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Computational Study of Veronicasroside and Vicenin-2 Ethanol Extracts from *Paraboea* Sp Leaves as EGFR Inhibitors

Fujiati[1]*, Joharman[2], Maria Ulfah[3], Nina Mulyani[4], William Luth[5], Andifa Anugerah Putra[6]
[1]Doctoral Program of Medical Science, Faculty of Medicine and Health Science, Universitas Lambung Mangkurat, Banjarmasin, South Kalimantan, Indonesia
[2,3,4,5]Undergraduate medical study program, Faculty of Medicine and Health Science, Universitas Lambung Mangkurat, Banjarmasin, South Kalimantan, Indonesia
[6]Faculty of Mathematics and Natural Sciences, Universitas Lambung Mangkurat, Banjarmasin, South Kalimantan, Indonesia
Corresponding Author: Fujiati dr.fujiati@ulm.ac.id

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A B S T R A C T
Paraboea sp., commonly known as limestone mistletoe, is widely distributed in the limestone mountainous region of Batulicin, South Kalimantan, and has been traditionally used by local communities as an anticancer remedy. However, scientific investigations on its secondary metabolites with potential anticancer activity remain limited. This study aimed to computationally explore the anticancer potential of secondary metabolites from *Paraboea* sp. leaves by evaluating their interactions with the epidermal growth factor receptor (EGFR). Molecular docking simulations were performed to predict the binding affinity and interaction stability of two selected secondary metabolites, veronicastroside and vicenin-2, against EGFR. The results revealed that both compounds exhibited favorable interactions with EGFR, with binding energies of −10.0 kcal/mol for veronicastroside and −9.0 kcal/mol for vicenin-2. The root mean square deviation (RMSD) values of the veronicastroside–EGFR and vicenin-2–EGFR complexes were 1.32 Å and 1.98 Å, respectively, indicating stable binding conformations. These findings suggest that veronicastroside, in particular, has promising potential for further development as an ethnomedicine-based supplement to support cancer health management.

INTRODUCTION

Cancer is a non-communicable disease that poses a global health burden. There were 19.3 million new cases of cancer in 2020. Cancer deaths are expected to continue to rise, reaching over 13.1 million by 2030 (Gondhowiardjo et al., 2021). Therefore, research leading to new discoveries to treat this disease is crucial.

Searching for alternative sources of new anticancer drugs from natural ingredients is necessary, given the relatively high cost of synthetic and modern drug treatments (Rahayu et al., 2021). One way to do this is by exploring local ethno-medicinal plants that have been used for generations (Radam et al., 2016).

Local communities possess a wealth of ethnomedicinal knowledge from the plants around them. However, this knowledge is acquired only through experience. verbal or personal (Omac et al., 2021). This provides the basis for scientific evidence supporting *Paraboea* sp. as a supplement to improve the health of cancer patients.

This study was conducted to explore the potential of secondary metabolites. *Paraboea* sp. leaves as a supplement for cancer patients through computational/molecular docking studies with target proteins related to cancer cellular regulation. The results of this study are expected to provide a basis for further clinical research, allowing *Paraboea* sp. leaves to be used as a supplement to improve public health.

LITERATURE REVIEW

Secondary metabolites from plants are significantly related topreventing cancer development (Mahmod et al., 2022). These therapeutic molecules serve as an important source of new drugs that interfere with cell proliferation, apoptosis, metastasis, and angiogenesis by regulating signaling pathways. These molecules affect several cellular signaling cascades, including EGFR, and are thus involved in the therapeutic management of cancer.

Cellular signaling pathways are complex signaling systems that regulate and manage key biological processes. Tumor cells often exhibit alterations in different cellular pathways as a result of complex cell signaling interactions. The epidermal growth factor receptor (EGFR) through the STAT3 pathway can promote cancer cell proliferation and invasion (Song et al., 2020). ERK is activated through EGFR in cancer, which is associated with inhibition of apoptosis. EGFR stimulates cellular signaling, including the MAPK, PI3K/AKT, and STAT3 pathways. The RAS/MEK and PI3K pathways are linked to cell proliferation and apoptosis (Zhu et al., 2021). Disruptions in these pathways have been found in tumor cells, promoting cancer cell growth and inhibiting apoptosis..

