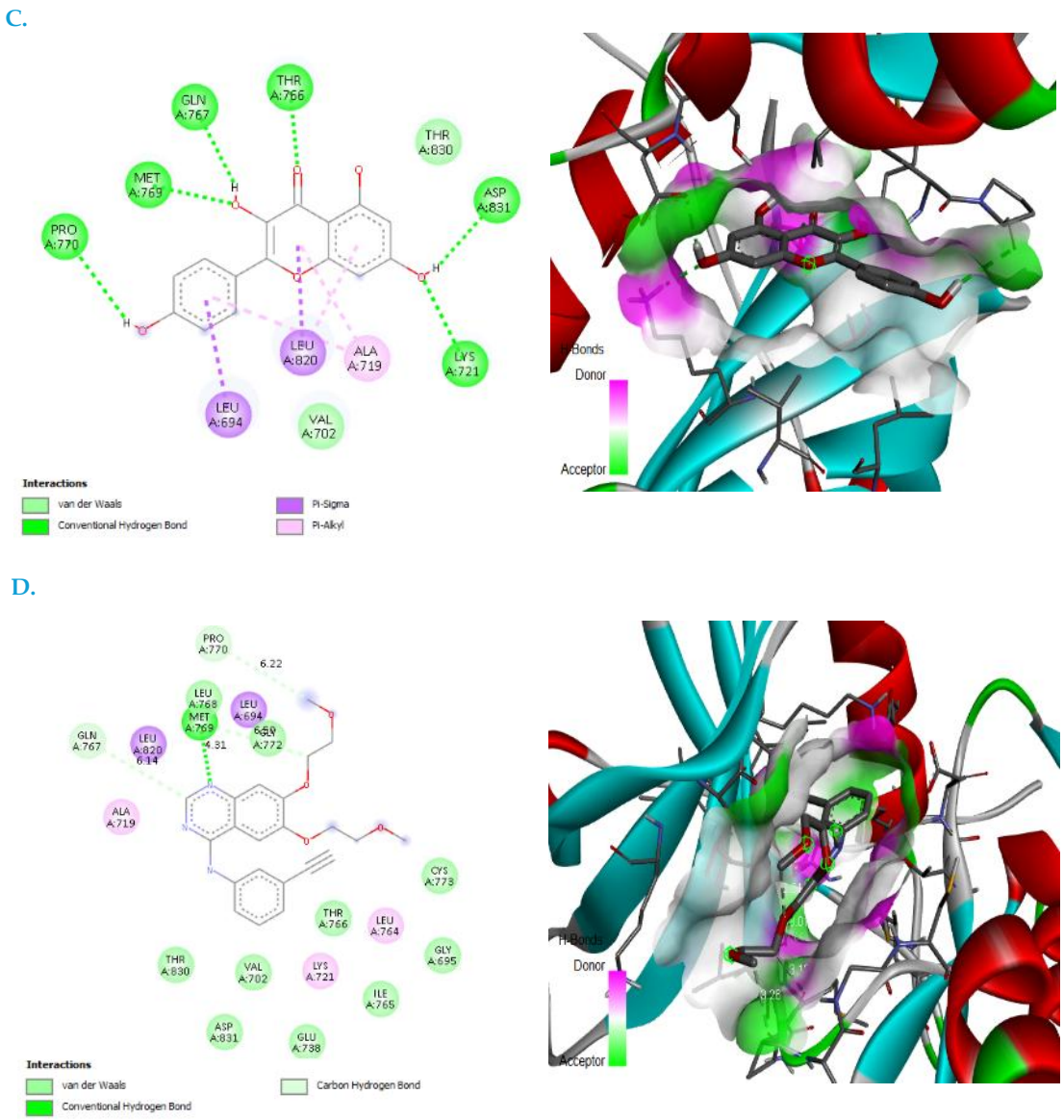

Figure 3. 2D and 3D interactions between ligands and EGFR proteins of tenylidone, quercetin, kaempferol, and native ligand compounds (a-d).

