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Integrating network pharmacology and molecular docking to assess *Catharanthus roseus* as a natural alternative for leukemia therapy

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Leukemia is a cancer caused by abnormal proliferation of leukocyte cells. Conventional treatments, although effective, often cause serious side effects. This study aims to explore the potential of *Catharanthus roseus* as an alternative therapy for leukemia using network pharmacology and molecular docking approaches. The active compounds of this plant were analyzed and mapped against leukemia biological targets using the PubChem, GeneCards, and KEGG databases. The interaction of compounds with targets was further analyzed through network visualization using Cytoscape and interaction validation was carried out using the molecular docking method using AutoDock4 software. Based on the target search results, 132 targets were found that were relevant to leukemia. PPI analysis showed a relationship between mTOR, HSP90AB1, and MAPK1 proteins with leukemia. Validation of the docking method showed good interaction between active compounds and targets, with an RMSD value of <2 Å. Docking simulations revealed that vindoline has good target binding energies. These results indicate the potential of *Catharanthus roseus* compounds as leukemia therapies, especially vindoline, which shows optimal interaction with key targets.

Keywords: Anticancer, Alternative therapy, *In silico* study, Leukemia disease

Leukemia is a type of cancer characterized by hyperproliferation cell leukocytes that cause expansion clonal in bone marrow bone[1]. This disease divided into a number of type main, including lymphocytic leukemia chronic (CLL), myelocytic leukemia chronic lymphocytic leukemia (CML), acute (ALL), and myelocytic leukemia acute leukemia (AML)[2]. Globally, leukemia has recorded 474,519 cases in 2020, with children average age 11 years becoming the most frequent group diagnosed[3]. In addition, leukemia also becomes the main death consequence of cancer, especially in individuals age carry on with comorbid, which reaches incidence as many as 311,594 cases in the same year[4]. Main risk factors that can increase the possibility somebody suffering from leukemia include a history family with cancer blood, exposure radiation, exposure material chemistry like benzene, and certain viral infections[5].

Leukemia begins from mutation genetics in cells myeloid and lymphoid precursors that disrupt the normal process of hematopoiesis. As a result, the cells blood produced become not perfect and hinder normal body functions, which causes symptompslike fever, bleeding, and lymphadenopathy[6]. Treatment for leukemia at the moment covers radiotherapy, transplantation marrow bones, and chemotherapy with use targeted drugs such as tyrosine kinase inhibitors (TKIs), BCL-2 inhibitors, and PI3K inhibitors[7]. Although treatment this shows level sufficient success, good, therapies this is also often accompanied by significant side effects, such as decline resistance medicine, decrease function immunity body, as well as organ damage[8]. The latest research shows potential treatment with targeting PTPN11 and MAPK to increase effectiveness therapy in elderly patients, while other research revealed potential combination of TKI for increase quality life leukemia patients[9,10]. This results underlies further research in the development of leukemia therapy using more multi-target agents that are easy to access, such as herbal plants.

Catharanthus roseus, is many herbal plants found in countries with climate tropical such as Asia, Africa,

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and South America, have long been known own various benefit drugs, including as analgesic, antihypertensive, antidiabetic, anti-inflammatory, and anticancer[11]. Many previous study have shown activity anticancer from *Catharanthus roseus,* including his ability to hinder growth of cancer lung, cancer cervical, and lymphocytic leukemia acute (ALL) *in vitro* study[11]. Potential anticancer this plant relates with his ability to enhance apoptosis and regulation cycle cell[12]. The alkaloid compounds contained in *Catharanthus roseus,* such as vinblastine, vincristine, and vindoline, have long been used in treatment of cancer, including leukemia[13]. However, although there is supporting evidence regarding the potential of this plant as a cancer therapy agent, its use still requires further research to optimize its effectiveness in treating leukemia.

Based on this background, this research aimsto explore potential *Catharanthus roseus* as alternative therapy for advanced leukemia that is more effective compared to conventional treatment. The network pharmacology approach will be used for analysing connection between compounds in *Catharanthus roseus* and the pathogenesis of leukemia, as well as for identifying relevant treatment targets[14]. In addition, the molecular docking test method will apply to verify strength binding energy between compounds and the target of treatment, which is expected to open a road for development of more leukemia therapy safe and effective[15].