Plant secondary metabolites are beneficial for various disease conditions by regulating numerous cellular and molecular pathways, including the regulation of inflammation, metabolic disorders, redox potential, and apoptosis.Plant secondary metabolites significantly stimulate cell death in several types of cancer by inhibiting the activity of the JAK/STAT

pathway and activating apoptosis, which stimulates cell death by preventing STAT3 activation and downregulating survivin and Mcl-1 (Seca et al., 2018 & , Martínez-García et al., 2019). Polyphenols have been shown to have regulatory effects on MAPK signaling. Some phytochemicals exhibit dual control over this signaling pathway by inhibiting the activation of the MAPK pathway associated with cell proliferation and affecting MAPK-related apoptosis.

GC-MS analysis results show that infusions and ethanol extracts of *Paraboea* sp. leaves contain important secondary metabolites such as polyphenols, flavonoids, triterpenoids, and others (Fujiati et al., 2023; Fujiati & Joharman, 2022). Plants that contain the same compounds as *Paraboea* sp. leaves has been proven as an anti-cancer study on Gesneriaceae plants with the *Paraboea martinii* species containing phenylethanolic glycosides significantly reduced damage induced by Aβ1-42 (Bharath et al., 2021 & Gismondi et al., 2020).

Molecular docking is a computational simulation that describes the binding of a ligand (small molecule) to a receptor (target protein). This technique helps predict the affinity and binding activity of molecules to target proteins. Currently, docking is used to predict binding parameters and complexity between receptors and ligands in advance. In this case, biological testing should be performed only with the most promising molecules, resulting in lower costs and shorter development times. Molecular docking serves as a foundation for in vitro and in vivo research.

METHODOLOGY

Types of research

This research was exploratory in nature. Extraction was conducted at the Pharmacology Laboratory, Faculty of Medicine, ULM. Metabolite profiling analysis was conducted at the Forensic Laboratory, Criminal Investigation Agency, Republic of Indonesia Police, Bogor Regency, West Java.

Drugs, Chemicals And Reagents

Chemicals for maceration came from CV. Chemedline Laboratory and Edomedia Banjarmasin), methanol (hypergrade for UPLC), formic acid (ultrapure for UPLC), acetonitrile (hypergrade for UPLC), and 0.05% water injection for UPLC from Puslabfor Bogor Regency, West Java.

Extract Preparation

Extraction of *Paraboea* sp leaves using the maceration method. A total of 330 grams of finely ground *Paraboea* sp leaf simplicia was placed into a maceration jar, 1.5 L of 70% ethanol was added, and stirred until all the simplicia was dissolved completely moistened and submerged, tightly closed and stored for 72 hours. After 72 hours, the extract was filtered, the filtrate was collected and the dregs were added again with 1.5 L of 70% ethanol, repeated up to 3 times. Then the ethanol was evaporated using a rotary evaporator at a temperature of 500C, then evaporated in a water bath until a

thick extract of *Paraboea* sp. leaves was obtained. The ethanol extract was weighed and its concentration was calculated against the weight of the simplex (Fujiati et al., 2022).

Metabolite Profiling of Ethanol Extract of Paraboea Sp Leaves with LC-MS/MS

Based on a modified procedure. A 1 mg subfraction sample was weighed and dissolved in 1 ml of methanol. 5 µl of the subfraction in methanol was injected into the sample holder and entered the UPLC-MS/MS column (replication was done 4 times) through a C18 column (1.8 µm 2.1x100 mm) HSS. The eluent used was a mixture of A) water:formic acid (99.9:0.1) and (B) acetonitrile:formic acid (99.9:0.1) with a gradient elution system. Eluted with a flow rate of 0.2 ml/min. The ions that have been produced by the detector will then be separated by the Q-ToF analyzer. The chromatogram with polar compounds will appear first, followed by compounds with lower polarity. The separation results are then read by a QToF-MS detector, resulting in chromatogram peaks. The chromatogram peaks are then interpreted using the Masslynx application (Hakim et al. 2018).

Molecular Docking

The study was conducted computationally using a virtual screening method of selected secondary metabolite compounds from *Paraboea* sp. leaves against the EFGR target protein. A collection of ligand compounds, veronicastroside (CID: Veronicastroside), and Vicenin-2 (CID: 3084407), was downloaded from the PubChem database. (http://pubchem.ncbi.nlm.nih.gov/)and stored in 3D format. The epidermal growth factor receptor (EFGR) protein (PDB ID: 1IVO). This protein structure can be downloaded from the RCSB PDB website (https://www.rcsb.org/).Molecular docking using AutoDock 4 and visualized with Discovery Studio Visualizer (DSV) involves a series of steps to predict the binding mode and affinity between a ligand and a receptor protein. This method combines computational algorithms with visualization tools to aid analysis and interpretation of docking results. Each ligand will interact with the protein in a blind docking process. After molecular docking is complete, binding affinity (Kcal/mol) and Root Mean Square Deviation (RMSD) values are obtained, which provide a potential ligand-protein binding model.

