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RESEARCH PAPER

Molecular docking study of catharanthus roseus compounds as potential ABL1 inhibitors for leukemia treatment

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Abstract: Leukemia is one type of cancer with a high mortality rate, caused by the proliferation of abnormal white blood cells that disrupt hematopoiesis function. Conventional therapies, such as chemotherapy and targeted therapy, often face challenges in the form of side effects and drug resistance. This study aims to evaluate the potential of *Catharanthus roseus* as a leukemia therapeutic agent through in silico. The docking process uses autodock, and ADMET prediction uses SwissADME and PKCMS. The study used the ABL1 protein (PDB ID: 4TWP) as a target with active compounds of *Catharanthus roseus*. The validation process of the docking method showed an RMSD value of 0.705 Å, indicating that the method used was valid. The results of the docking simulation showed that vindoline had the best affinity after native ligands with a binding energy of -8.64 kcal/mol, followed by catharanthine -6.16 kcal/mol and tryptophan -3.87 kcal/mol. ADMET prediction analysis showed that vindoline and catharanthine had promising pharmacokinetic and toxicity profiles, such as good blood-brain barrier (BBB) permeability and did not inhibit the CYP3A4 enzyme. These results indicate that vindoline and catharanthine are potential alternative leukemia treatments with high efficacy and low risk of side effects. This study provides a basis for further exploration of *Catharanthus roseus* in the development of effective and safe leukemia therapies.

Keywords: Leukemia, ABL1, *Catharanthus roseus*, molecular docking, ADMET

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INTRODUCTION

Leukemia is a group of cancers characterized by uncontrolled proliferation of white blood cells in the bone marrow or peripheral blood [1]. This disease is classified into several main types, such as acute lymphocytic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CLM). This disease has shown a global incidence of 474,519 cases with a median age of 11 years [2]. Globally, leukemia is one of the leading causes of cancer death, with a higher incidence in children and the elderly. Risk factors for leukemia include exposure to radiation, chemicals such as benzene, certain viral infections, and a family history of blood cancer [3]. The pathophysiology of leukemia involves genetic mutations that disrupt the normal process of hematopoiesis, resulting in abnormal cells that dominate the blood and bone marrow, inhibiting normal body functions (1). Current treatments for leukemia include chemotherapy, radiotherapy, bone marrow transplantation, and targeted therapies such as tyrosine kinase inhibitors (TKIs). It is indeed effective, but this

therapy is often accompanied by significant side effects, such as organ damage, decreased immunity, and drug resistance [4].

ABL1 is a gene encoding a non-receptor tyrosine kinase protein, which is involved in various cellular processes, including proliferation, differentiation, and migration [5]. Leukemia pathogenesis shows chronic myelocytic progression, mutations or fusions of the BCR-ABL1 gene result in constitutive tyrosine kinase activity that causes abnormal cell proliferation [6]. In addition to leukemia, ABL1 also plays a role in the pathogenesis of other diseases, such as fibrosis, neurodegeneration, and non-hematological cancers (5). BCR-ABL plays a crucial role in leukemia progression, with its inhibition by therapies such as imatinib and dasatinib resulting in significant responses in many patients [7]. Thus, ABL1 is an important target in the development of therapies for various pathological conditions. Studies by Aisyi et al. (2020) have shown that BCR-ABL1 affects 73.3% of patients with CML, and 11.8% of patients with ALL. These results confirm the importance of ABL1 mutations in leukemia pathogenesis, so targeting this protein can be considered a promising treatment strategy for the future [8].

Catharanthus roseus, also known as the tapak dara plant, is a tropical plant widely found in Asia, Africa, and South America [9]. This plant contains active compounds such as vinblastine, vincristine, catharanthine, and vindoline, which have high pharmacological potential [10]. In traditional practice, tapak dara is used to treat various diseases, such as diabetes, hypertension, and infections [11]. Its alkaloid compounds, especially vinblastine and vincristine, have long been used to treat cancer, including leukemia. One way to prevent further cancer development is by increasing apoptosis [12]. The use of this plant still requires further research to maximise its potential as a therapeutic agent. Research on *Catharanthus roseus* as an alternative treatment for leukemia through in silico methods is important to explore its efficacy and safety. This method allows efficient simulation of molecular interactions before preclinical trials, thus accelerating the development of more effective drugs with minimal side effects.