Materials and Methods

Candidates and targets of *Catharanthus roseus*

This study used compounds identified as active through HPLC-MS technique by Zweil[16]. The five main compounds found were vinblastine, catharanthine, tryptophan, vindoline, and vincristine[16]. The five compound the then entered to in PubChem (https://pubchem.ncbi.nlm.nih.gov/) for to obtain structure chemistry and information Simplified Molecular Input Line Entry System(SMILES), which is a digital representation of structure molecule chemistry. After that, SMILES information was used to get potential targets by accessing the Super-PRED website (https://prediction.charite.de/), which allows prediction possibility interaction between compound chemistry with various biological targets.

Target identification for Leukemia

Search for relevant biological targets with leukemia using the GeneCards database (https://www.genecards.org/) with the keyword "Leukemia". Search results are relevant targets then filtered based on mark of more than 1 to increase specifications and accuracy of targets found[17]. The next steps areto analysis cross between target active compounds from *Catharanthus roseus* with related targets with leukemia, which is done use Venny 2.1.0 (https://bioinfogp.cnb.csic.es/tools/venny/). This cross allow the identification overlapping targets,providing an overview of potential interaction between active compound and leukemia. Furthermore, the results this target cross-over analyzed were further analyzed using the Kyoto Encyclopedia of Genes and Genomes(KEGG) database, which explore track biological related with leukemia. The KEGG database provides information on metabolic track and protein interactions involved in leukemia development[18]. Identification biological track relevant to leukemia helps understand how active compound from *Catharanthus roseus* can affect molecular mechanism underlying disease.

Network construction

The construction of a network pharmacology linking *Catharanthus roseus* with leukemia requires all data obtained from analysis previously arranged using Microsoft Excel. Furthermore, Cytoscape software was used to visualize the network interaction between active compound and leukemia targets. Cytoscape is a common visualization tool used in analysis network biological and pharmacological. To obtain more information about network interactions, the top ten targets with highest relationship with the network were further analyzed using CytoHubba tools, which can identify targets with the highest interaction in network[19]. Top three core targets that have been obtained, will then be searched for their structure via the PDB database website (https://www.rcsb.org/).

Molecular docking

Molecular docking analysis was used to verify potential interaction between active compound of *Catharanthus roseus* with biological targets, molecular docking analysis was performed. Molecular docking used to calculate the binding energy between compounds and targets, which reflect how many strong interactions can be formed. Three main proteins that have the highest interaction in network were analyzed through the docking process. Before docking was performed, the protein target structure

was performed using Biovia 2024 software, which separates the protein chains, native ligands, and others co factors.The structure of the active compound was optimized using Avogadro and Chem3D software to obtain the best molecular structure[20]. The docking process was performed using AutoDock4 software, which allows simulation of the interaction between the compounds and targets individually more accurate.The validation method is carried out by redocking, where the Root Mean Square Deviation(RMSD) calculation is estimated to be less than2Å to ensure accuracy of the model[21]. The binding energy generated from the docking simulation is analyzed to determine the best interaction, where the greater and lower the bond energy value, the stronger the interaction. The best docking results are then visualized using Biovia to identify amino acid residues that play a role in bond formation[21].

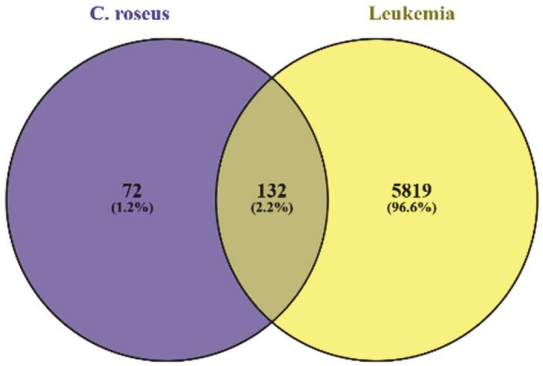

Fig. 1 — Crossing between *Catharanthus roseus* and leukemia

Results

The five active compounds that have been got the SMILES,then a target search was carried out using Super-PRED. The results showed that vindoline has 102 targets, vinblastine has 120 targets, tryptophan has 95 targets, catharanthine has 106 targets, and vincristine has 124 targets. The target genes associated with leukemia 18,300 through the GeneCard database, after screened mark confidence >1 found 5,951 targets. Cross between 204 active compounds target from *Catharanthus roseus* with 5,951 associated targets with leukemia, there are 132 matching targets were found (Fig. 1).Visualization of the PPI formed of the 132 matching targets,the average node degree of 12.09, the number of nodes of 132, and the number of edges of 849 found (Fig. 2).

