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In Silico Study and Pharmacokinetics Prediction of ε-Viniferin Compound as Anticancer Drug Candidate

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ABSTRACT

The ε-Viniferin (ε-VNF) is a resveratrol dimer found in grapes (*Vitis vinifera*) which is thought to have anticarcinogenic activity. Breast cancer is one of the biggest causes of mortality in women. Current conventional chemotherapy can give negative side effects for cancer patients. Therefore, exploration to find an alternative modality is required. HER2 (Human Epidermal Growth Factor Receptor 2) and CDK6 (Cyclin Dependent Kinase 6) are two proteins that play an important role in breast cancer cell proliferation and differentiation. This study aimed to determine the potential of ε-VNF in inhibiting HER2 and CDK6 by molecular docking study. This research was conducted in silico using AutoDockTools v1.5.7 software. The results were validated with PyMOL and visualized in Discovery Studio Visualizer software to see the amino acid residues generated. Prediction of pharmacokinetics and toxicity profiles of the compound were performed with SwissADME and ADMETLab web tools. The results showed that ε-VNF was able to bind to HER2 and CDK6 receptors with binding energies of -10,45 kcal/mol and -7,56 kcal/mol, respectively. In silico pharmacokinetics and toxicity studies showed that ε-VNF fulfills Lipinski's Rule of Five and has the potential to be used as a drug candidate. Overall, the results of this study indicate that ε-VNF has the potential to be further investigated and developed as an anticancer drug candidate through inhibition of HER2 and CDK6 receptors.

***Keywords*:** Breast cancer; Drug discovery; ε-Viniferin; HER2; CDK6

INTRODUCTION

Stilbenoids known as phytoalexins are plant phenolics synthesized as a defense mechanism against microbial infections, toxins, or UV radiation. Stilbenoids are classified in the form of monomers or oligomers. The most popular stilbenoids is resveratrol. The most famous source of stilbenoids comes from *Vitis vinifera*.[1,2] The compound of ε-VNF is a dimer of resveratrol that exhibits antioxidant, anti-inflammatory, anticarcinogenic, and cardioprotective effects in vitro.[3] In vivo study of resveratrol acts as a proteasome inhibitor leading to accumulation of HER2 which triggers cancer growth and proliferation.[4]

Breast cancer is frequently diagnosed cancer with a total of 2.3 million new cases (11.7%). According to American Cancer Society, global cancer burden will be 28.4 million cases in 2040 which is 47% increase over 2020 cancer burden.[5]

HER2 receptor is a membrane tyrosine kinase when activated affects cell proliferation and survival. HER2 oncogene is located on chromosome 17q12.[6] HER2 amplification is the main pathway of HER2 receptor overexpression and cancer tumor progression.[7]

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CDK6 is kinase that plays a major role among other CDKs in mediating the cellular transition from G0/G1 phase to the S phase during the cell cycle. Dysregulation of CDK6 uncontrolled cell division, malignant transformation, and found in most human cancers.[8] The effects of anticancer drugs generally cause oxidative stress, DNA damage, and induction of apoptosis. However, most of these drugs have serious side effects due to cytotoxicity on normal cells. The main chemotherapy classes used in cancer treatment are anthracyclines, antimicrotubular (taxanes), alkylating agents (cyclophosphamide), antimetabolites (5-fluorouracil, capecitabine), platinum (cisplatin), and several other drugs. Despite their proven benefits in patients' quality of life, their side effects and toxicity are influential in left ventricular cardiotoxicity, hematological, reversible alopecia, neurotoxicity, and hand-foot syndrome. These are major concerns that affect treatment outcomes.[9]

Potential chemo-preventive agents should exhibit their antioxidant or cytoprotective effects at lower concentrations than their cytotoxic effects. Meanwhile, chemotherapeutic agents should induce cytostatic and apoptosis of cancer cells at lower concentrations than those are cytotoxic non-proliferating cells.[10]

Molecular docking is a process of interaction between two molecules in three-dimensional space. This method is widely used to predict the binding mode of ligands to proteins. Applications of docking techniques include the prediction of drug binding modes and active screening of compounds.[11,12] However, the studies elucidating the potential role of ε-VNF to inhibit HER2 and CDK6 are still limited. This study aimed to predict the binding potential of the ε-VNF compound to receptors targeted in breast cancer using *in silico* model.

