



**Original Article**

### Identification of Potential Anti-Blood Cancer Compounds from *Centella asiatica* via In Silico Approaches: Molecular Docking, ADMET Prediction, and Drug-Likeness Evaluation

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#### Abstract

Blood cancer is a hematological malignancy characterized by abnormal proliferation of blood cells due to genetic mutations. Conventional therapies such as chemotherapy and radiotherapy often cause significant side effects, highlighting the need for safer alternatives. Natural products, including *Centella asiatica*, have been widely explored as potential anticancer agents. This study aimed to evaluate the binding affinity, pharmacokinetic properties, and drug-likeness of bioactive compounds from *Centella asiatica* using an in silico approach. Molecular docking was performed using AutoDock 1.5.6 to determine binding free energy ( $\Delta G$ ), followed by ADMET prediction and Lipinski's Rule of Five evaluation. The results showed that quercetin, centellin, labiatic acid, kaempferol, and asiatic acid exhibited binding affinities of -6.51, -4.92, -5.07, -6.16, and -6.97 kcal/mol, respectively, with asiatic acid demonstrating the strongest interaction. ADMET analysis indicated generally favorable absorption and low toxicity profiles, although variability in permeability and metabolic interactions was observed. Drug-likeness evaluation revealed that most compounds met key Lipinski parameters, with minor deviations related to lipophilicity and molecular weight. In conclusion, *Centella asiatica* contains promising bioactive compounds with potential anti-blood cancer activity supported by favorable pharmacokinetic and drug-likeness profiles. Further in vitro and in vivo studies are required to validate these findings.

**Keywords:** *Centella asiatica*; In silico; Blood cancer; Anticancer activity; Bioactive compounds.

#### INTRODUCTION

Cancer is a disease characterized by dysregulated mechanisms controlling cell survival, proliferation, and differentiation. Uncontrolled cancer progression can ultimately lead to mortality (Brown et al., 2023). Cancer arises when normal cellular growth undergoes genetic alterations, transforming cells into malignant forms that proliferate rapidly and uncontrollably. This condition can occur in various tissues, including blood tissue, resulting in hematological malignancies (Ahmad & Kumar, 2011; Aizawa et al., 2016).

Continuous and excessive division of blood cells leads to abnormal cellular conditions and disease progression, particularly in hematological malignancies such as leukemia, including chronic myeloid leukemia (CML), which is characterized by uncontrolled proliferation of myeloid cells (Sundaryono et al., 2013).

Natural products have gained considerable attention as alternative therapeutic agents due to their potential efficacy and relatively lower toxicity. *Centella asiatica* is a wild medicinal plant with promising pharmacological potential.

It has been recognized as a traditional medicinal plant since 1884 (Sutardi, 2008). Traditional medicine refers to remedies prepared and used based on inherited knowledge, customs, and local practices (Degu, 2024). Its utilization continues to increase due to accessibility, affordability, and availability within the community (Sastroamidjojo, 1997). Moreover, *Centella asiatica* is considered to have minimal side effects and low toxicity (Rusmiati, 2007). It contains various bioactive compounds such as asiaticoside, flavonoids, and triterpenoids. Several of these compounds, including asiatic acid, quercetin, and kaempferol, have been reported to exhibit anticancer activities through mechanisms such as induction of apoptosis, inhibition of cell proliferation, and modulation of signaling pathways involved in cancer progression (Brotoisworo, 1979).

In this study, the interactions and stability of bioactive compounds from *Centella asiatica* were evaluated using an *in silico* approach. Molecular docking was

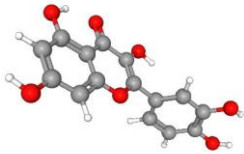

employed to predict binding affinity and interaction patterns with target proteins associated with blood cancer. Furthermore, pharmacokinetic and toxicity profiles were assessed using PreADMET analysis, while drug-likeness properties were evaluated based on Lipinski's Rule of Five. These integrated approaches are expected to provide comprehensive insights into the potential of *Centella asiatica* compounds as candidates for anti-blood cancer drug development.