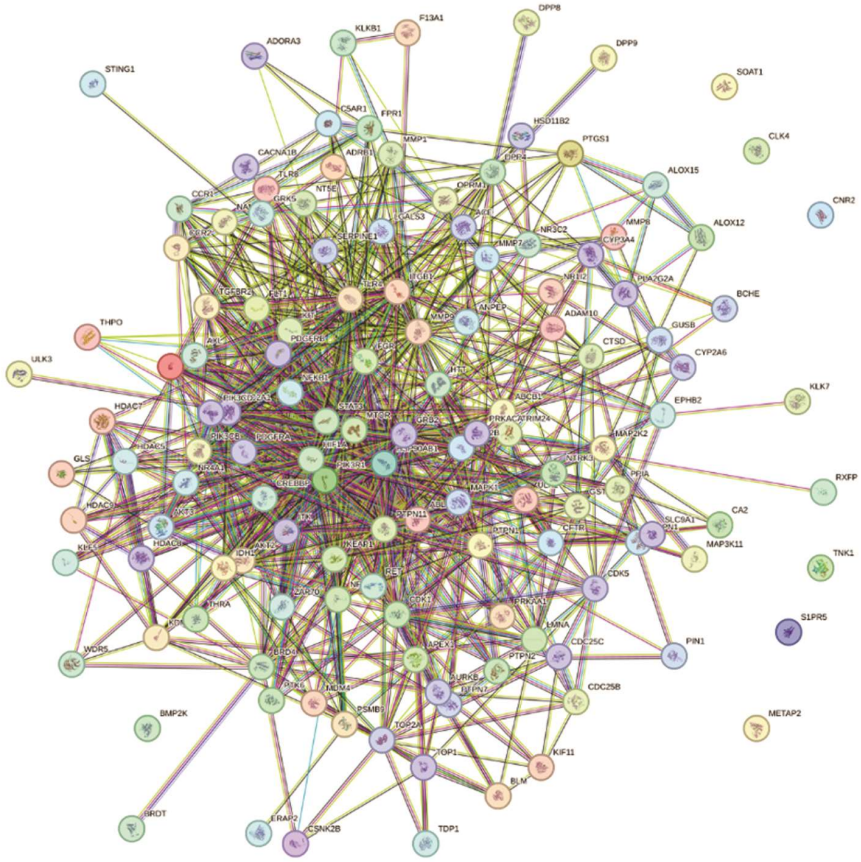

Fig. 2 — Protein-protein interactions targeting *Catharanthus roseus*

Table 1 — Validation of docking methods

Native Ligand	Grid Points			Grid Coordinates			Grid Spacing	RMSD
4JSV	X	Y	Z	X	Y	Z	0.375 A	1.813 A
	40	40	40	-19.142	-31,629	-58,726		
3NMQ	X	Y	Z	X	Y	Z	0.375 A	1.623 A
	40	40	40	2.323	10,362	27.130		
6G8X	X	Y	Z	X	Y	Z	0.375 A	0.677 A
	40	40	40	0.965	10,898	41,035		

The alignment of the leukemia-related pathways resulted in 38 potential core targets as treatment targets. The top three targets to be used in the verification process using docking were found to enter PPI 38 targets into cytohubba. Based on the analysis of results, the top proteins ranking with potential as a therapeutic target is mTOR with score 23, followed by HSP90AB1 with score 22, and MAPK1 with score 21. These protein play an important role in tracking signal related mobile with proliferation, differentiation, and survival cell life. These result show that inhibition of mTOR (PDB ID: 4JSV), HSP90AB1 (PDB ID: 3NMQ), and MAPK1 (PDB ID: 6G8X)may be an effective therapeutic strategy to inhibit the development of leukemia.