METHODS

Materials and Methods

The equipment are hardware, software, and webserver such as AutoDockTools v1.5.7., PyMOL Educational v4.3.3., OpenBabel v3.0.0, and Discovery Studio Visualizer v21.1.0.20298. Materials used in the form of proteins obtained from Protein Data Bank (PDB) and ligands from PubChem in three-dimensional form.

Procedure

Protein preparation

The structures of HER2 (PDB ID: 3POZ) and CDK6 (PDB ID: 5L2S) target macromolecules were downloaded in PDB file format from RCSB protein data bank (Figure 4). Polar hydrogen and Kollman charges were added to proteins. Considering water molecules are not involved in the receptor-ligand binding process, water molecules were removed. This step of removing water molecules can also significantly improve calculations and prevent possible distortions.[13]

Ligand preparation

The molecular structure of ε-VNF can be seen in Figure 3. The structure was obtained from the PubChem web server, it was downloaded in SDF format, then the ligand was saved in PDB format using OpenBabel software. Ligand was prepared into AutoDockTools v1.5.7. Polar hydrogen and gasteiger charge were added to the ligand.[13]

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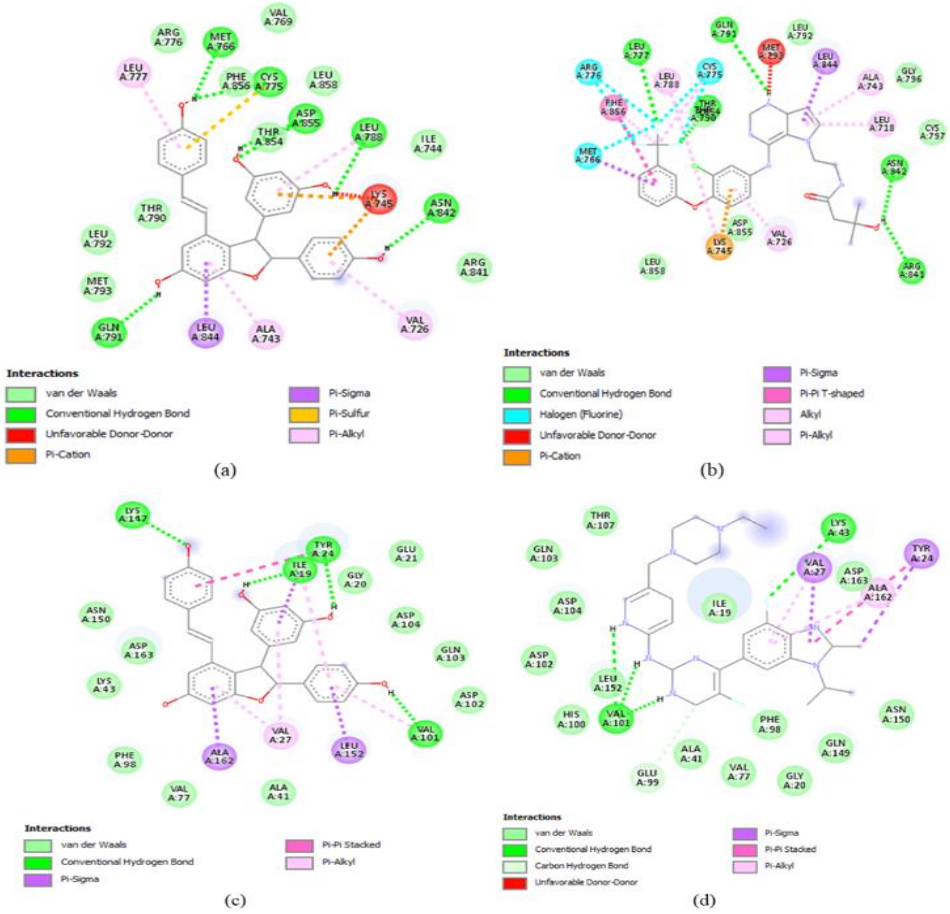