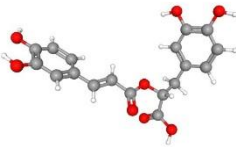
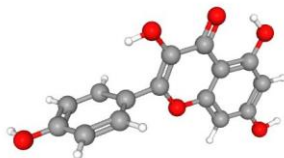
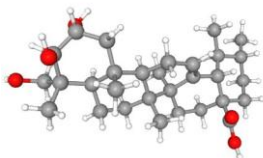
## METHODS

### Data collection and molecular modeling of compounds from *Centella asiatica*.

The compounds contained in *Centella asiatica* in this study were tested using the software AutoDock 1.5.6. As comparison data, a ligand, Imatinib, was prepared using a 3D structure in sdf format downloaded from <https://pubchem.ncbi.nlm.nih.gov/>. This site provides a database of compound structures for virtual screening purposes. The five compounds are shown in **Table 1**.

**Table 1.** Images of compounds from *Centella asiatica*

No	Molecule Name	Formula	Molecular Structure
1	Quercetin	C <sub>15</sub> H <sub>10</sub> O <sub>7</sub>	
2	Centellin	C <sub>15</sub> H <sub>22</sub> O <sub>3</sub>	

No	Molecule Name	Formula	Molecular Structure
3	Labiatic Acid	$C_{18}H_{16}O_8$	
4	Kaempferol	$C_{15}H_{10}O_6$	
5	Asiatic Acid	$C_{30}H_{48}O_5$	

### Preparation of the protein target and simulation.

In this preparation, the receptor used is 8IS4, which can be downloaded from the Protein Data Bank website (<http://www.rcsb.org/pdb>). The receptor was then visualized using Discovery Studio 2016 Client®. In this program, the downloaded receptor was prepared by removing water molecules and native ligands. The result is a purified receptor, which is then saved in Protein Data Bank format (.pdb).

### Analysis

The analysis results display the binding positions between the fifteen compounds and the protein, including the groups involved in hydrogen bonds and

hydrophobic interactions with amino acids, as well as the binding strength shown in the form of Gibbs free energy values ( $\Delta G$ ). This parameter indicates the strength of the ligand-receptor interaction. The lower the  $\Delta G$  value, the more stable the ligand-receptor binding. Additionally, inhibition constants ( $K_i$ ) are presented to determine the binding affinity.

### In Silico ADMET and Drug-Likeness Analysis

Pharmacokinetic and toxicity properties of the selected compounds were predicted using pkCSM. The SMILES structures of each compound were obtained from chemical databases and submitted to the pkCSM web server. Parameters analyzed included absorption, distribution,

metabolism, excretion, and toxicity (ADMET), such as intestinal absorption, blood–brain barrier permeability, CYP3A4 interactions, total clearance, and Ames toxicity.

Drug-likeness properties were evaluated using SwissADME based on Lipinski's Rule of Five. The evaluated parameters included molecular weight, lipophilicity (LogP), hydrogen bond donors, and hydrogen bond acceptors. Compounds meeting Lipinski's criteria were considered to have favorable drug-like properties.

## RESULTS

Binding of compounds from *Centella asiatica* was performed to obtain the lowest free energy binding with the receptor. The results indicate that three compounds from *Centella asiatica* have the best binding affinity, producing free energies of -6.97 kcal/mol, -6.51 kcal/mol, and -6.16 kcal/mol (Abdel, 2013). The docking results of Imatinib with protein 8IS4 can be seen in **Table 2**, while the docking results of *Centella asiatica* compounds with the same protein are presented in **Table 3**.