Validation docking methods used show that the method used has successfully validated for each target (Table 1). The results of the Root Mean Square Deviation (RMSD) analysis on the three treatment targets show good value, namely <2 Å[20]. The mTOR target (4JSV) has RMSD value of 1.813 Å, while the HSP90AB1target (3NMQ) has higher RMSD value low, namely 1.623 Å. TheMAPK1target (6G8X) shows the lowest RMSD value, which is 0.677 Å. All targets have the same parameters, namely 40 grid points and a grid spacing of 0.375 Å. These results indicate that the docking method used has succeeded in producing accurate binding poses and can reliably predict the interaction between the ligand and the target protein.

The results of the docking simulation of the five *Catharanthus roseus* compounds against the top three leukemia targets are shown in (Table 2). Based on the simulation, it was found that daunorubicin hydrochloride has the best binding energy when interacting with mTOR and compared to other test ligands with ΔG value -8.44 kcal/mol, followed with vindoline -6.39 kcal/mol and native ligand -6.09 kcal/mol. The interactions that occur on HSP90AB1 show that the native ligand has bond best with ΔG value -9.08 kcal/mol, followed by vindoline -8.73 kcal/mol and daunorubicin hydrochloride with ΔG value -8.50 kcal/mol. Temporary MAPK1 interaction points that the native ligand has bond best with ΔG value -7.30 kcal/mol, followed by daunorubicin hydrochloride with ΔG value -8.25kcal/mol vindoline -6.20 kcal/mol. Overall, the five compounds of *Catharanthus roseus* have good interactions, but vincristine has a fairly high binding energy when interacting poorly with HSP90AB1.

Table 2 — Docking simulation results

Target	Test Ligand	Binding Energy (ΔG)
mTOR (PDB ID: 4JSV)	Native Ligand	-6.09 kcal/mol
	Tryptophan	-4.84 kcal/mol
	Catharanthine	-5.84 kcal/mol
	Vincristine	-3.68 kcal/mol
	Vinblastine	-4.56 kcal/mol
	Vindoline	-6.39 kcal/mol
	Daunorubicin Hydrochloride	-8.44 kcal/mol
HSP90AB1 (PDB ID: 3NMQ)	Native Ligand	-9.08 kcal/mol
	Tryptophan	-6.76 kcal/mol
	Catharanthine	-5.97 kcal/mol
	Vincristine	+0.42 kcal/mol
	Vinblastine	-3.94 kcal/mol
	Vindoline	-8.73 kcal/mol
	Daunorubicin Hydrochloride	-8.50 kcal/mol
MAPK1 (PDB ID: 6G8X)	Native Ligand	-7.30 kcal/mol
	Tryptophan	-5.44 kcal/mol
	Catharanthine	-5.84 kcal/mol
	Vincristine	-4.67 kcal/mol
	Vinblastine	-5.09 kcal/mol
	Vindoline	-6.20 kcal/mol
	Daunorubicin Hydrochloride	-6.25 kcal/mol

Discussion

The network pharmacology analysis shown in (Fig. 3) is a network construction that connects compounds from *Catharanthus roseus* with leukemia treatment. *Catharanthus roseus* plays a role as a center in thisnetwork, which describes potential specifically in leukemia therapy. The five active compounds used in this study, namely vinblastine,