Figure 1. Interaction Proteins Target and Ligand (a) ε-VNF with HER2; (b) Native ligand HER2; (c) ε-VNF with CDK6; (d) Native ligand CDK6

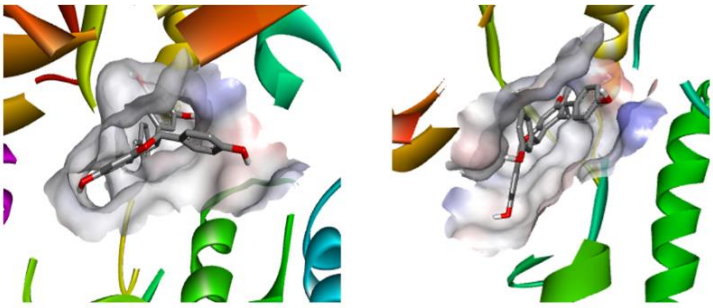

Figure 2. Visualization of Binding Sites (a) ε-VNF with HER2; (b) ε-VNF with CDK6

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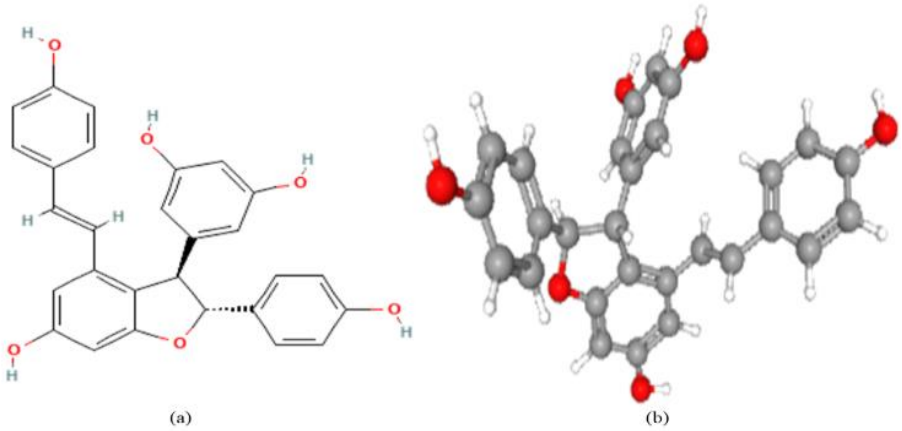