**Table 2.** Docking results of Imatinib with protein 8IS4

No	Drug Name	Interaction Bonds		RMSD (Å)	Inhibition Constant (Ki)	Free Energy (G Gibbs) No
		Hydrogen Bons	Hydrophobic Bonds (Van der Waal interactions)			
1	Imatinib	TYR256	HIS234, PRO209, ARG214, VAL212, SER213, PHE210, SER208, LEU91, TYR95, SER211, LEU168, GLY167, GLY166, LYS165	5.256 Å	8.04 nM	-11.04 kcal/mol

**Table 3.** Molecular docking results of *Centella asiatica* compounds with protein 8IS4

No	Compound Name	Interaction Bonds		RMSD (Å)	Inhibition Constant (Ki)	Free Energy (G Gibbs)
		Hydrogen Bons	Hydrophobic Bonds (Van der Waal interactions)			
1	Asiatic acid	LYS165, SER208	LEU91, TYR95, SER211, PHE210, GLY167, GLY166	3.336 Å	7.83 uM	-6.97 kcal/mol
2	Quercetin	SER240, ASP241, PHE210, VAL161, MET159	GLY167, SER211, SER208, TYR95, TYR130	4.379 Å	16.77 uM	-6.51 kcal/mol
3	Kaempferol	VAL161, PHE210, SER240, MET159	GLY167, TYR244, ASP241, LEU168, SER208, TYR95, SER211	4.093 Å	30.61 uM	-6.16 kcal/mol
4	Labiatic acid	TYR244, ASP241, SER211	HIS248, GLY167, LEU168, MET159, CYS207, SER208, GLY166, PHE210, MET159, SER208	4.375 Å	191.54 uM	-5.07 kcal/mol

No	Compound Name	Interaction Bonds		RMSD (Å)	Inhibition Constant (Ki)	Free Energy (G Gibbs)
		Hydrogen Bonds	Hydrophobic Bonds (Van der Waal interactions)			
5	Centellin	LEU168, VAL161	SER240, ASN238	LEU87,	4.289 Å	246.58 µM
			TYR244, VAL212, GLY167, SER160, GLY162	PRO209, TYR95, SER211, VAL174,		

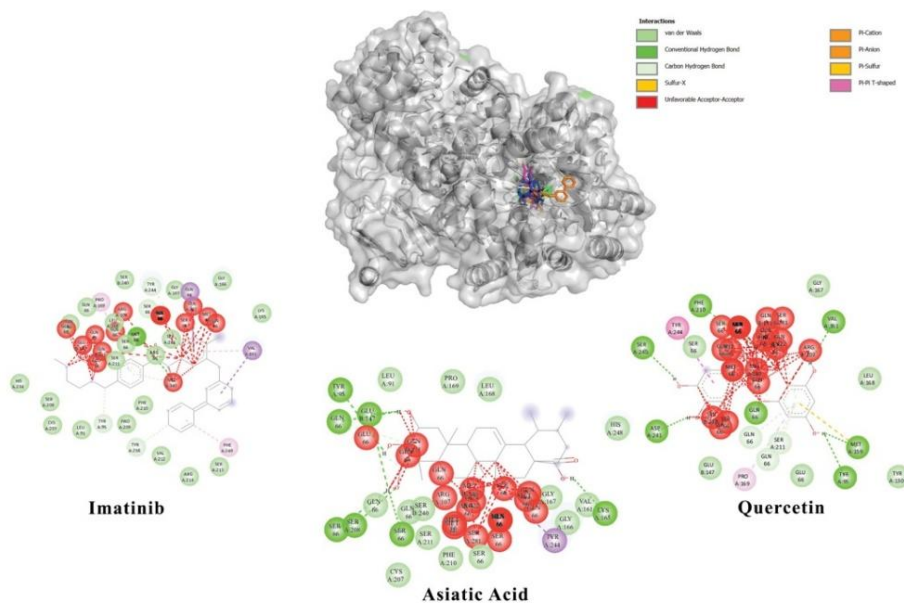
A control docking experiment was conducted to validate the docking parameters to be used in screening compounds from *Centella asiatica*. The best docking position of the compound was selected based on the most densely clustered results, followed by the interaction forms between the ligand and receptor (Ahmad, 2011). Next, the lowest binding energy after the docking search was considered. The simulation results showed that the structural deviation in terms of RMSD value was 3.336 Å.