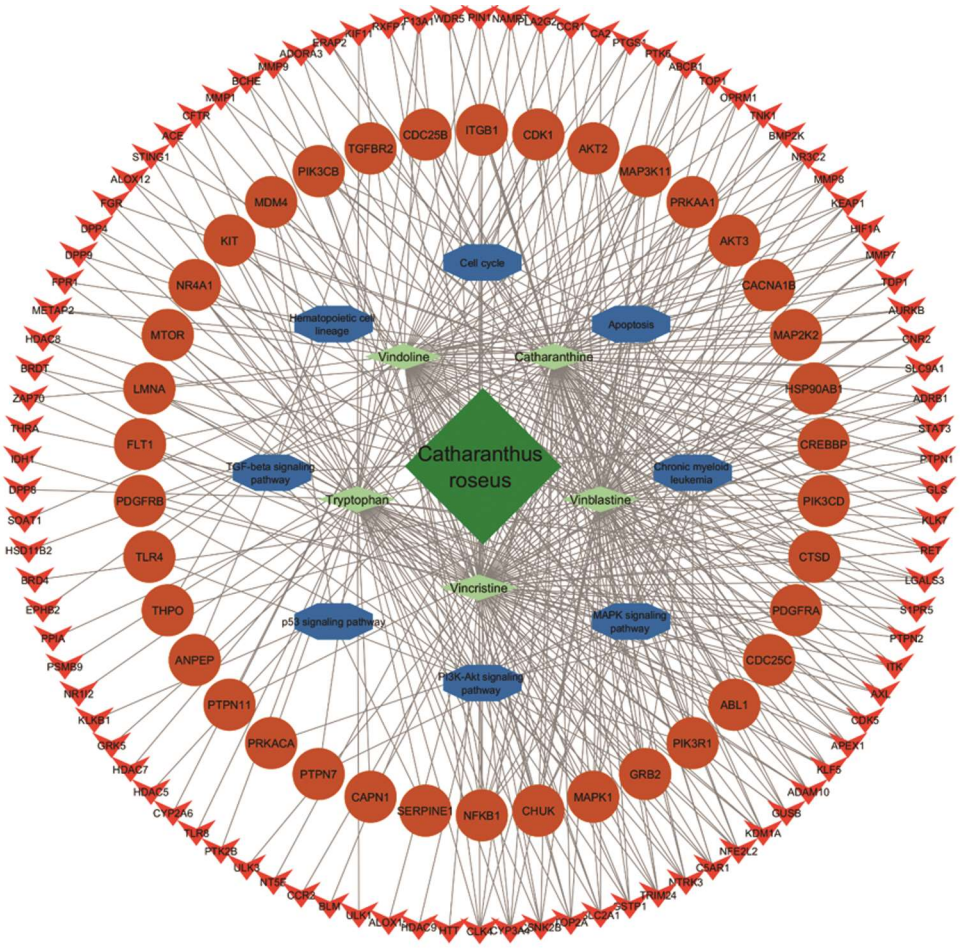

Fig. 3 — Visualization of network pharmacology between *Catharanthus roseus* and leukemia

catharanthine, tryptophan, vindoline, and vincristine are linked directly with *Catharanthus roseus* as the component main that rotates it in the network[16]. In further analysis, eight pathways related to leukemia were found, which revolve around these active compounds. These pathways include Chronic Myeloid Leukemia, MAPK Signaling Pathway, Cell Cycle, p53 Signaling Pathway, PI3K-Akt Signaling Pathway, Apoptosis, TGF-beta Signaling Pathway, and Hematopoietic Cell Lineage. These pathways indicate various biological mechanisms that can be modulated by active compounds in *Catharanthus roseus*, which are very relevant in leukemia treatment. Furthermore, in the network analysis, there are 38 core targets directly related to eight pathways related to leukemia, which are indicated by the brown circle image. These core targets are very important in understanding how the active compound affects the biological pathways related to leukemia. Outside the brown circle, there are targets that revolve around the outer network, which are targets of the active compound but do not have their own pathways directly related to leukemia. This is a description of potential compounds that affect a wider range of biological pathways, although not all pathways are directly related to leukemia.

The results of the analysis using cytohubba to identify the top ten core targets based on the best network scores, shown in (Fig. 4).The analysis results show that mTOR is a top protein target with score 23, followed by HSP90AB1 with score 22, and MAPK1 with score 21. The other four protein targets, namely NFKB1, PIK3R1, and GRB2, have higher score low, namely 20, 18, and 18. While that, PTPN11, ABL1, KIT, and PDGFRB have the lowest scores, namely 17 and 16. These results show that mTOR, HSP90AB1, and MAPK1 are the most potential protein targets. For development therapy. The magnitude of these values is illustrated by the color gradation in (Fig. 4), with red indicating higher values and yellow indicating lower values.

