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Original Article

In Silico Studies of Sesquiterpene Lactones from *Vernonia amygdalina* Delile on the Expression of EGFR and VEGFR as a New Anticancer Potential

N Nerdy[1,*], P Lestari[1], F Fahdi[1], EDL Putra[2], SAB Amir[2], F Yusuf[3], TK Bakri[4]

ABSTRACT

Objective: To assess the inhibition activity of sesquiterpene lactones from *Vernonia amygdalina* Delile as a new anticancer potential on the expression of cancer therapeutic target-proteins, namely: epidermal growth factor receptor (EGFR), and vascular endothelial growth factor receptor (VEGFR). **Methods**: The in silico screening, target-based approach (docking) was performed by the Prediction of Activity Spectra for Substances (PASS) website and AutoDock Vina program. The therapeutic cancer target proteins model of EGFR and VEGFR were downloaded from Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank (PDB) with 5HG7 and 4AG8 as their respective codes. **Results**: The test compounds have anticancer activity as predicted by the Prediction of Activity Spectra for Substances (PASS) website and AutoDock Vina program. The molecular docking analysis of the test compounds showed strong interactions and good inhibition activity with the targeted proteins with a low docking score value predicted by the AutoDock Vina program. **Conclusion**: The test compounds have the potential to be used in anticancer drugs through the inhibitory qualities of EGFR and VEGFR.

Key words: *In silico*, Sesquiterpene lactones, EGFR, VEGFR, *Vernonia amygdalina* Delile.

N Nerdy[1,*], P Lestari[1], F Fahdi[1], EDL Putra[2], SAB Amir[2], F Yusuf[3], TK Bakri[4]

[1]Department of Pharmacy, Faculty of Pharmacy, Institut Kesehatan Deli Husada Deli Tua, Deli Tua Timur, Deli Tua, Deli Serdang, Sumatera Utara, INDONESIA.
[2]Department of Pharmacy, Faculty of Pharmacy, Universitas Sumatera Utara, Padang Bulan, Medan Baru, Medan, Sumatera Utara, INDONESIA.
[3]Department of Pharmacy, Sekolah Tinggi Ilmu Kesehatan Arjuna, Pintubosi, Laguboti, Toba Samosir, Sumatera Utara, INDONESIA.
[4]Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala, Kopelma Darussalam, Syiah Kuala, Banda Aceh, Aceh, INDONESIA.

Correspondence

N Nerdy

Department of Pharmacy, Faculty of Pharmacy, Institut Kesehatan Deli Husada Deli Tua, Deli Tua Timur, Deli Tua, Deli Serdang, Sumatera Utara, INDONESIA.

E-mail: nerdy190690@gmail.com

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INTRODUCTION

With millions of deaths in 2020, cancer is one of the top causes of mortality worldwide. Around half of all cancer deaths each year are caused by lung, colorectal, liver, and stomach cancers.[1] Every year, roughly 9 million fatalities and up to 14 million new cases of cancer are recorded worldwide.[2] According to the American Cancer Society, the estimated number of new cancer cases in 2021 was about 2 million, while there were an estimated 1 million cancer deaths in the United States.[3] Thus, any work bringing us closer to more effective treatment is vitally important.

Targeted therapy is very crucial in order to comprehend cancer therapy. Protein kinase is usually a key protein involved in targeted cancer therapy.[4] Radiation therapy, surgery, and systemic chemotherapy are the most common cancer treatments, but are more likely to have clinical efficacy limitations. For example, radiation therapy frequently causes indirect damage to surrounding tissues, resulting in wound complications and surgery that heals poorly; it also may cause microscopic and metastatic disease. Chemotherapy frequently causes systemic toxicity and the development of cancer.[5] Therefore, there is reason to create a better clinical agent with more targeted activities and a lower risk, as well as the ability to reduce adverse effects. Thus, medicines that target more specific tumorigenic pathways are being developed. In this case, the epidermal growth factor receptor (EGFR) and vascular endothelial growth factor receptor (VEGFR) are the main focus for this study.