MATERIALS AND METHODS

Tools and materials

Hardware laptop 5-1235U @4.50 GHz 16GB processor, accompanied by 512GB of RAM and internal memory. The software used was BioVia Discovery Studio 2024, Avogadro, ChemDraw 3d 2019, and Autodock 1.5.7. Several websites were used to obtain research materials and data analysis, such as: pubchem, protein data bank, swisADME, and PKCM.

The material used is the ABL1 protein structure obtained through the PDB website, with ID: 4TWP. All active compounds of *Catharanthus roseus* will be tested as ligands obtained through the PubChem website. The compounds used are the results of the analysis of Zweil et al. (2019): Tryptophan, Catharanthine, Vincristine, Vinblastine, Vindoline. These five compounds have great potential as anticancer agents through apoptosis induction and antiproliferation mechanisms that have been proven in vitro [10].

Protein and ligand repair

Proteins and compounds obtained from PDB and pubchem will undergo a repair process. This process uses biovia software to separate the protein chain from native ligands, water, and other cofactors. The test compound that will be optimized to obtain its best structure uses avogadro, then post-optimization minimization is carried out using ChemDraw 3D.

Method Validation

The redocking process using native ligands as test ligands is used to validate the docking method used. This produces a "root mean square deviation" (RMSD) as a validation parameter. The RMSD value <2 Å indicates that the test results are close to those that are not much different from the original ligand. This process will show the position of the native ligand, which will be the specific point of docking performed. The position of the native ligand can be obtained by creating a grid box in the redocking process. The redocking process and docking simulation use autodock 1.5.7 with a genetic algorithm as a docking parameter.

Docking Simulation and Results Visualization

The structure of the active compound that has been optimized and minimized, will then go through the docking process as a test ligand. This simulation must adjust to the position of the native ligand, through the gird box results during redocking. The docking results are analyzed through the binding energy value (ΔG), as the main parameter of the bond

between the test compound and the protein. The docking results are visualised to determine the bonds of the amino acid residues formed. This visualization process uses biovia discovery studio to obtain the bond [13].

ADMET prediction analysis of Test compounds

Prediction of pharmacokinetics in the form of absorption, distribution, metabolism, excretion, and toxicity (ADMET) analysis using the SwisADME and PKCMS websites. It increases the knowledge of the chances of the test ligand to reach its target, analysis using SMILES for each test ligand to be entered on the website. The parameters to be used in this analysis are viability or lipiski rule of 5, intestinal absorption, Blood brain barrier (BBB) permeability, CYP3A4, total clearance, ames toxicity, and hepatotoxicity [14].

RESULTS AND DISCUSSION

The crystal structure T315I mutation in ABL1 is known to confer resistance to first-generation kinase inhibitors such as imatinib. Axitinib, originally developed as a VEGFR inhibitor, has shown potential in overcoming this resistance by effectively binding to the active pocket of ABL1 T315I. Crystal structure analysis shows that axitinib interacts with key residues in the active site of ABL1 T315I, including the formation of hydrogen bonds and stabilizing hydrophobic interactions [15]. Binding of axitinib causes conformational changes in the kinase domain, which contribute to the inhibition of its enzymatic activity. These findings provide important insights into the molecular mechanism of axitinib binding to ABL1 T315I and open up opportunities for the development of more effective kinase inhibitors to overcome drug resistance in cancer therapy [16]. Figure 1 is the crystal structure of the gatekeeper mutant kinase domain T315I of human ABL1 protein in complex with axitinib (PDB ID: 4twp), as revealed by X-ray crystallography [16].