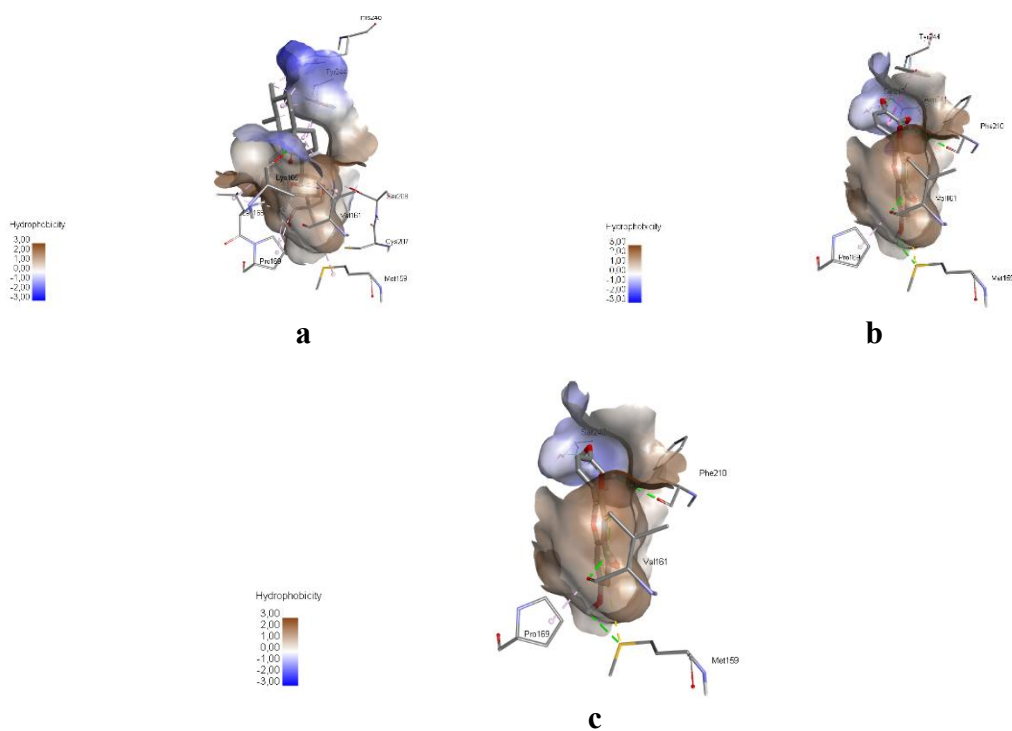
**Figure 1.** The VCZ complex (PDB ID 8IS4)

For asiatic acid, as the active site, the coordinates are: center  $x = 0.470$ ,  $y = -0.345$ ,  $z = 0.358$ , with a distance of 0.375 Å. The preparation of the main protease receptor using AutoDock 1.5.6 is shown in **Figure 1**.

The docking results of *Centella asiatica* compounds against the VCZ complex showed that five compounds have potential in inhibiting blood cancer, but three of these compounds exhibit better inhibitory potential, namely asiatic acid, quercetin, and kaempferol, with free energies of -6.97 kcal/mol, -6.51 kcal/mol, and -6.16 kcal/mol, respectively. The inhibition constants (Ki) for each compound are 7.83 µM, 16.77 µM, and 30.61 µM. Hydrogen bonds formed between these compounds and the VCZ complex involve asiatic acid, quercetin, and kaempferol. The results are shown in **Figure 2 and 3**.



**Figure 2.** Visualization of molecular interaction



**Figure 3.** Visualization of hydrogen bonds formed between (a) asiatic acid, (b) quercetin, and (c) kaempferol with the VCZ complex

To further evaluate the pharmacokinetic characteristics of the

identified compounds, in silico ADMET prediction was performed. This analysis

provides essential information on absorption, distribution, metabolism, excretion, and toxicity profiles, which are critical parameters in determining the

suitability of compounds as drug candidates. The predicted ADMET properties of the compounds are presented in **Table 4**.