The EGFR expression in cancer is associated with disease aggressiveness. The activation of EGFR stimulates tumor growth and progression through several mechanisms, namely promoting proliferation, angiogenesis, invasion, metastasis and inhibiting apoptosis, adhesion and differentiation. Therefore, EGFR is a rational target for antitumor strategies.[6] The expression of transcription, mutation and/or gene amplification may be the cause of EGFR activation in tumor cells. The increased protein and transcribed levels of EGFR will correspond to poor prognosis in several cancers such as lung cancer and colorectal cancer.[7]

The VEGFR is known to have a major contribution to angiogenesis. In vitro experiments on capillary endothelial cells have shown that VEGFR is a potential stimulator of angiogenesis because its presence as a growth factor causes endothelial cell proliferation and migration, and even tube formation in capillary junctions.[8] VEGFR has multiple immediate effects on cancer cells.[9] Stimulation of VEGFR signaling could enhance cancer cell growth by being involved in the angiogenesis process which requires solid tumor growth.[10]

Natural products, medicinal plants, and plant-based foods have their own role in the prevention, treatment, and management of cancer.[11] Plants containing secondary metabolites such as alkaloids, flavonoids, saponins, terpenoids, and steroids have shown good anticancer activity *in vitro* and *in vivo*.[12] The *Vernonia amygdalina* Delile is a plant that has many antimicrobial, antidiabetic, antimalarial, and anticancer properties.[13] Several medicinal plants have played a part in cancer prevention, treatment, and management. Plants are a great and consistent source of new anticancer medicines, estimated to be used in more than 60% of all existing anticancer drugs.[14]

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Various active compounds isolated have shown to have anticancer and cytotoxic properties. The sesquiterpene lactones play a main role in the anticancer effect.[15] Preliminary study of pharmacokinetic properties and toxicity properties by *in silico* show good results in absorption, distribution, metabolism, excretion, and toxicity.[16] Despite this encapsulating research, there is no study on molecular interactions between phytoconstituents and proteins implicated in angiogenesis of cancer. Therefore, molecular interactions with EGFR and VEGFR were investigated in this study using *in silico* prediction.

MATERIALS AND METHODS

Materials

The computer used in this study were Omen laptop by Hewlett Packard operating with a Windows 10 system, Intel® Core™ i7-7700HQ processor, 2.81 GHz speed, and 8 GB random access memory.

The software used were the AutoDock Vina program version 4.2, Biovia Discovery Studio Visualizer program version 17.2.0.16349, ChemDraw program version 19.1, and Prediction of Activity Spectra for Substances (PASS) website (http://www.way2drug.com/PASSOnline/index.php).

The molecular structures of the test compounds were vernodalol, vernodalin, vernolepin, vernomygdin, vernolide, and hydroxyvernolide. Also used were standard compounds. Cyclophosphamide was obtained from PubChem website (https://pubchem.ncbi.nlm.nih.gov) in the Simplified Molecular Input Line Entry System (SMILES) format.

The crystal structures of EGFR and VEGFR were obtained from Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank (PDB) website (http://www.rcsb.org/pdb) with protein data bank (PDB) codes of 5HG7 and 4AG8, respectively.

Methods

The preliminary screening for pharmacological activity of test compounds, namely: vernodalol, vernodalin, vernolepin, vernomygdin, vernolide, and hydroxyvernolide also with standard compound, namely: cyclophosphamide were done by inserted the Simplified Molecular Input Line Entry System (SMILES) of the compounds to Prediction of Activity Spectra for Substances (PASS) website.[17]

The three dimensional crystal structures of human EGFR and human VEGFR with their own native ligands were retrieved from the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank (PDB) websitewith protein data bank (PDB) codes of 5HG7 and 4AG8. The native ligands were 630 for human EGFR and AXI for human VEGFR. The consisting natural residues were separated from the proteins using the Biovia Discovery Studio Visualizer.[18] The protein structures were cleaned, water molecules were removed, polar hydrogens were added, Gasteiger charges were calculated, and non-polar hydrogens were merged by AutoDock Vina.[19]

Validation by redocking of the native ligand was performed using AutoDock Vina. The docking simulations were performed, resulting in 10 different conformations of the ligands interacting with the receptor, which were ranked by the value of binding energy. The root mean square deviation (RMSD) of the conformation that gives the lowest binding energy was further calculated by overlapping the native ligand initial conformation and the native ligand redocking conformation.[20]