This study uses ABL1 protein as a target; before the docking simulation is carried out, validation must be carried out. The method is carried out to determine the shift that occurs in the native ligand before and after docking; this can be seen through the RMSD results formed in the native ligand after docking. The redocking results show good results, namely 0.705 A, which indicates that the method used is valid or precise because it has a value of <2 A [16]. Validation of this method can be seen in the native ligand crystal in Figure 2, which shows that there are no significant changes in the ligand before and after redocking. The findings of the grid box during redocking show the position of the specific ligand so that it can provide a point on the test ligand during the simulation. The positions are X: 60.303, Y: 16.211, Z: 51.811, with a grid distance of 0.375 A and the number of grids each 40 points.

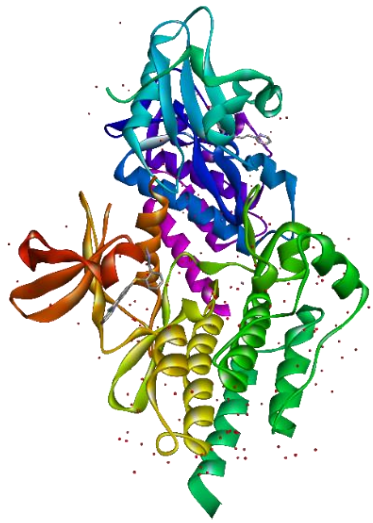

Figure 1. The crystal structure ABL1 (PDB ID: 4TWP)

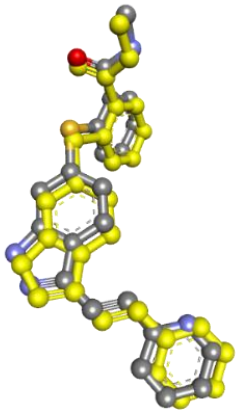

Figure 2. Overlap of Natural Ligand (Gray) and Post-Redocking Ligand (Yellow)

The docking simulation results on the test ligands that have been optimised and minimised can be seen in Table 1. Through native ligand docking, the results become the ligand with the best energy affinity, with a mark of -11.06 kcal/mol. Through this analysis, some dominant amino acid residues that frequently appear are TYR253, LYS271, GLU316, and ASP381. TYR253 is an aromatic residue that is often involved in pi interactions, such as pi-sigma and T-shaped, which help maintain the orientation of the ligand within the active pocket of the protein.

Vindoline exhibits a strong binding affinity of -8.64 kcal/mol, outperforming other test ligands except for the native ligand. It shows a greater affinity compared to Daunorubicin with an energy affinity of -7.45 kcal/mol as a control medication, so that opens an opportunity for big leukemia treatment using vindoline. Catharanthine, with the energy affinity of -6.16 kcal/mol, shows that the opportunity for leukemia alternative with marked energy affinity that is not far different from the control drug. Tryptophan has an affinity bond energy of -3.87 kcal/mol, which has the potential to become an alternative treatment. While Vincristine with affinity energy +36.87 kcal/mol and Vinblastine with affinity energy +49.60 kcal/mol, have the opportunity to have small consequences from the bad affinity energy bonds formed to the target protein. This result can become a consideration for conducting preclinical and clinical trials on both compounds, so that it can become further input for research.

Each ligand shows a pattern of interaction specific to the ABL1 protein. Native ligands, in comparison, interact with residues important, such as TYR253, ALA269, LYS271, GLU316, and MET318 through a combination of hydrogen bonds and hydrophobic interactions [17]. TYR253 is an aromatic residue that often appears in various interactions, especially pi-alkyl and T-shaped, and provides stable structural stability in the ligand-protein complex [18]. Catharanthine forms significant interactions with ASP381 via pi-anion bonds and with TYR253 and LYS271, contributing to hydrophobic stability [19]. Vindoline also prefers residues, especially ARG367, which is involved in hydrogen interactions. Figure 3 shows the results of redocking visualisation, while Figure 4 shows the interaction amino acids formed during docking.

Through this analysis, some dominant amino acid residues that frequently appear are TYR253, LYS271, GLU316, and ASP381. LYS271 and GLU316 are polar residues that play an important role in forming hydrogen bonds, directly affecting the complex's stability [20]. ASP381 also stands out for its ability to form pi-anion interactions with certain ligands, strengthening the atomic binding. Its hydrophobic residues, such as LEU370, LEU248, and ALA269, provide additional contributions through hydrophobic interactions [21]. This stability is important for active compounds such as vincristine and vinblastine, which have large and complex structures. The combination of these interactions indicates the importance of these residues in determining the affinity and specificity of ligands for the ABL1 protein.

