

# Exploring the anticancer potential of scopoletin against HER-2 positive breast cancer: an *in silico* molecular docking study

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**Abstract:** Cancer, defined by the unchecked growth and invasive potential of abnormal cells, remains a global health challenge. Within this context, scopoletin, a compound isolated from the leaves of *Impatiens balsamina* L., has garnered attention for its potential as an anti-breast cancer agent. This study employed *in silico* molecular docking techniques to explore scopoletin's interaction with the HER-2 protein, a known target in breast cancer therapy. The docking analysis revealed that scopoletin exhibits affinity towards the HER-2 protein, with a binding energy of -6.3 kcal/mol. Notably, the binding energy of scopoletin is comparable to that of gefitinib, an established cancer drug, further underscoring its potential therapeutic value.

**Keywords:** scopoletin, anticancer, HER-2, molecular docking

## Introduction

Cancer is defined by the growth of abnormal cells that proliferate uncontrollably, capable of invasion and metastasis across cellular boundaries and tissues. According to Globocan (The Global Cancer Observatory) in 2022, Indonesia witnessed 66,271 new breast cancer cases, constituting 16.2% of the total 408,661 new cancer incidences, with deaths surpassing 242,988 cases [1]. Breast cancer originates as a malignant tumor within the mammary gland's ductal or lobular epithelium [2].

The human epidermal growth factor receptor 2 (HER-2) is crucial for cell proliferation, migration, survival, and growth. Overexpression of HER-2 is linked with aggressive disease progression, increased recurrence rates, and reduced survival, alongside a heightened propensity for brain metastasis in breast cancer cases [3].

*Impatiens balsamina* leaves contain the scopoletin compound, identified for its potential antitumor and anticancer properties, exhibiting promising results [4]. Scopoletin has been shown to mediate the inhibition of ERK1, VEGF-A, and FGF-2 proteins, which is attributed to its antitumor activity, possibly through anti-angiogenic effects [5]. Other study reported scopoletin's impact on breast cancer cell proliferation and metastasis, which is capable of inducing cell

cycle arrest in the G0/G1 phase and enhancing p21 expression [6]. Notably, a concentration of 500 µg/ml of scopoletin resulted in 60.12% ± 3.13% of cells being arrested at the G1 phase over 24 hours, demonstrating significant proliferation inhibition.

This study employs molecular docking, a predictive method for the binding efficacy of macromolecules (receptors) to small molecules (ligands), considering binding sites, energy, conformation, orientation, and molecular interactions [7]. This study aims to investigate the activity of scopoletin from *Impatiens balsamina* leaves against HER-2 in breast cancer, evaluating by affinity energy and bond types.

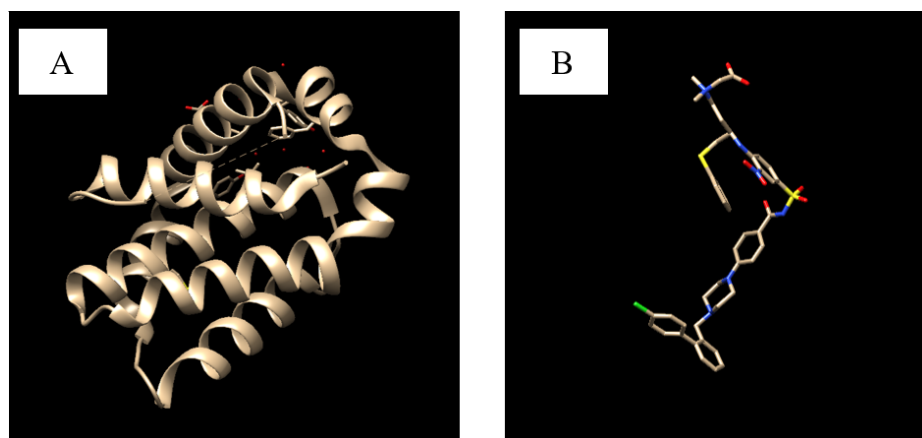
## Methods

### Protein preparation

The HER-2 protein (PDB ID: 3PP0) was retrieved from the RCSB Protein Data Bank (<http://www.rcsb.org/>). Preparation of this target protein was conducted using Chimera version 1.11.1. Initial steps included the removal of water molecules. Subsequently, the native ligand, denoted as 03Q, was separated from the protein sequence to expose the ligand-binding pocket cavity.

### Validation of docking

The molecular docking method was validated using the AutoDock Tools 1.5.6 suite, which includes



**Figure 1.** The result of protein preparation. (A) Structure of prepared HER-2 protein target (B) 03Q native ligand

**Table 1.** The grid box setting on target protein

Protein target	Grid box	
	Grid size	Grid center
HER-2	X = 40 Y = 40 Z = 40	X = 16.387 Y = 17.394 Z = 26.218

**Table 2.** Validation parameters of the target protein and native ligand

Protein Target	Ligand	Conformation	RMSD (Å)	Binding Energy (kcal/mol)
HER-2	03Q	1	2.66	-10.15
		2	1.73	-10.11
		3	0.62	-10.67
		4	2.84	-9.16
		5	0.65	-10.67
		6	1.76	-10.03
		7	5.2	-5.6
		8	1.9	-7.58
		9*	0.47	-10.28
		10	2.68	-7.98

AutoDock4 and AutoGrid4. Validation involved redocking the native ligand 2-{2-[4-({5-chloro-6-[3-(trifluoromethyl)phenoxy]pyridin-3-yl}amino)-5H-pyrrolo[3,2-d]pyrimidin-5-yl]ethoxy}ethanol (03Q) to the prepared HER-2 protein. The validation parameter of the docking protocol was the value of root mean square deviation (RMSD), with an RMSD  $\leq 2$  Å indicating a valid docking approach [8].