Figure 3. Chemical structure of ε-VNF (a) Two dimensional; (b) Three-dimensional

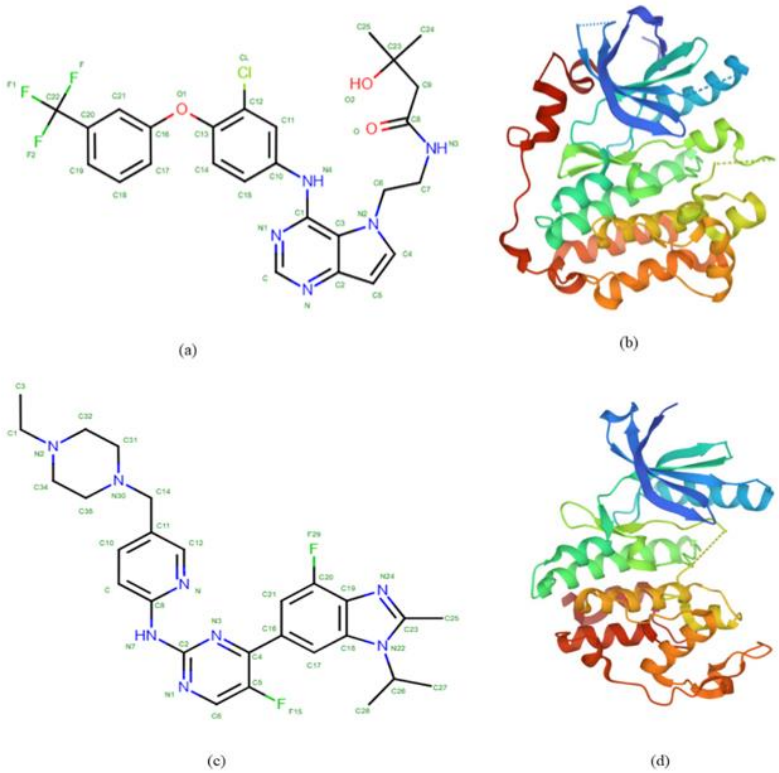

Figure 4. Structure of proteins target (a) Two dimensional 3POZ ligand 03P in HER2; (b) Three-dimensional protein HER2; (c) Two dimensional 5L2S ligand 6ZV in CDK6; (d) Three-dimensional protein CDK6

Validation

Validation was performed on docking results of protein target using PyMOL Educational v4.3.3 software for evaluation of validation through root mean square distance (RMSD) value.[14]

Analysis

Molecular docking was performed using AutoDockTools v.1.5.7. Docking parameters and algorithm were validated from re-docking native ligand to receptor target. Docking parameters were set as default, except the docking process was set as 50 for both tests of ligand and native ligand. Lamarckian Genetic Algorithm (LGA) was generally set to provide the results of molecular docking study.[13]

Visualization

The docked protein-ligand complex was visualized with Discovery Studio Visualizer v21.1.0.20298 software. It can characterize chemical bond interaction between protein target and ligand

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compared to protein target with ligand test.[13]

ADMET prediction

Prediction of pharmacokinetics and toxicity profiles of compounds using ADMETLab v2.0 and SwissADME webserver with canonical SMILES code of the compound.

RESULTS AND DISCUSSION

Most of the research related to ε-VNF compound currently focused on its anticancer activity. Chemical structures (2D and 3D) of ε-VNF are shown in Figure 3. Natural antioxidant properties of ε-VNF are known to have antiproliferative activity, cell cycle arrest in G1 phase and S phase, and induce DNA damage followed by induction of cell death including apoptosis and necrosis.[2] However, data regarding the effectiveness of this compound to inhibit proteins that play an important role in the development of breast cancer cells are still limited, especially through mechanism inhibition of HER2 and CDK6 receptors. This study was focused to explore the potential of ε-VNF inhibiting HER2 and CDK6 which was reported to be over-expression in breast cancer.

The docking protocol was validated through re-docking experiments using native ligands. RMSD value of less than 2Å indicates that confirmation between ligand and receptor has high docking accuracy.[13] Before docking analysis, the structure of the protein target (Figure 4) was validated to ensure deviation during the docking process. Validation results showed HER2 (RMSD = 1.320Å) and CDK6 (RMSD = 0.000Å) proteins have met validation requirements with RMSD values less than 2Å.

The molecular docking of ε-VNF against HER2 (3POZ) and CDK6 (5L2S) receptors obtained using AutoDockTools v1.5.7 is presented in Table 1. The visualization of ε-VNF binding to protein targets is shown in Figure 2. Docking results showed that the compound has the same binding sites as the native ligand. ε-VNF has the ability to occupy the binding pocket of HER2 and CDK6 proteins. The similarity of interaction with amino acid residues suggests that the compound might exhibit inhibitory activity against receptor targets.[14] Based on the results, it was found that ε-VNF against HER2 has the lowest energy required to bind to the targeted receptor compared to CDK6.