Three test compounds demonstrated favorable affinity for ER-α (PDB ID: 1A52), with values of −8.21 kcal/mol for fisetin, −8.16 kcal/mol for nomelidine, and −7.95 kcal/mol for tenylidone. In comparison, the natural ligand exhibited a lower affinity value (−9.76 kcal/mol), characterized by the formation of a hydrogen bond with the Glu363 amino acid residue. Nomelidine was among the test compounds that shared this specific hydrogen-bonding interaction with Glu363 (Figure 4). The natural ligand displayed a broader range of interactions—including hydrophobic and van der Waals interactions—which likely contributed to its lower affinity value relative to the other test compounds. Meanwhile, tamoxifen, the anticancer drug used as a reference, exhibited the lowest affinity value (−10.08 kcal/mol). Consequently, the test compounds cannot yet be considered superior to the existing drug, given the respective affinity differences of 1.87, 1.92, and 2.13 kcal/mol for fisetin, nomelidine, and tenylidone.

The lower predicted binding affinities of fisetin, nomelidine, and tenylidone may reflect differences in their overall interaction patterns and structural complementarity within the ER-α ligand-binding pocket [21,24]. Although nomelidine shared the Glu363 hydrogen-bond interaction with the native ligand, this shared residue alone does not necessarily indicate an equivalent binding mode or binding stability, because docking performance for flavonoid–ER-α complexes depends on the combined contribution of different intermolecular interactions rather than hydrogen bonding [23]. Structural analyses of ER-α have identified several residues, including Ala350, Glu353, Leu387, Arg394, Phe404, Gly521, His524, and Leu525, as important determinants of flavonoid recognition within the ligand-binding pocket [23,24]. Variations in ligand orientation and interaction patterns within this pocket can further influence receptor conformation and ligand-mediated

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functional responses [25]. Therefore, the weaker predicted affinities of the three Dendrophthoe glabrescens-derived compounds may be associated with differences in their binding orientation and overall interaction networks relative to the native ligand. Taken together, fisetin, nomelidine, and tenylidone may be considered potential ER-α-targeting candidates, although their predicted binding profiles require further experimental validation to determine whether these interactions translate into biologically relevant receptor modulation or inhibition.

The chemical profile, ADME characteristics, and toxicity predictions can provide additional information for assessing the predicted potential of candidate drug compounds. The three leading compounds for each target exhibited characteristics that remain worthy of consideration for lead prioritization, although differences were observed in their safety profiles (Table 2). Tenylidone showed the most promising overall profile, as it exhibited the most favorable binding affinity toward EGFR while also ranking among the top three candidates against ER-α. Its ADME profile was also favorable, with relatively limited predicted interactions with CYP enzymes. However, its relatively high LogP and predicted neurotoxicity represent potential liabilities that require further experimental validation. Kaempferol demonstrated the most favorable balance between predicted activity and safety among the EGFR-targeting candidates and exhibited the lowest predicted acute oral toxicity.