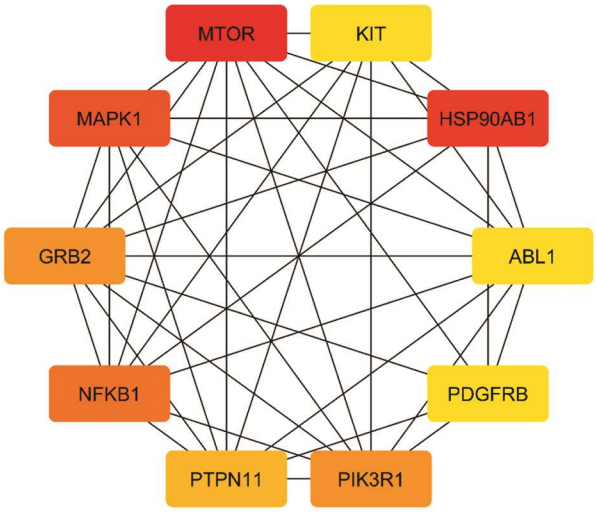

Fig. 4 — Top 10 treatment targets *Catharanthus roseus* in leukemia

The mammalian target of rapamycin (mTOR) signaling pathway plays a critical role in leukemia progression, especially through regulation growth and proliferation that affect leukemogenesis[22]. Acute lymphoblastic leukemia (ALL), shows mTOR is often hyperactivated through upstream signaling pathways such as PI3K/Akt, which contributes to uncontrolled cell division and resistance to apoptosis[23]. The mTOR pathway also affects the tumor microenvironment, which supports survival of malignant cells and contributes to immune evasion, further complicating treatment[22]. Activation of mTOR causes dysregulation of metabolic processes and increased survivalin leukemia cells, making it a strategic target for therapy[24]. Previous study has shown that dual targeting of mTOR can effectively inhibit leukemia cells growth[25]. Thus, mTOR is an important node in tracking the molecular pathogenesis of leukemia, offering a potential therapeutic target for novel interventions.

Heat shock protein 90 alpha family class B member1 (HSP90AB1) plays a key role important in pathogenesis of leukemia, especially chronic myeloid leukemia (CML), by stabilize and facilitate maturation various oncoproteins, including Bcr-Abl, which is a hallmark of CML[26]. In CML cells, the interactions between HSP90AB1 and Bcr-Abl affects cytoplasmic localization and function of this fusion protein, thereby promoting leukemogenesis. HSP90AB1 helps maintain the stability of Bcr-Abl and other important signaling molecules, making it a key regulator of cell survival and proliferation[27]. Given its critical role in maintaining leukemia cell function, HSP90AB1 has emerged as a promising therapeutic target. Targeting HSP90AB1 is being explored as a potential treatment for CML, with several inhibitors in development aimed at disrupting the activity of this important chaperone molecule, potentially resulting in improved therapeutic outcomes.

MAPK1 pathogenesis plays a role important in development of leukemia, especially in leukemia subtypes associated withRUNX1-RUNX1T1 gene fusion[28]. Activation of the MAPK/ERK pathway involving MAPK1 can promote leukemia cell proliferation and inhibit cell differentiation. Recent studies have shown that interventions against MAPK1, either through MAPK1/ERK2 inhibitors or by modifying the expression of related genes, can reduce leukemia cell growth and induce growth arrest[29]. For example, the combination of oridonin and a MAPK1/ERK2 inhibitor has been shown to in a way synergistically suppress leukemia growth[29]. In addition, studies in pediatric lymphoblastic leukemia have also shown that dysregulation of miR-335 targeting MAPK1 is associated with poor outcomes, highlighting the potential of MAPK1 as a therapeutic target in leukemia treatment[30]. Therefore, the development of therapies targeting the MAPK1 or ERK pathways has the potential to provide new effective solutions in the management of this disease[31].

Validation results of the docking method on three protein targets showed good agreement between the ligand positions obtained through redocking and the native ligand placement, although there was a slight difference in the resulting RMSD value. Validation of the method on the 4JSV protein showed an RMSD value of 1.813 Å, reflecting a shift in position in the X, Y, and Z coordinates, with a consistent grid spacing of 0.375 Å which is still within the acceptable range. The validation results of 3NMQ with an RMSD value of 1.623 Å showed a smaller difference in position, while 6G8X produced the best docking results with an RMSD of 0.677 Å and the selection of the right grid box showed stability in the composed docking system, which is very important to ensure accurate prediction of the position and orientation of the ligand in the active site of protein[32]. Overall, despite variations in RMSD values, all ligands showed valid results, with insignificant position shifts, supporting the validity of the docking method to evaluate the potential of ligands as therapeutic agents.