**Table 4.** In Silico ADMET Prediction Results

No	Compound	MW (g/mol)	Log P	H Donor	H Acceptor	Formula	Conclusion
1	Quercetin	302.24 g/mol	1.63	5	7	C15H10O7	Complies
2	Centellin	250.33 g/mol	3.39	1	3	C15H22O3	Complies
3	Labiatic Acid	360.31 g/mol	1.48	5	8	C18H16O8	Complies
4	Kaempferol	286.24 g/mol	1.70	4	6	C15H10O6	Complies
5	Asiatic Acid	488.70 g/mol	3.41	4	5	C30H48O5	Complies

In addition to ADMET evaluation, drug-likeness analysis was conducted based on Lipinski's Rule of Five to assess the potential of the compounds for oral administration. This approach serves as an initial screening to evaluate whether the

physicochemical properties of the compounds meet the general criteria for good bioavailability. The results of the drug-likeness and related pharmacokinetic parameters are summarized in **Table 5**.

**Table 5.** Prediction of Drug-Likenes

No	Compound	Absorption		Distribution		Metabolism	Excretion	Toxicity
		Caco2 permeability	Intestinal absorption	BBB permeability	CNS permeability	CYP3A4	Total Clearance	AMES toxicity
1	Quercetin	-0.229	77.207	-1.098	-3.065	No	0.407	No
2	Centellin	1.414	94.924	-0.16	-0.16	No	1.92	No
3	Labiatic Acid	-0.937	32.516	-1.378	-3.347	No	0.25	No
4	Kaempferol	0.032	74.29	-0.939	-2.228	No	0.477	No
5	Asiatic Acid	0.479	62.855	-0.646	-1.984	Yes	0.202	No

## DISCUSSION

As a positive control, Imatinib demonstrated a strong binding affinity toward protein 8IS4, confirming its established inhibitory activity. Interestingly, several bioactive compounds from *Centella asiatica*, particularly asiatic

acid, showed comparable binding affinity values, indicating potential inhibitory activity against the target protein. This suggests that *Centella asiatica* compounds may interact with the active site of the protein in a manner similar to the control

ligand, supporting their potential as alternative therapeutic candidates.

The analysis used to evaluate the validation results is based on the RMSD. In addition to binding energy and RMSD values, asiatic acid can interact with most of the amino acid residues similar to imatinib, such as pi-sigma bonds with TYR244, hydrophobic bonds with GLY167, GLY166, SER211, TYR95, SER208, LEU91, and PHE210 (Aizawa, 2016).

Based on these analytical results, compounds from *Centella asiatica* plant can interact with key amino acid residues in the binding pocket of the VCZ complex. The three potential compounds from *Centella asiatica* such as asiatic acid, quercetin, and kaempferol form hydrogen bonds with the receptor similarly to Imatinib. These three compounds exhibit the strongest binding affinities at the active site of the VCZ complex.

Pre-ADMET analysis was conducted to complement the evaluation by assessing the pharmacokinetic profile of the compounds, including absorption, distribution, metabolism, excretion, and toxicity. This approach is essential, as the success of a drug candidate is not solely determined by its biological activity but also by how the compound is processed within the body. Recent studies have shown that *in silico* ADMET prediction can improve the efficiency of drug candidate selection and reduce failure rates in advanced stages of drug development (Pirie et al., 2024). The predicted Pre-ADMET results using pkCSM are presented in **Table 4**.

In terms of absorption, parameters such as Caco-2 permeability and intestinal absorption indicated variability among the compounds. Centellin exhibited the highest absorption value, suggesting good oral

bioavailability. In contrast, labiatic acid showed low permeability, indicating limited absorption in the gastrointestinal tract. These findings suggest that physicochemical properties, such as molecular size and lipophilicity, significantly influence compound absorption (Karami et al., 2022)

Regarding distribution, all compounds demonstrated low blood-brain barrier (BBB) permeability, indicating limited penetration into the central nervous system. This suggests that the compounds are more likely to be distributed in peripheral tissues. Such a profile may be advantageous when the therapeutic target is outside the central nervous system, as it reduces the risk of neurological side effects (Su'aida et al., 2025).