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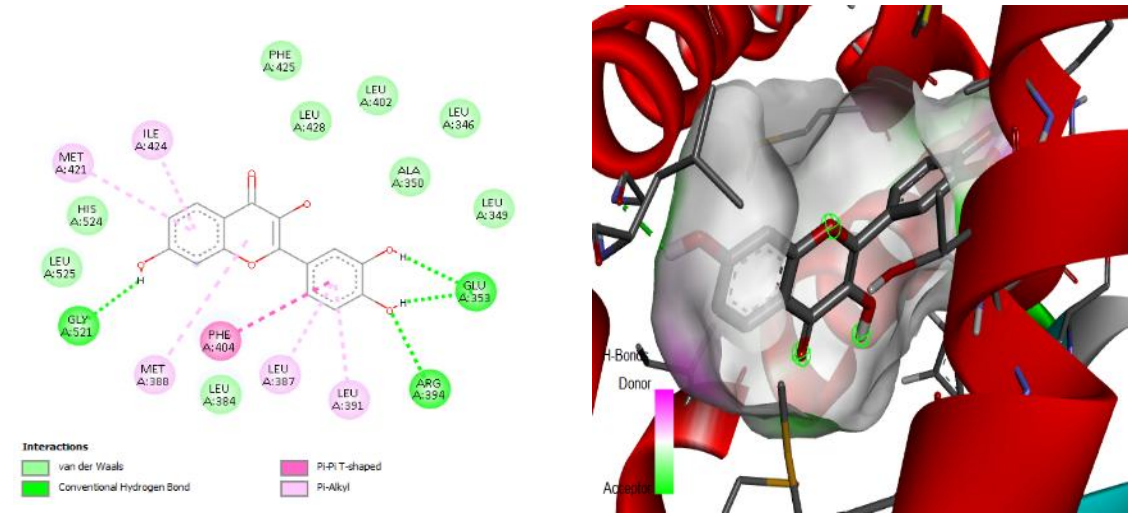

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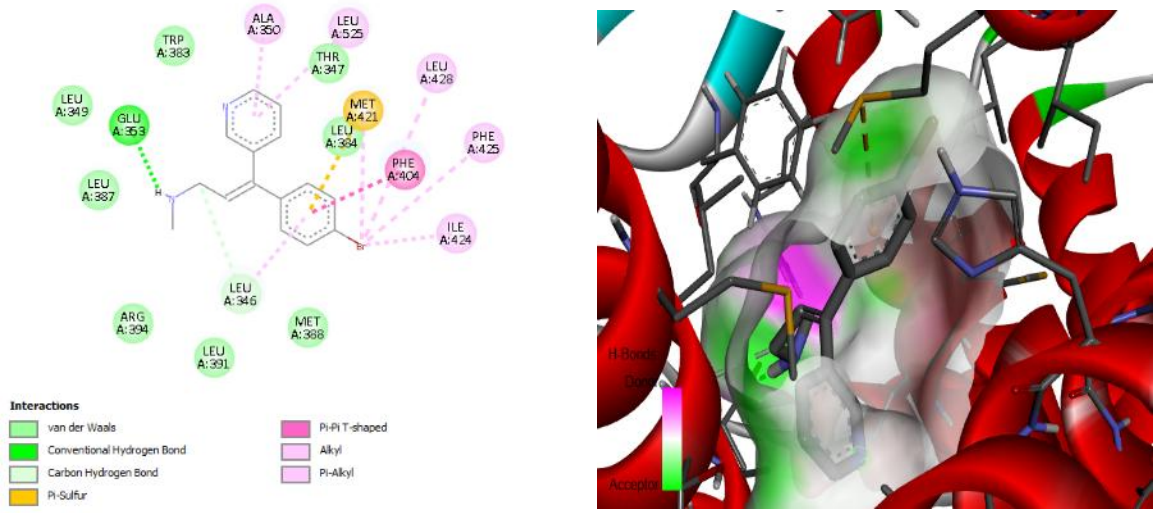