RESEARCH RESULT

Metabolite Profile of Ethanol Extract of Paraboea Sp Leaves

Metabolite profile analysis of ethanol extract from *Paraboea* sp leaves (EEPL) in this study used "Ultra High Performance Liquid Chromatography-Mass Spectrometry" (UPLC-MS). According to data obtained from the interpretation of chemical content analysis carried out by UPLC-MS. Figure 1 displays the EEPL spectrum.

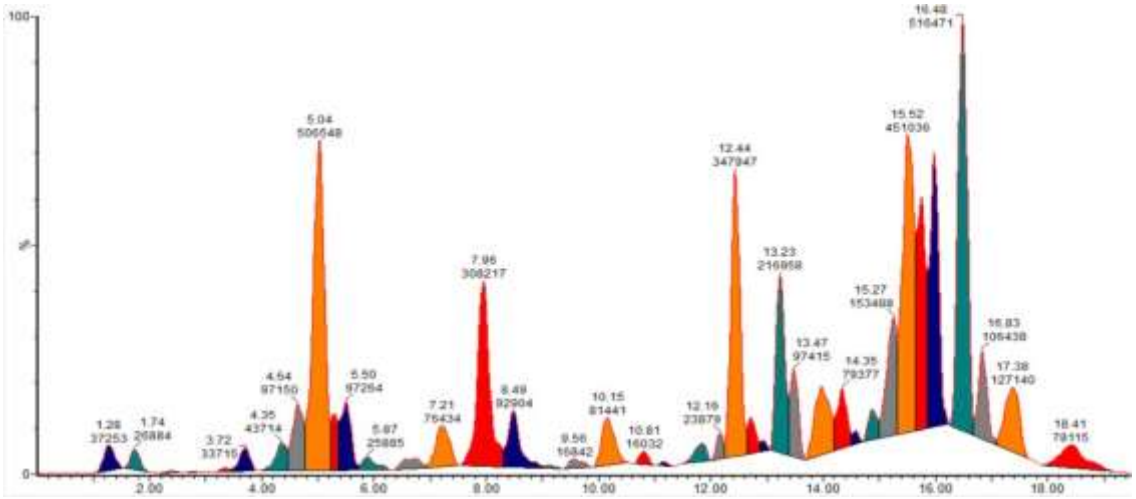

Figure 1. UPLC-MS chromatogram of ethanol extract of paraboea sp leaves

UPLC-MS/MS analysis showed that the major compound that could be predicted in the ethanol extract of *Paraboea* sp leaves was veronicastroside or vicenin-2 (% area: 25, R/T: 5.04, RM: C27H30O15, M/Z: 594.5 gram/mol).

Molecular docking

Molecular docking data, namely binding affinity and RMSD values in the table 1. The 3D visualization results are shown in Figure 2.

Table 1. Molecular docking results

Target Protein	**Ligand**	**Binding Affinity (Kcal/mol)**	**RMSD (Å)**
EGFR	Veronicastroside	-10.0	1,310
	Vicenin-2	-9.0	1,981