Analysis showed that bond position between compound and protein and cluster between hydrogen bond with amino acid as well as bond strength are expressed in the dorm of Gibbs free energy value (ΔG). This value plays a role in parameterizing the strength of the bond with the receptor. Low binding energy value indicates the stability of the interaction between ligand and receptor.[15,16] Binding energy obtained for HER2 was -10,45 kcal/mol, whereas, that of CDK6 was -7,56 kcal/mol. The compound interaction with both targeted receptors has hydrogen bonds. HER2 receptor in Figures 1a and 1b, forms six hydrogen bonds and hydrophobic interaction namely π-sigma bond at LEU A:844, π-alkyl bond at ALA A:743, VAL A:726. Meanwhile, the CDK6 receptor in Figures 1c and 1d, forms three hydrogen bonds and hydrophobic interactions namely the π-alkyl bond at VAL A:27 and π-π stacked bond at TYR A:24. Therefore, comparing the binding energies of two complexes, its presence of hydrophobic interactions for binding affinity is comparable to electrostatic interactions.[17]

In vitro studies show that resveratrol can suppress TGF-β1-induced epithelial–mesenchymal transition (EMT) in human breast cancer cell line MDA-MB-231.[18] ε-VNF is a trans-resveratrol dehydrodimer. However, the anti-EMT effect of ε-VNF has not been well studied.[17] Other studies showed that resveratrol and its natural or synthetic analogs can inhibit tumor cell proliferation, metastasis, epigenetic changes, and apoptosis induction as well as sensitization to chemotherapeutic drugs in various

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Table 1. Molecular Docking and Interaction of Amino Acid Residues of ε-VNF with Proteins Target

Proteins	Ligand	Binding Energy (kcal/ mol)	Interaction Amino Acid Residues	
			Hydrogen	Non-Hydrogen
HER2 (3POZ)	Native ligand	-9,91	Leu777, Gln791, Asn842, Arg841	Ala743, Gly796, Leu718, Cys797, Val726, Asp855, Lys745, Leu858, Met766, Phe856, Arg776, Leu788, Thr790, Thr854, Cys775, Met793, Leu792, Leu844
	ε-VNF	-10,45	Met766, Cys775, Asp855, Leu788, Asn842, Gln791	Leu777, Arg776, Phe856, Val769, Leu858, Thr854, Ile744, Lys745, Arg841, Val726, Ala743, Leu844, Met793, Leu792, Thr790
CDK6 (5L2S)	Native ligand	-8,78	Lys43, Val101	Asn150, Gln149, Gly20, Phe98, Val77, Ala41, Glu99, His100, Leu152, Asp102, Asp104, Gln103, Thr107, Ile19, Val27, Asp163, Ala162, Tyr24
	ε-VNF	-7,56	Lys147, Tyr24, Ile19, Val101	Asn150, Asp163, Lys43, Phe98, Val77, Ala162, Ala41, Val27, Leu152, Asp102, Gln103, Asp104, Gly20, Glu21

in vitro and in vivo models of breast cancer.[20] Resveratrol is considered a phytoestrogen that has both agonist and antagonist effects on estrogen. In several experimental animal models, resveratrol was shown to reduce the incidence of tumor formation in breast glands.[21]

Aberrant signal transduction of ErbB family human epidermal growth factor 2 (HER2) found in many human cancers. HER2 expression predicts the occurrence of recurrence and prognosis of human disease. Inhibitors of small molecule kinase HER2 are used in cancer treatments. Selected crystal structures of the HER2 kinase domain in complex with inhibitors are selective in the mechanism of activation, inhibition, and protein function molecular level. The mechanism of HER2 inhibition guides the design and development of new cancer drugs with improved potency and selectivity.[22,23]

Serine/threonine protein kinases such as CDK4/6 are proteins that have important roles in both physiology and disease states making attractive and challenging drug targets. They regulate the G1 restriction cell cycle checkpoint that maintains genomic integrity for preventing chromosome duplication until necessary proteins are formed. Activation D-type cyclin protein that phosphorylates retinoblastoma protein (pRb) and E2F protein-mediated transcription of cell cycle genes and transcription factors.[24,25]