The docking results on the three protein targets showed significant variations in binding energy (ΔG) between the ligands tested. Interaction on the mTOR target, showed the daunorubicin hydrochloride strongest binding energy -8.44 kcal/mol, followed by vindoline -6.39 kcal/mol, catharanthine -5.84 kcal/mol, tryptophan -4.84, vinblastine -4.56 kcal/mol, and vincristine -3.68 kcal/mol. Meanwhile, on the HSP90AB1 target, the native ligand showed the strongest binding energy of -9.08 kcal/mol, followed by vindoline -8.73 kcal/mol, daunorubicin hydrochloride -8.50 kcal/mol, while vincristine was the one that showed a binding energy of +0.42 kcal/mol. MAPK1 interaction showed the native ligand the strongest binding energy of -7.30 kcal/mol, followed by Daunorubicin Hydrochloride -6.25 kcal/mol, Vindoline -6.20 kcal/mol, Tryptophan -5.44 kcal/mol, and Catharanthine -5.84 kcal/mol.

Generally,compounds from *Catharanthus roseus* showed good potential with quite stable energy binding to several protein targets. However, vincristine showed very poor results on HSP90AB1, which can be an important consideration if used as a therapy, because its interaction is not optimal. Meanwhile, vindoline is a compound that shows better binding energy than the native ligand on MTOR, on HSP90AB1 this compound has better binding energy than daunorubicin hydrochloride as a control drug, while MAPK1 this compound shows little difference from daunorubicin hydrochloride as a control drug. This finding makes it a very potential leukemia therapeutic candidate. Compounds such as catharanthine and tryptophan also show quite stable interactions, making them potential candidates in the development of more effective therapies.

The interactions that occur in vindoline as the best test ligand from compound *Catharanthus roseus* against the MTOR proteinis shown in (Fig. 5). Vindoline forms four hydrogen bonds with amino acid residues such as SER2342, ASP2357, ASN2343, and LYS2187. In addition, there is also a Pi-alkyl bond involving PRO2169, ILE2163, LEU2185, and ILE2356, which also acts as Pi-Sigma. Pi-alkyl and Pi-Stacked bonds are also found in TRP2239. When compared to native ligands, there are some similarities, such as the Pi-Sigma bond in ILE2356 and Pi-Stacked in TRP2239, but there is a difference in LYS2187 which forms a Pi-Sulfur bond. Several interactions found in daunorubicin hydrochloride show similarities with native ligands, such as hydrogen bonds in LYS2187 and ASP2357, and Pi-alkyl bonds in LEU2185 and ILE2356 which are also Pi-Sigma.

The interaction between vindoline and HSP90AB1 protein (Fig. 6), vindoline shows various bonds, including hydrogen bonds with PHE138, which can also form non-hydrogen bonds such as Pi-alkyl and Pi-T-Shaped. In addition, several other non-hydrogen