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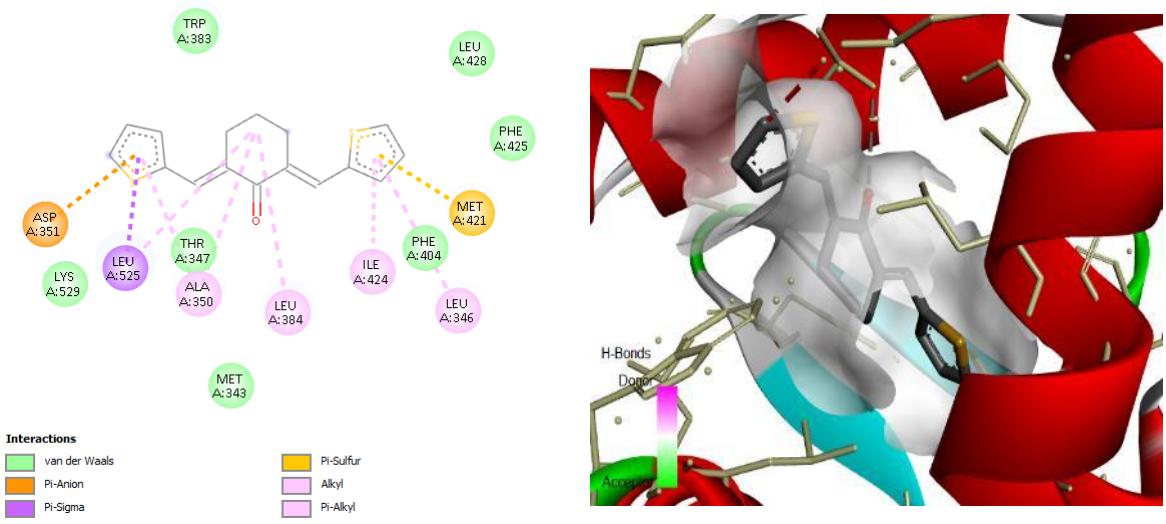

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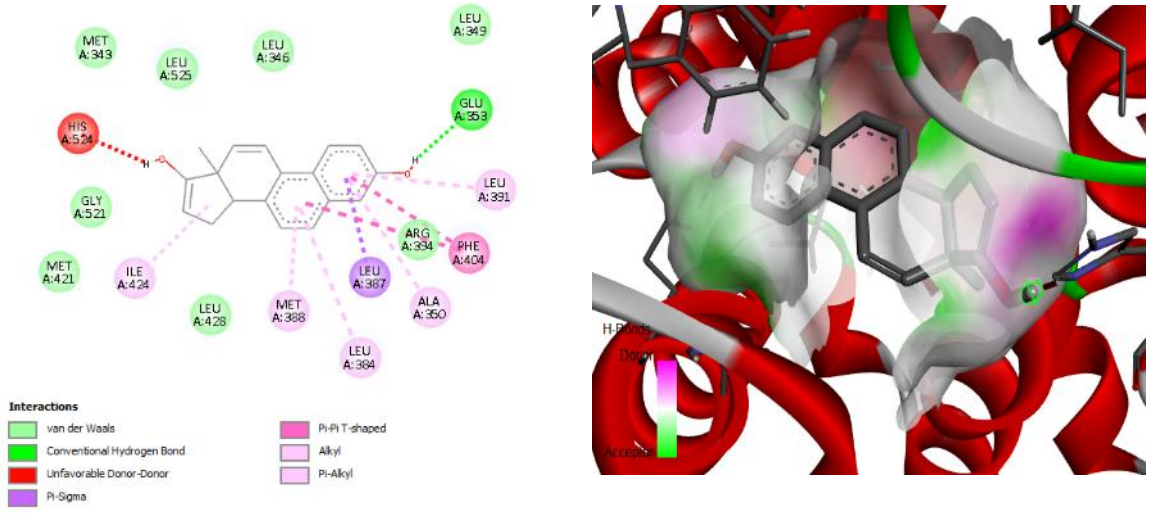

Figure 4. 2D and 3D interactions between ligands and ER-α proteins of the compounds fisetin, nomelidine, tenylidone, and native ligand (a-d).

There is no universally established requirement that a prospective drug candidate must fall within a specific toxicity class. However, according to the GHS classification, toxicity class 5 (oral LD50 >2,000–5,000 mg/kg) is associated with relatively low acute toxicity, whereas class 4 (300–2,000 mg/kg) is categorized as harmful if swallowed, and class 3 (50–300 mg/kg) indicates a comparatively higher degree of acute toxicity [26]. Based on these criteria, kaempferol, tenylidone, and nomelidine, which were classified within toxicity classes 5 and 4 in the present prediction, may be considered for further investigation. Nevertheless, these in silico predictions should be regarded as preliminary assessment tools for lead prioritization and should not be interpreted as definitive evidence of safety. Accordingly, the toxicity predictions generated by ProTox-3.0 should be considered preliminary safety signals that require confirmation through appropriate experimental toxicological studies.