In breast cancer and normal breast epithelial cells, D-type cyclin and kinases act as key regulators of cell cycle progression, tumor cell formation, and proliferation. Activation of CDK4/6 and D-cyclins influenced by mitogenic signaling pathways including estrogen receptor signaling pathway, receptor tyrosine kinases (RTK), and Pl3K-AKT-mTOR or RAS - RAF - MEK - ERK pathways. Hyperactivation and dysregulation of cyclin D-CDK4/6 components in breast cancer have potential as therapeutic targets. Preclinical and clinical trials prove the beneficial effects of CDK4/6 inhibitors that can target estrogen receptors. CDK inhibitors have potential and selectivity in future kinase-specific drugs design.[26]

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Table 2. Drug Likeness Lipinski's Rule of Five ε-VNF compound with SwissADME

Parameters	Results
Molecular weight (MW)	454,47 g/mol
Hydrogen bond donor (HBD)	5
Hydrogen bond acceptor (HBA)	6
LogP	4,525

To evaluate the chance for ε-VNF to become a marketed drug, we assessed the drug-likeness prediction of ε-VNF. Drug-likeness prediction results are presented in Table 2. The Ro5 (Rule of Five) is designed to predict the bioavailability of molecules.[27] The requirements of Lipinski's Rule of Five are molecular weight less than 500g/mol, hydrogen bond donor not exceeding 5, hydrogen bond acceptor not exceeding 10, and logP value not exceeding 5.[28] The ε-VNF is a resveratrol dimer that fulfills all these parameters. According to the pharmacokinetics analysis of ε-VNF shown in Table 3, this compound has high absorption in the digestive tract. It does not have good permeability to the blood-brain barrier penetration system. In addition, ε-VNF is not a substrate for P-gp, a transporter that acts as a biological barrier that removes toxins and xenobiotics from cells.[27]

Based on the predicted toxicity profile in Table 4, ε-VNF compounds do not cause mutations, liver injury, and carcinogenesis. Overall, from the results of this study, the ε-VNF compound has the potential to be further studied as an anticancer, especially in breast cancer through the inhibition of HER2 and CDK6 proteins.

Table 3. Pharmacokinetics Profile of ε-VNF with SwissADME and ADMETLab

Parameters	Results
Absorption	
GI absorption	High
Blood Brain Barrier penetration	No
P-glycoprotein inhibitor	++
P-glycoprotein substrate	---
Distribution	
Plasma protein binding (PPB)	99,360%
Volume distribution (Vd)	0,816 L/kg
Fraction unbound in plasma (Fu)	1,780%
Metabolism	
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Excretion	
Clearance (Cl)	11,765 mL/min/kg (Moderate)
Half-life ($T_{1/2}$)	0,681 (Long half-life)

Note: Prediction of Probability Value (---)0 - 0,1; (--)0,1 - 0,3; (-)0,3 - 0,5; (+)0,5 - 0,7; (++)0,7 - 0,9; (+++)0,9 - 1,0

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Table 4. Toxicity Profile of ε-VNF with SwissADME and ADMETLab

Parameters	Results
AMES toxicity	--
Carcinogenicity	---
Genotoxic rule	No Alert
NonGenotoxic rule	No Alert
Acute toxicity rule	No Alert
Skin sensitization rule	7 Alerts
Human hepatotoxicity (H-HT)	--
Drug-induced liver injury (DILI)	---
Rat oral acute toxicity	--
Eye corrosion	---
Eye irritation	++
Respiratory toxicity	--

Note: Prediction of Probability Value (---)0 - 0,1; (--)0,1 - 0,3; (-)0,3 - 0,5; (+)0,5 - 0,7; (++)0,7 - 0,9; (+++)0,9 - 1,0

Despite the widespread application of molecular docking studies, it also has limitations, such as incorrect binding sites to target receptors, selection of interaction patterns, uncertainty whether a compound is classified as a true antagonist or agonist, and non-linearity of docking and molecular dynamics simulation.[28] Molecular dynamics simulation was conducted as a further test to see the stability of the binding pattern between ligand and receptor.[29]

CONCLUSION

The ε-VNF compound has the potential to be further developed as a breast anticancer drug candidate through inhibition of HER2 and CDK6 receptors, therefore more research is required.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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