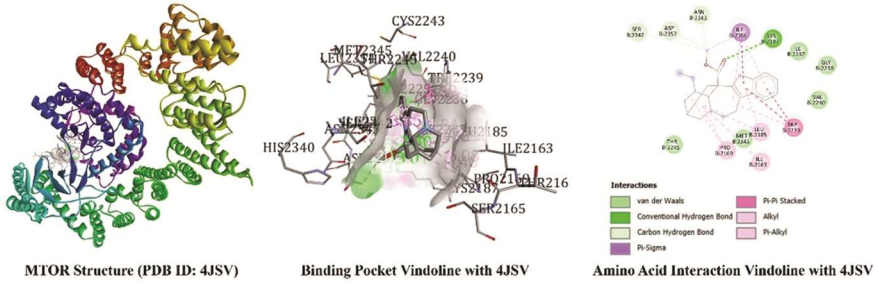

Fig. 5 — Visualization docking simulation resultsof vindoline with mTOR

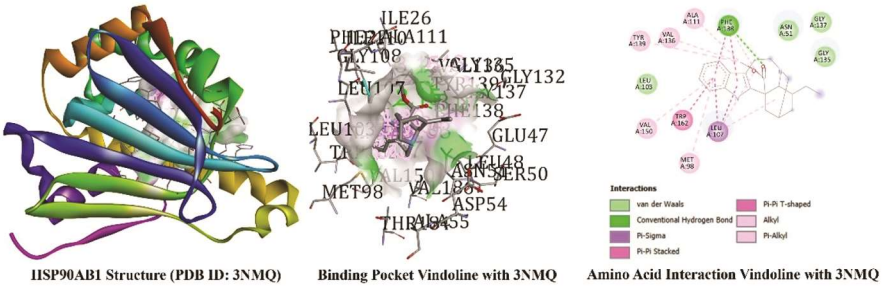

Fig. 6 — Visualization docking simulation results of vindoline with HSP90AB1

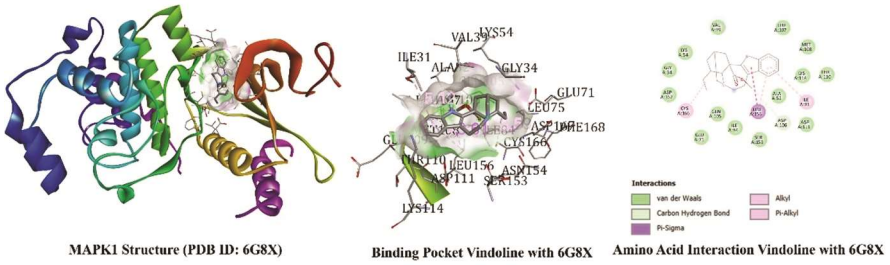

Fig. 7 — Visualization docking simulation resultsof vindoline with MAPK1

bonds were found in MET98, VAL150, TYR139, VAL136, ALA111, and LEU107, which also form Pi-Sigma bonds. In native ligands, hydrogen bonds are formed at residues THR184, ASP102, and ASP93, while non-hydrogen bonds in the form of Pi-Alkyl are found in ALA55, LEU107, VAL150, LEU103, and PHE138, which also form Pi-Stacked. Several other amino acids, such as TRP162 and MET98, also form Pi-alkyl and Pi-Sigma bonds, with MET98 showing Pi-Sulfur bonds. In daunorubicin hydrochloride, several bonds found are similar to native ligands, such as hydrogen bonds at ASP102 and non-hydrogen bonds at ALA55, LEU107, and MET98.

The interaction between vindoline and MAPK1 protein shows a hydrogen bond with ASP106, as well as non-hydrogen bonds such as Pi-Alkyl involving CYS166, ILE31, and LEU156, which also form Pi-Sigma bonds shown in (Fig. 7). In contrast, in the MAPK1 complex with daunorubicin hydrochloride, all amino acids involved form hydrogen bonds, including LYS114, ASP11, ASP167, ASN154, LYS54, and GLU33.

Several active compounds contained in *Catharanthus roseus*, such as vindoline, vinblastine, and alpha-tabersonine, have shown potential anticancer properties. Vindoline plays a role in the synthesis of Vinblastine, which has antimitotic properties and can inhibit microtubule formation, thereby inhibiting the development of cancer cells during cell division, *in vitro*[33,34]. In addition, Alpha-Tabersonine has also been known to have anticancer activity that can inhibit the development of cancer, especially leukemia. These results indicate that the active compounds in *Catharanthus roseus* have the potential as effective anticancer agents[35].

Conclusion

This study identified 132 targets related to leukemia and found that active compounds from *Catharanthus roseus* have the potential to inhibit the development of this disease. Validation of the docking method showed accurate results with low RMSD, supporting the use of this technique to predict ligand-protein interactions. In addition, the mTOR, HSP90AB1, and MAPK1 pathways play an important role in the pathogenesis of leukemia and can be targeted for therapy.The vindoline compound showed better interactions compared to control ligands on several key targets, such as mTOR and HSP90AB1.These findings make *Catharanthus roseus* compounds, especially vindoline, a promising therapeutic candidate. The direction of further research can be further validation through *in vitro* and *in vivo* experimental studies.

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Conflict of interest

All authors declare no conflict of interest.

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