The test compounds were vernodalol, vernodalin, vernolepin, vernomygdin, vernolide, and hydroxyvernolide and the standard compound was cyclophosphamide. The analysis of these compounds in EGFR and VEGFR were performed using AutoDock Vina. Visualization of the docking results was performed by using Biovia Discovery Studio Visualizer to observe the bond interactions that occur between ligands and receptors, and as well as the residues which are directly involved in the interaction process.[21]

RESULTS AND DISCUSSION

The receptors EGFR and VEGFR used in this study were obtained through the Research Collaboratory for Structural Bioinformatics (RCSB) protein data bank (PDB) website with protein data bank (PDB) codes of 5HG7 and 4AG8. Selection of the receptors were based on experimental data, with the organism name as *Homo sapiens* (human) and resolution values less than 3.0 Å. The resolution value and organism name are the parameters in receptor selection. Molecular docking using a receptor with a lower resolution value will indicate a better receptor stability.[22]

Preliminary pharmacology activity prediction of the test compounds listed above was done by inserting the Simplified Molecular Input Line Entry System (SMILES) of the compounds to Prediction of Activity Spectra for Substances (PASS) website. The pharmacology activity prediction results of test compounds and standard compound can be seen in Table 1.

The results showed that the test compounds have these main pharmacology activities: antineoplastic, apoptosis agonist, and cytostatic. The three main activities of the test compounds have anticancer effects. Antineoplastic drugs are antiproliferative, anticancer drugs that can affect the process of cell division by damaging the deoxyribonucleic acid (DNA) which prevents the development and the spread of cancer cells.[23] Cytostatic effects inhibit and kill cancer cells in the body.[24] Apoptosis is an important mechanism for preventing cancer cell proliferation and serving as one of the control checkpoints in the cell cycle.[25] The test compounds shown the high anticancer activity that were not significantly different than in the standard compound. The compounds that provide anticancer activity with probable activity of more than 0.7 are categorized as active compounds.[26]

Validation of the method and re-docking was done by using the AutoDock Vina program between the original ligand from the crystal structure of respective receptors through the evaluation of the root mean square deviation (RMSD) values. The results of the redocking analysis will give a RMSD values. In this study, the values obtained were 1.7818 Å for EGFR and 1.6819 Å for VEGFR. This means that the method used is accepted according to the standard root mean square deviation (RMSD) value which is less than 2.0 Å.[27]

Molecular docking is one of the in silico techniques which predicts the mechanism of interaction of binding site between a ligand and a

Table 1: The pharmacology activity prediction results of test compounds and standard compound.

Compound	Activity	Probable Activity
Vernodalol	Antineoplastic	0.949
	Apoptosis Agonist	0.748
Vernodalin	Antineoplastic	0.960
	Apoptosis Agonist	0.845
Vernolepin	Antineoplastic	0.960
	Apoptosis Agonist	0.749
Vernomygdin	Antineoplastic	0.967
	Apoptosis Agonist	0.858
	Cytostatic	0.840
Vernolide	Cytostatic	0.948
	Antineoplastic	0.943
	Apoptosis Agonist	0.911
Hydroxyvernolide	Antineoplastic	0.972
	Apoptosis Agonist	0.910
	Cytostatic	0.906
Cyclophosphamide	Antineoplastic	0.996
	Cytostatic	0.917

Figure 1: The distance and interaction of amino acid residue with test compounds and standard compound against EGFR and VEGFR.

*A: vernodalol; B: vernodalin; C: vernolepin; D: vernomygdin; E: vernolide; F: hydroxyvernolide; G: cyclophosphamide; 1: EGFR; 2: VEGFR.

Table 2: The docking score and interaction of amino acid residue with test compounds and standard compound against EGFR and VEGFR.