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Table 2. ADMET profiles of the three best compounds against the EGFR and ER-α receptors were evaluated using SwissADME and ProTox-3.0.

Chemical Profile	Ligand Compound*				
	1	**2**	**3**	**4**	**5**
Lipinski's Parameter					
BM (g/mol)	286.24	286.24	303.2	286.41	302.24
Hydrogen Donor	4	4	1	0	5
Hydrogen Acceptor	5/6	5/6	2	1	6/7
LogP	2.28	2.28	3.89	5.03	1.99
ADME					
GI absorption	high	high	high	high	high
BBB permeability	no	no	yes	no	no
P-gp substrate	no	no	no	no	noo
CYP1A2 inhibitor	active	active	inactive	inactive	active
CYP2C19 inhibitor	active	active	inactive	inactive	active
CYP2C9 inhibitor	active	active	active	active	active
CYP2D6 inhibitor	inactive	inactive	active	inactive	inactive
CYP3A4 inhibitor	inactive	inactive	active	inactive	inactive
CYP2E1 inhibitor	inactive	inactive	inactive	inactive	inactive
Skin permeation (Log Kp) cm/dt	-7.06	-6.67	-5.71	-4.86	-7.01
Toxicity					
Hepatoxicity	inactive	inactive	active	inactive	inactive
Carsinogenicity	active	inactive	active	inactive	active
Imunogenicity	inactive	inactive	inactive	inactive	inactive
Mutagenicity	inactive	inactive	inactive	inactive	active
Nephrotoxicity	active	active	inactive	Inactive	active
Neurotoxicity	inactive	inactive	inactive	active	inactive
Respiratory toxicity	active	active	active	inactive	active
LD 50 (mg/kg)	159	3919	341	1000	159
Toxicity class	3	5	4	4	3

**Fisetin (1), Kaempferol (2), Nomelidine (3), Tenylidone (4), Quersetine (5)*

Conclusions

This study identified several potential phytochemical compounds from DG leaves against EGFR and ER-α through molecular docking analysis. Tenylidone was the most promising candidate for EGFR, exhibiting the strongest binding affinity (-8.12 kcal/mol) among the evaluated compounds and interacting with key residues including Met769 and Thr830. Fisetin showed the most favorable binding affinity in ER-α (-8.21 kcal/mol). Among the leading compounds, kaempferol showed the most favorable predicted acute toxicity class of 5 and LD_{50} 0f 3919 mg/kg. Tenylidone has classified toxicity class 4 but still predicted has potential in neurotoxicity. Tenylidone demonstrated the most potentiaal predicted binding profile and need further investigation. These findings provide a basis for subsequent experimental studies to confirm their anticancer activity, mechanism and safety.

This study represents an initial predictive investigation and is subject to limitations inherent to molecular docking, including assuptions regarding protein and ligand structures, molecular flexibility, binding site selection, and scoring functions. The predicted ADMET profiles are computational estimates and should not be considered as definitive evidence of safety. Therefore, experimental validation through in vitro an in vivo studies is essential to confirm the molecular interactions, anticancer activity, pharmacological mechanisms, and safety of the identified candidates.

Conflict of Interest

The authors declare that there is no conflict of interest.

Electronic ISSN : 2656-3088
Homepage: https://www.journal-jps.com

Acknowledgment

The research would not have been possible without the generous financial support from the Ministry of Higher Education, Science and Technology of Republic Indonesia from DPPM under grant number 007/LL6/PL/AL.04/2025, 168.72/A.3-III/LRI/VI/2025 and supported by Badan Amil Zakat Nasional (BASNAZ), Republik of Indonesia.

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