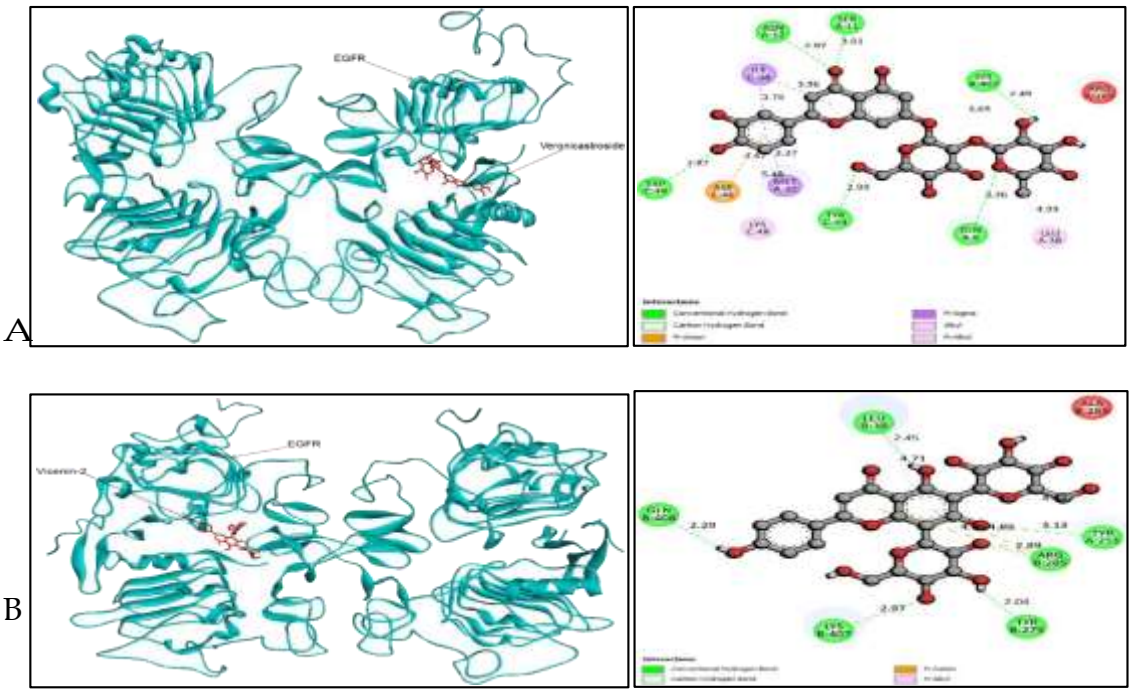

Figure 2. Visualization of protein docking - ligand: A. EGFR - Veronicastroside, B. EGFR -Vicenin-2 using Discovery Studio Visualizer

Table 2. Visualization results of EGFR docking with Veronicastroside and Vicenin-2

Target Protein	Ligand	Types ofBonds	Amino acids
EGFR	Veronicastroside	Hydrophobic	AspC:46, IleC:38, leuA:38, LysC:48, MetA:20
		Hydrogen	AsnA:12, GlnA:8, LysA:207, SerA:11, TrpA:49, TyrC:44
Vicenin-2		Hydrogen	ArgB:285, GlnB:408, LeuB: 38, LysB:407,TyrA:251 TyrB:275

DISCUSSION

LC-MS Analysis

The results of the identification of compounds in the ethanol extract of *Paraboea* sp. leaves using LC-MS are in the form of a chromatogram and molecular weight of the compound. The chromatogram results show that there is a compound identified with the largest area, namely veronicastroside or vicenin-2 with a molecular weight of 594.5 grams/mol identified at a retention time of 5.04 minutes as the compound with the largest abundance, which has an area of 25%. This indicates that the veronicastroside or vicenin-2 compound is present in large quantities in Paraboes sp. leaves. Veronicastroside (Luteolin-7-rutinoside) is a phenolic compound that has been proven to be antibacterial against foodborne pathogens (Zhang et al., 2023). Other studies have proven luteolin-7-rutinoside extracted from plants as an antiradical and a strong

reducing agent (Saunoriūtė et al., 2023). Saunoriūtė The compound vicenin-2 belongs to the flavone group that has anticancer activity in non-small cell lung carcinoma (Yapanto, 2022). In addition, Vicenin-2 has anti-inflammatory activity. Vicenin-2 has been shown in vitro to negatively regulate cytokine secretion (TNF-α and IL-1β) and increase the expression of IL-10 and IL-1Ra in LPS-induced mononuclear cells. Furthermore, vicenin-2 inhibits the activity of the inflammatory transcription factor NF-κB and increases homodimerization of the transcription factor P50 subunit through heterodimerization of P50/P65 (Chagas et al., 2022). Another study conducted by Mouna et al (2022) showed that the compound vicenin-2 can arrest the cell cycle and induce apoptosis.

Molecular Docking

Based on the results of molecular docking of 2 types of compounds from *Paraboea* sp leaf extract showed inhibitory activity against EGFR, STAT3, and MAPK1 proteins at certain amino acid positions.

The extracellular region of EGFR contains four domains: Domain I (amino acids 1–165), domain II (amino acids 165–310), domain III (amino acids 310–480), and domain IV (amino acids 480–620). Veronicastronide forms hydrophobic bonds and hydrogen bonds primarily in domain I at amino acid positions (1–165) of the extracellular region. Vicenin-2 is more likely to form hydrogen bonds in domains 2 and 3 of the extracellular region of EGFR. These two types of bonds are key factors in stabilizing the ligand with its energy preference, in the conformational environment of the open protein structure. Hydrophobic interactions between ligands and target proteins increase the binding affinity between the drug/ligand-protein interface. The binding affinity and effectiveness of ligands related to hydrophobic interactions can be optimized by combining at the hydrogen bond sites. Increasing the number of hydrophobic atoms in the active core of the ligand-protein interface further enhances the biological activity of the ligand.