TYR253 is the most frequently involved residue in ligand binding, mainly through stable pi interactions [22]. Previous studies have shown that aromatic residues in protein kinases are often key in ligand interactions, especially for small molecules with aromatic groups. In addition, polar residues such as LYS271 and GLU316 make important contributions to binding specificity through hydrogen bonds. These two residues are often found in the active pocket of protein kinases, indicating their biological significance in the binding mechanism. Charged residues such as ASP381 play unique roles in interactions with positively charged ligands like catharanthine. Meanwhile, hydrophobic residues such as LEU248 and LEU370 help to keep the ligand-protein complex stable through non-polar interactions [23]. This combination of hydrogen and hydrophobic interactions provides a strong basis for stable and efficient ligand binding.

Vindoline is a crucial precursor in the biosynthesis of vincristine and vinblastine, two well-known chemotherapy drugs used to treat various cancers, including leukemia and lymphoma [12]. Although vindoline exhibits some biological activity, its primary significance lies in its role within a complex biosynthetic pathway that produces compounds with therapeutic effects on cancer cells [24, 25]. Catharanthus roseus, the plant from which vindoline is derived, has shown considerable potential as an anticancer agent, particularly in the treatment of leukemia, breast cancer, and colorectal cancer [26]. Previous studies have highlighted the effectiveness of *Catharanthus roseus* as an antiproliferative agent in vitro, particularly in Jurkat leukemia cells [27]. Additionally, its pro-apoptotic and antiproliferative effects have been demonstrated in HL60 cells through ROS mediation regulated by BCL2 [28]. Other research also indicates the pro-apoptotic properties of *Catharanthus roseus* in chronic lymphocytic leukemia cells, enhancing drug sensitivity in vitro [29]. These findings emphasize the therapeutic potential of *Catharanthus roseus* and its bioactive compounds, like vindoline, in developing more effective cancer treatments.

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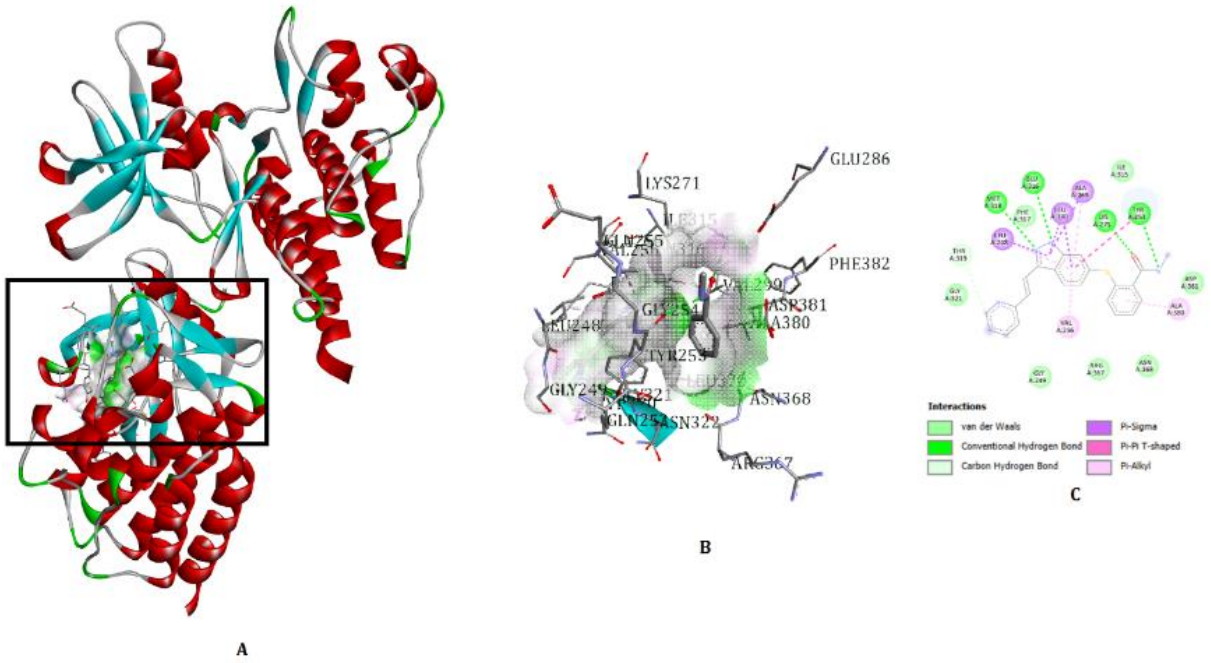