Protein	Ligand	Docking Score (Kcal per Mol)	Interaction Amino Acid Residue
EGFR	Vernodalol	−6.4	Ala 722, Phe 723, Arg 841, Asn 842,
	Vernodalin	−8.0	Val 726, Met 793, Cys 797, Phe 856
	Vernolepin	−7.9	Ser 720, Gly 796, Cyc 797
	Vernomygdin	−7.6	Gly 719, Gly 796, Cys 797, Arg 841
	Vernolide	−7.8	Leu 718, Gly 719, Cys 797, Arg 841
	Hydroxyvernolide	−7.8	Gly 719, Val 726, Met 793, Gly 796, Leu 844, Phe 856
	Cyclophosphamide	−4.8	Asp 837, Arg 841, Pro 877
VEGFR	Vernodalol	−6.9	His 1026, Asp 2046
	Vernodalin	−7.4	Leu 889, His 1026, Asp 1046, Gly 1048
	Vernolepin	−7.5	Ile 888, Cys 1024, Ile 1025, Asp 1046
	Vernomygdin	−8.0	Leu 1019, His 1026, Ile 1044
	Vernolide	−8.1	Leu 1019, His 1026, Ile 1044, Asp 1046
	Hydroxyvernolide	−7.6	Ile 888, Ile 1025, His 1026, Arg 1027
	Cyclophosphamide	−5.0	Leu 889, Val 898, Val 899, His 1026, Asp 1046

target protein.[28] The affinity of the binding is measured by the value of docking scores. As a potential medication candidate, a molecule with a lower binding energy is always preferred.[29] There are several cell biology markers associated with apoptosis and angiogenesis, including EGFR and VEGFR.[30] Activation of EGFR and VEGFR will induce various important cellular responses such as increased angiogenesis, increased tumor survival, increased cell proliferation, decreased apoptosis, increased invasion and increased metastasis.[31] Both EGFR and VEGFR have the potential ability to repair the DNA of tumor cells damaged by chemotherapy.[32] Thus, the success of cancer treatment can be increased by inhibiting EGFR and VEGFR.[33]

The test compounds were docked with EGFR and VEGFR to obtain the docking score values with AutoDock Vina. These docking score values were compared to the standard compound. This was done to compare whether the test compounds have a better or worse activity compared to the standard compound. Table 2 showed the docking score and interaction of amino acid residue with the test compounds and standard compound against EGFR and VEGFR. Figure 1 shows the distance and interaction of amino acid residue with the test compounds and standard compound against EGFR and VEGFR.

The results showed that the overall docking scores of test compounds against EGFR and VEGFR were lower than the docking score of the standard anticancer drug (cyclophosphamide). This phenomenon also shows that test compounds have better activity of inhibition of EGFR and VEGFR compared to standard compound. The value of free energy produced when the receptor-ligand complex that is formed can indicate the affinity of the ligand for the receptor. If the affinity of the ligand to the receptor is high, the free energy value or docking score decreases. Alternatively, if the affinity is small, the free energy value or docking score increases.[34]

The results showed that various amino acid residues on the EGFR and VEGFR have interactions with test compounds and standard compound against EGFR and VEGFR. The overall interaction has a distance between the ligand and the amino acid residue of the receptor which is less than 6.0 Å. A distance of less than 12.0 Å indicates a good interaction between the ligand and the amino acid residue of the receptor.[35]

Cyclophosphamide is often used as first-line cancer therapy.[36] The existence of side effects from the use of chemotherapy drugs and resistance of cancer cells to chemotherapy drugs is a challenge in cancer treatment.[37] Serious problems in side effects and resistance to chemotherapy drugs drive the need for new chemotherapy drugs that are safer and more effective.[38] The search for anticancer drugs from natural ingredients has great potential for the discovery of new treatment options. The results showed that the use of natural ingredients had lower side effects and could still optimize the selectivity of cancer treatment.[39] Extracts of natural ingredients contain various phytochemicals in varying amounts, and have been shown to have a synergistic effect. Thus, the expected minimal dose or concentration can provide maximum effect.[40]

CONCLUSION

The intention of this study is to discover a potent inhibitor of EGFR and VEGFR expression as a possible anticancer targeted therapy through *in silico* methods. The results of this study show that the binding energy as well as interactions of test compounds with EGFR and VEGFR were promising for future research for their use in anticancer drugs. This research can be continued by carrying out *in vitro* and *in vivo* investigations to confirm the physiological implications of these findings.

AUTHORS CONTRIBUTION

Contribution of the authors in: conceptualization, N.N. and S.A.b.A.; methodology, N.N. and S.A.b.A.; resources, N.N. and S.A.b.A.; writing the original draft preparation, N.N. and S.A.b.A.; writing the review and editing, N.N.; visualization, N.N.; supervision, E.D.P.; project administration, F.F., P.L. and F.Y.; funding acquisition, N.N., P.L., S.A.b.A. and F.Y. All authors have read and agreed to the published version of the manuscript.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest in this research and no conflicts of interest in this manuscript.