The second target protein of both ligands is STAT3. The STAT3 protein consists ofof 770 amino acids and is characterized by the presence of 6 functional domains, the amino-terminal domain (NH2), the coiled-coil domain (CCD), the DNA-binding domain (DBD), the linker domain, the SRC homology 2 (SH2) domain, and the carboxyl-terminal transactivation. The results of the in silico analysis explain that two superior compounds of Paraboea sp. leaf ethanol extract can function as inhibitors of EGFR, STAT3, and MAPK1, namely, veronicastronide, and vicenin-2. The binding affinity values that bind them are favorable. The low binding free energy values of both compounds on the three target proteins mean that binding between the ligand and the target molecule is easy, resulting in strong inhibitory activity of EGFR, STAT3, and MAPK1. The more negative the binding energy, the stronger the ligand in binding to the active site of the receptor. Therefore, it is estimated that compounds with higher binding values will have stronger biological activity because they can bind to the target ligand and molecule.

RMSD is used as a parameter to assess the similarity between the docked ligand and the crystallographic results. A very small value indicates

the position of the binding between the standard ligand-protein complex and the validated ligand-protein complex in each precision replicate (Luthfia et al., 2021). According to Kheldafaoui et al. (2020), a Gibbs free energy value of less than or equal to -7 kcal/mol and an RMSD of less than 2 Å are the best scoring criteria for validating molecular docking results.

Hydrogen bond analysis

Hydrogen and hydrophobic bonds play a crucial role in ligand binding to EGFR. The hydrogen bonds formed during the simulation were calculated using the H_bond module of gromacs 5.1.1. Initially, a file containing the hydrogen atom indexes present in the binding sites was created, and then the H_bond command-line module was implemented to calculate the hydrogen bonds formed by each complex studied. The hydrogen bonds formed by Veronicastronide and vicenin-2 with EGFR during the MD simulation were found to be 6 each (Roberts & O'Connell, 2010; Khan et al., 2020).

Simulation stability

The structural stability of the complex in the simulation was assessed using RMSD. RMSD values were determined from the backbone atom X-ray coordinates and the ligand-EGFR binding free energies. Table 1 shows the RMSD distributions of the veronicastroside–EGFR and vicenin-2–EGFR complexes, calculated from 50 replicates in a single MD simulation. The average RMSD, energy, and entropy of the same time point across all replicates are provided in the electronic supplementary material. The backbone atom coordinates from the EGFR crystal structure (PDB id 2J6M) were used for all RMSD calculations (Khan et al., 2020). The RMSD and energy for the Gefitinib–EGFR complex exhibited similar behavior to those of veronicastroside–EGFR and vicenin-2–EGFR (data not shown).

Simulations show reasonable distributions for structural deviations (RMSDs) and binding free energies (ΔGcalc). The backbone atoms of different ligand-EGFR complexes show similar deviations from the X-ray structure. The RMSD distribution for the backbone atoms is approximately normal, i.e. veronicastroside-EGFR is 1.31 Å and vicenin-2 is 1.98 Å. Values >2 Å are due to variability in protein flexibility.

CONCLUSIONS AND RECOMMENDATIONS

Computational research offers promising prospects in drug development for cancer therapy, including predicting drug sensitivity and resistance at the genotype level. Molecular docking performed on a federated high-performance computing grid featuring a petascale supercomputer was used in this study to correctly rank the binding affinities of veronicastroside and vicenin-2 from the ethanol extract of *Paraboea* sp. leaves with EGFR.

Free energy analysis revealed that the binding specificityEGFR inhibitor activity is largely determined by the total electrostatic interaction, and the binding strength is determined by the bonding interactions that occur, which provides a clear explanation of the drug's effectiveness. This method is able to

determine the binding affinity ranking of a drug with EGFR, as well as the drug's efficacy against a single EGFR sequence. From the binding affinity and RMSD values, the effectiveness of secondary metabolites/ligands of candidate cancer drugs can be predicted. Two candidate secondary metabolites from the ethanol extract of *Paraboea* sp. leaves that have the potential to be continued as anti-cancer candidates are veronicastroside.

ADVANCED RESEARCH

This research is the basis for continuing with in vitro and in vivo anticancer tests.

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