Figure 3. Redocking results (A) Grid box positions (B) Protein binding complex between native ligand and ABL1 (C) Amino acid bond interaction

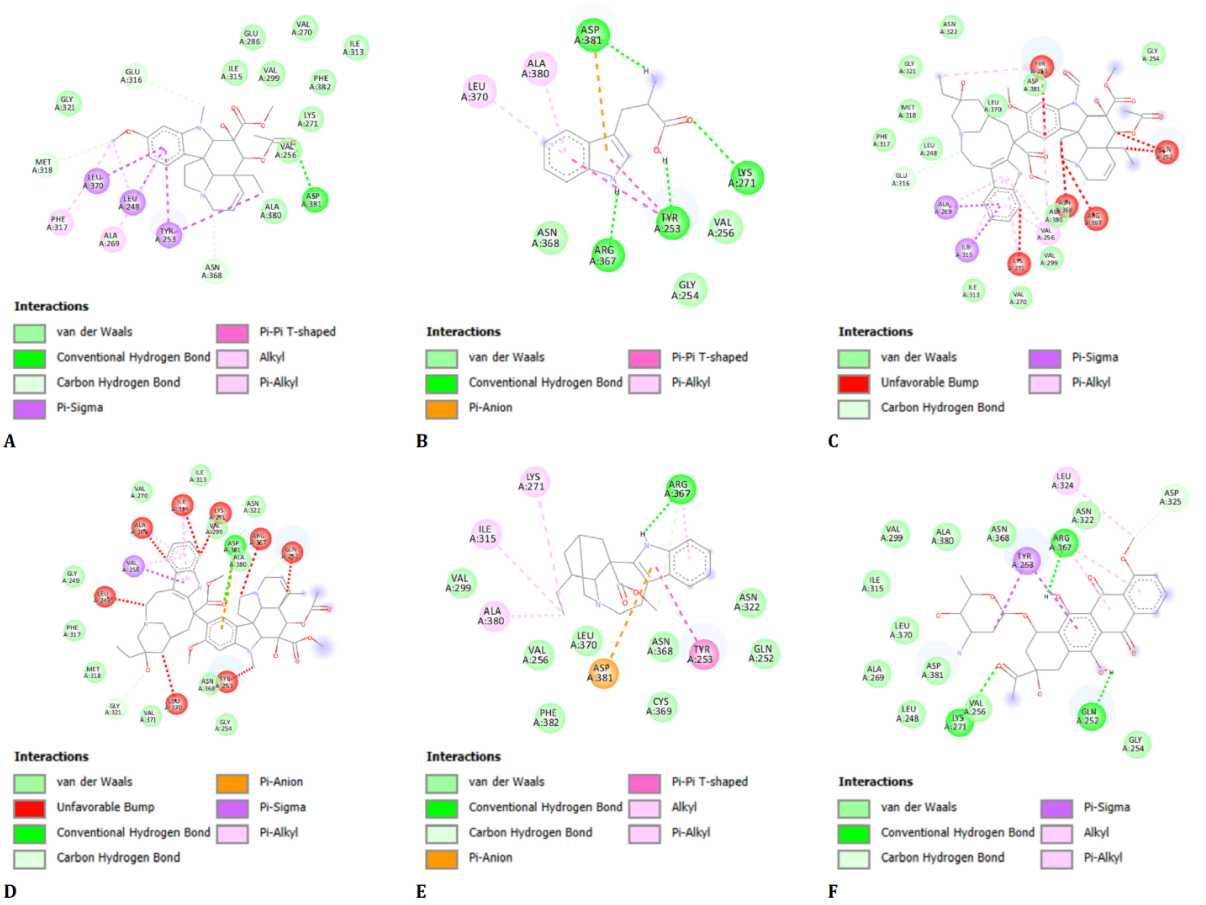

Figure 4. Amino acid bond interaction (A) Tryptophan (B) Catharanthine (C) Vincristine (D) Vinblastine (E) Vindoline (F) Daunorubicin Hydrochloride

The results of ADMET prediction analysis using the SwissADME and PKCMS websites are shown in Table 2. This result shows lipiski rule of 5, intestinal absorption, Blood brain barrier (BBB) permeability, CYP3A4, total clearance, ames toxicity, and hepatotoxicity. Catharanthine and vindoline had high compliance values as candidates for leukemia treatment that were more effective and safe than other compounds and control drugs.

The distribution ability of compounds in the body, including the permeability of the blood-brain barrier (BBB), is determined by their lipophilicity and polarity. Catharanthine has the best BBB permeability of 0.287, followed by Vindoline -0.261, making it a potential candidate for application in the central nervous system [30]. Tryptophan shows a moderate BBB permeability of -0.495, which allows effects on the brain under certain conditions. In contrast, compounds with high TPSA, such as Vincristine -1.239, Vinblastine -1.078, and Daunorubicin -1.416, have very low BBB permeability.

The inhibition of the CYP3A4 enzyme, which plays a key role in drug metabolism in the liver, is a crucial parameter in understanding drug interactions. Tryptophan and Catharanthine do not inhibit CYP3A4, suggesting a low risk for drug interactions in the liver [31]. In contrast, vincristine, vinblastine, vindoline, and daunorubicin are inhibitors of CYP3A4, indicating a significant potential for interactions when used alongside other drugs metabolized by this enzyme. It highlights the importance of carefully managing drug combinations in clinical settings to minimize adverse interactions.

Clearance, which describes the body's efficiency in eliminating compounds through excretion or metabolism, varies among these compounds. Catharanthine and daunorubicin show the highest total clearances of 1.167 and 1.333 (ml/min/kg), indicating their rapid elimination from the body. On the other hand, vincristine 0.53, vinblastine 0.41, and vindoline 0.511 exhibit lower clearances, which could prolong their half-lives and increase the duration of their action [32].