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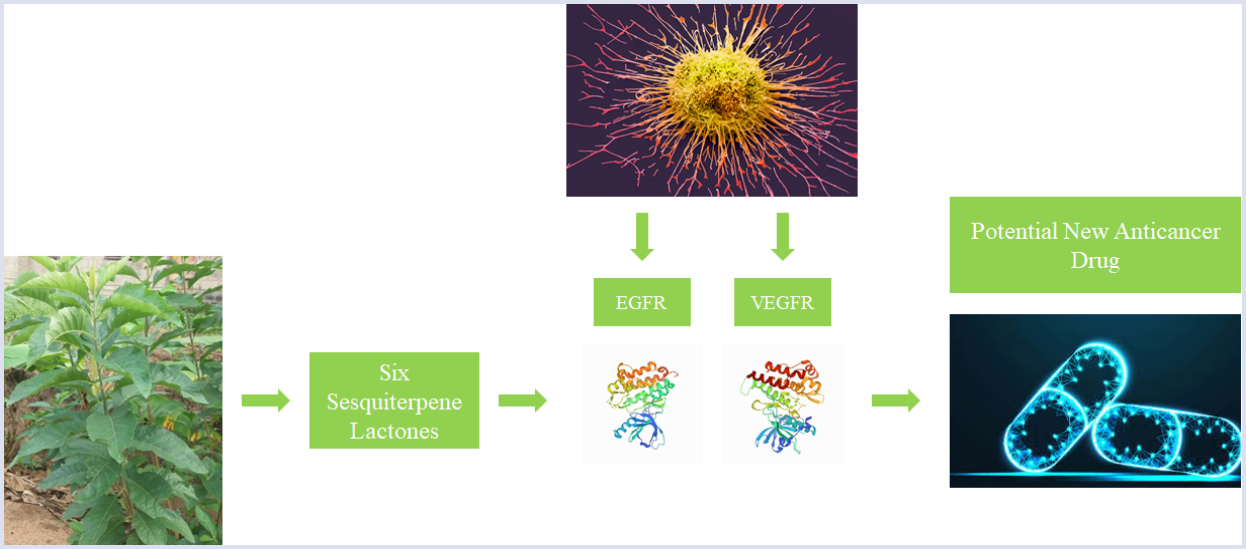
GRAPHICAL ABSTRACT



ABOUT AUTHORS

Nerdy Nerdy has been a doctoral in the pharmaceutical field and associate professor at the Faculty of Pharmacy, Institut Kesehatan Deli Husada Deli Tua since 2019. His research fields are pharmaceutical chemistry, biology, technology, and pharmacology.

Puji Lestari is a Bachelor of Pharmacy and a master of science from Universitas Sumatera Utara. She joined the Faculty of Pharmacy, Institut Kesehatan Deli Husada Deli Tua in 2019 as a lecturer in pharmacology and toxicology.

Firdaus Fahdi is a lecturer at the Faculty of Pharmacy, Institut Kesehatan Deli Husada Deli Tua. His research scope ranges from pharmacology to natural product and biology pharmacy.

Effendy De Lux Putra is a professor at the Faculty of Pharmacy Universitas Sumatera Utara. His research field is pharmaceutical chemistry, especially pharmaceutical analysis and medicinal chemistry.

Siti Amira Binti Amir is a student at Faculty of Pharmacy, Universitas Sumatera Utara. Her research field is the pharmaceutical analysis and medicinal chemistry.

Faisal Yusuf is a pharmacist and a Master of Management degree; currently, the research focuses on developing a product from natural products and the management of pharmaceutical products. He joined the Faculty of Pharmacy, STiKes Arjuna Laguboti as lecturer of pharmacy.

Tedy Kurniawan Bakri is a lecturer at the Department of Pharmacy, Faculty of Mathematics and Natural Sciences, Universitas Syiah Kuala. He also serves as a clinical pharmacist in Aceh Mental Hospital. His research scope ranges from pharmacology to clinical pharmacy.

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