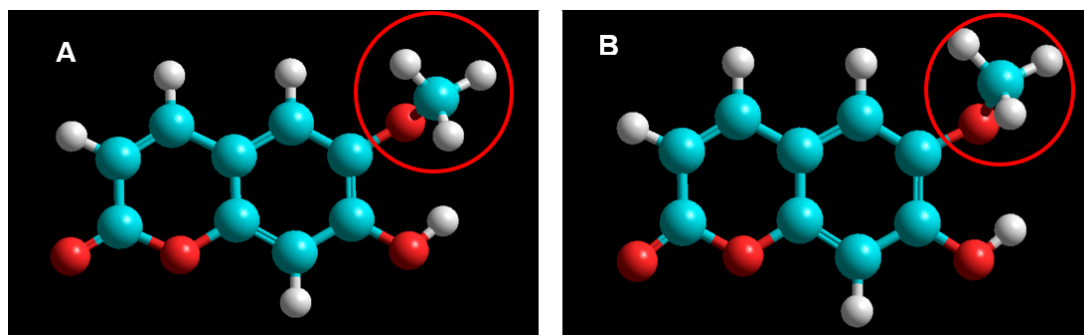
### Compounds structure optimization

The 3D structure of scopoletin was downloaded and optimized using HyperChem version 8. This

optimization utilized the Austin Model 1 (AM1) semi-empirical computational method, including single-point calculations and geometry optimization to refine the molecular structure.

### Docking of test compounds to the HER-2

The optimized scopoletin structure underwent docking against the prepared HER-2 target protein using AutoDock 4.2. This step aimed to identify the conformation exhibiting the lowest binding energy towards HER-2. Analyzed conformations revealed interactions such as hydrogen bonding, Van der Waals



**Figure 2.** 3D structure scopoletin. (A) single point calculation result, and (B) geometry optimization result

**Table 3.** Docking result on HER-2 protein

Ligand	Protein target	Vdw_Hb_Desolv	Elec (kcal/mol)	Binding energy	Amino acid residue
Native ligand	HER-2	-13.58	-0.02	-10.28	Met801
Scopoletin	HER-2	-7.33	-0.19	-6.3	Thr798

forces, hydrophobic interactions, and electrostatics, providing insights into the binding mechanisms of scopoletin to HER-2.

## Results

### Preparation of HER-2 protein target

Preparation of HER-2 target proteins provided with 03Q native ligands (Figure 1).

### Docking validation

The validation of the docking protocol was assessed via the root mean square deviation (RMSD) value. An RMSD value of 0.47 Å was achieved for the HER-2 protein, which is within the valid range (< 2.0 Å), indicating a high degree of accuracy in the redocking process. Furthermore, the interaction between HER-2 and the native ligand, 03Q, revealed a binding energy of -10.28 kcal/mol for the conformation with the lowest RMSD (Table 2).

### Optimization of compound test

The three-dimensional (3D) structure of scopoletin underwent optimization through single-point energy calculations and geometric optimizations. The initial single-point energy calculation yielded a value of 3065.3631 kcal/mol, while the energy of geometric optimization was -3100.4343 kcal/mol. Figures illustrating the 3D structures post-single-point and geometric optimization are provided in Figure 2.

### Docking of scopoletin to HER-2 protein

Docking scopoletin to the HER-2 protein generated ten potential conformations. The conformation with the lowest binding energy, indicative of the most stable interaction, was selected. The binding energy comparisons between the native ligand, 03Q, and scopoletin with the HER-2 protein were recorded at -10.28 kcal/mol and -6.3 kcal/mol, respectively (Table 3). These negative values signify that scopoletin exhibits affinity towards the HER-2 protein, capable of forming stable bonds.

## Discussion

The docking protocol was validated with an RMSD value of 0.47 Å for the HER-2 protein, confirming its reliability within the acceptable range ( $\leq 2.0$  Å). Comparative analysis of binding energies revealed that the native ligand and scopoletin bound to the HER-2 target protein with energies of -10.28 kcal/mol and -6.3 kcal/mol, respectively. Although the binding energy of scopoletin was higher than that of the native ligand, but still has potential as an anticancer agent on target proteins indicated by the negative value of binding energy. This finding suggests scopoletin's potential as an anticancer agent, underscored by its negative binding energy. Furthermore, in the context of other research, gefitinib, a known cancer inhibitor, exhibits a binding energy of -7.05 kcal/mol when targeting HER-2 [9]. The proximity of scopoletin's binding energy to that of gefitinib highlights its promising efficacy.

## Conclusion

Scopoletin demonstrates an affinity for the HER-2 protein, evidenced by its binding energy of -6.3 kcal/mol. This study supports the potential of scopoletin as an anti-breast cancer agent, comparable to established treatments such as gefitinib. The results advocate for further investigation into scopoletin's utility in cancer therapy research, particularly for HER-2-positive breast cancer.

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## Declaration of interest

The authors declare no conflict of interest.

## Contributors

INMPA, NPLL conceptualized the study design; PAKS, MFAP investigated the data, INMPA, PAKS wrote the original draft, INMPA, PAKS, MFAP, NPLL reviewed and edited the final version. All authors have read the final manuscript.

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