The toxicity profile of compounds is an important consideration in drug development. Based on the AMES test, all compounds did not show mutagenic potential, so they are safe from the risk of genotoxicity [14]. However, Daunorubicin, as a control drug, was identified as a hepatotoxic compound, so its use requires careful monitoring in patients with impaired liver function. Other compounds, such as Tryptophan, Catharanthine, Vincristine, Vinblastine, and Vindoline, did not show hepatotoxic potential, providing additional development advantages as drug candidates. It shows the great potential of periwinkle (Catharanthus roseus) as a more effective and safer alternative treatment.

Despite Vindoline and Catharanthine showing weak cytotoxicity and strong binding, this finding suggests that they have the potential to be developed into drugs with a lower toxicity profile but still effective in treating leukemia. Modifying their structures or enhancing their affinity for targets such as α/β-tubulin could make Vindoline and Catharanthine safer alternatives, with the potential to overcome drug resistance often observed with Vincristine or Vinblastine [33]. Additionally, drug delivery enhancers, such as liposomes, could help improve these compounds' bioavailability and therapeutic efficacy, mitigating their limitations as CYP3A4 inhibitors [34]. This approach could provide a pathway for optimising their therapeutic potential while reducing the risk of drug interactions and side effects.

The docking simulation and ADMET prediction results showed that there were 2 compounds with high potential to be alternative leukemia treatments. Catharanthine and vindoline had high compliance values as candidates for leukemia treatment that were more effective and safe than other compounds and control drugs. The ability to not inhibit CYP3A4 is a major advantage of catharanthine, because it reduces the possibility of side effects due to metabolic interactions. However, in the vindoline compound, which is a CYP3A4 inhibitor, dose adjustments may be needed to avoid adverse pharmacokinetic effects.