In the metabolism phase, most compounds showed no interaction with the CYP3A4 enzyme, suggesting a relatively low potential for drug–drug interactions. However, asiatic acid indicated a possible interaction with this enzyme, which should be considered in further development. Interactions with metabolic enzymes may affect compound stability and increase the risk of drug–drug interactions (Londhe et al., 2024).

In terms of excretion, total clearance values indicated differences in elimination rates among the compounds. Centellin exhibited a higher clearance value, suggesting faster elimination, whereas asiatic acid showed lower clearance, indicating a longer retention time in the body. These differences are important in determining the duration of drug action and dosing frequency (Cherian & Vadivel, 2024).

Initial evaluation of compounds as potential oral drug candidates was performed using Lipinski's Rule of Five, which remains a fundamental parameter for

assessing drug-likeness. This rule states that compounds with a molecular weight  $\leq 500$  g/mol,  $\log P \leq 5$ , hydrogen bond donors  $\leq 5$ , and hydrogen bond acceptors  $\leq 10$  are more likely to exhibit good oral absorption. However, recent studies indicate that this rule is not absolute, but rather serves as an initial screening tool in drug discovery (Karami et al., 2022). Therefore, compounds that do not fully comply with these criteria may still be considered for development, particularly if supported by favorable pharmacokinetic properties.

Based on the analysis, most compounds met the criteria for hydrogen bond donors and acceptors but showed deviations in  $\log P$  values and molecular weight (Gurung et al., 2020). Quercetin and kaempferol exhibited low  $\log P$  values, indicating hydrophilic characteristics. This may enhance solubility in biological fluids but potentially reduce membrane permeability. In contrast, asiatic acid showed higher lipophilicity and a molecular weight approaching the upper limit, which may improve permeability but could reduce solubility. These findings highlight that the balance between lipophilicity and polarity plays a crucial role in determining compound absorption (Pirie et al., 2024).

Furthermore, the presence of compounds that do not fully comply with Lipinski's criteria reflects the limitations of this approach, particularly for natural product-based compounds, which often possess complex structures (Ding et al., 2016). Recent studies have demonstrated that many natural compounds retain significant biological activity despite violating one or more Lipinski rules, leading to the emergence of the "beyond rule of five" concept in modern drug development (Harkat-Madouri et al., 2015).

Therefore, further comprehensive analyses are required to more accurately evaluate the drug potential of these compounds.

## CONCLUSION

Based on the in-silico analysis, bioactive compounds from *Centella asiatica* demonstrated promising potential as anti-blood cancer agents, particularly against targets associated with chronic myeloid leukemia. Molecular docking results revealed that asiatic acid exhibited the strongest binding affinity toward protein 8IS4, followed by quercetin and kaempferol, indicating stable and favorable interactions with the target protein, comparable to the positive control, Imatinib. Furthermore, ADMET predictions showed that these compounds generally possess favorable pharmacokinetic properties, including good absorption and low toxicity, although some variability was observed in permeability and metabolic stability.

Drug-likeness evaluation based on Lipinski's Rule of Five indicated that most compounds met the required criteria, supporting their potential as orally active drug candidates. Overall, these findings highlight the potential of *Centella asiatica* as a source of bioactive compounds for anti-blood cancer drug development. However, further validation through in vitro and in vivo studies is necessary to confirm their biological activity and safety profiles.

## CONFLICT OF INTEREST

The authors declare that they have no conflict of interest regarding the publication of this paper.

## AUTHORS' DECLARATION

The authors declare that this manuscript is original, has not been

published previously, and is not under consideration elsewhere. All authors have approved the final version of the manuscript and declare no conflicts of interest.

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