Table 1. Docking Simulation Results

Ligand	Binding Energy (ΔG)	Amino Acid Bond Interaction	
		Hydrogen Bond	Non-Hydrogen bond
Native ligands	-11.06 kcal/mol	Tyr253, Lys271, Glu316, Met318, Thr319	Tyr253 (T-Shaped), Ala280, Val256, Leu248, Ala269 (Pi-Alkyl), Ala269, Leu370, Leu370, Leu248 (Pi-Sigma)
Tryptophan	-3.87 kcal/mol	Asp381, Asn368, Met318, Glu316	Leu248, Leu370, Tyr253 (Pi-Sigma), Leu248. Ala269, Phe317 (Pi-Alkyl),

Ligand	Binding Energy (ΔG)	Amino Acid Bond Interaction	
		Hydrogen Bond	**Non-Hydrogen bond**
			Tyr253 (T-Shaped)
Catharanthine	-6.16 kcal/mol	Asp381, Lys271, Tyr253, Arg367	Asp381 (Pi-Anion), Tyr253, Tyr253 (T-Shaped), Leu370, Ala380 (Pi-Alkyl)
Vincristine	+36.87 kcal/mol	Glu316	Gln252, Gln252, Arg367, Asn369, Lys271, Tyr253 (Unfavourable Bump). Lys271, Tyr253, Val256, Val256, Val256, Ile315, Ala269 (Pi-Alkyl), Ile315, Ala269 (Pi-Sigma)
Vinblastine	+49.60 kcal/mol	Gln 252, Asp381 and Gly 321	Tyr253, Leu370, Lue248, Gln 252, Arg367, Lys271, Ile315, Ala269 (Unfavorable Bump). Ile315, Ala26, Val 256 (Pi-Alkyl), Val266 (Pi-Sigma)
Vindoline	-8.64 kcal/mol	Arg367 And Arg367	Arg367, Lys271, Ile315, Ala380 (Pi-Alkyl), Tyr253 (T-Shaped), Asp381 (Pi-Anion)
Daunorubicin Hydrochloride	-7.45 kcal/mol	Arg367, Gln252, LYS271, Asp352	Tyr253, Tyr253 (Pi-Sigma), Leu324, Arg367, Arg367 (Pi-Alkyl)

Table 2. ADMET Analysis Results

ADMET Parameters	Tryptophan	Catharanthine	Vincristine	Vinblastine	Vindoline	Daunorubicin Hydrochloride
Molecular weight	204.23 g/mol	336.43 g/mol	824.96 g/mo	810.97 g/mol	456.53 g/mol	563.98 g/mol
H-Bond Acceptor	3	3	12	11	7	11
H-Bond Donor	3	1	3	3	1	5
Log P	-1.66	2.96	2.35	2.35	1.74	-1.15
TPS	79.11 Å²	45.33 Å²	171.17 Å²	171.17 Å²	88.54 Å²	185.84 Å²
Intestinal absorption	77,224	93,597	79.88	78.106	96,576	72,932
BBB permeability	-0.495	0.287	-1.239	-1.078	-0.261	-1.416
CYP3A4 inhibitor	No	No	Yes	Yes	Yes	Yes
Total Clearance	0.64	1.167	0.53	0.41	0.511	1,333
AMES toxicity	No	No	No	No	No	No
Hepatotoxicity	No	No	No	No	No	Yes

CONCLUSION

Catharanthine and vindoline showed compliance with pharmacokinetic and toxicological parameters with high energy affinity and good ADMET profiles. Catharanthine, with the advantage of not inhibiting CYP3A4, reduces the risk of drug interactions, while vindoline, despite inhibiting CYP3A4, has a higher energy affinity than the control drug. This study highlights the potential of *Catharanthus roseus* as a source of new active compounds for cancer therapy, especially leukemia, opening up opportunities for the development of more effective and safe drugs.

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The authors declare no conflict of interest in this research. All data and information have been presented in full in this article.

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