ORIGINAL ARTICLE

Anticancer activity prediction of *Curcuma longa* and *Phyllanthus urinaria* through computational analysis

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ABSTRACT

Traditional Indonesian medicine has long been recognized for its curative qualities, although concerns remain over the efficacy and safety of medicinal herbs. The application of computational methods in novel drug discovery is one of the promising new insights offered by recent technical advancements. This study attempts to find putative anticancer chemicals in two extensively used plants in Southeast Asia, *Curcuma longa* and *Phyllanthus urinaria*, using a computational technique. AKT1, a model protein implicated in the development of cancer cells, was used in this investigation. In these two plants, 28 different chemicals were found. We use strict selection standards, like Lipinski's rule of five, to ensure the identification of potential candidates. The findings demonstrated that 24 compounds had comparable binding affinities to the reference ligands, indicating encouraging therapeutic potential. Subsequent investigation showed that the compounds' chemical structures differed and that their similarities to the reference ligand were <10%. However, for both plant-derived drugs, the amino acid binding patterns revealed remarkable similarities that went above 50% similarity, suggesting that both may be useful.

Key words: AKT1, anticancer, computational, *Curcuma longa*, *Phyllanthus urinaria*

INTRODUCTION

Cancer is a disease whose rates of morbidity and death are constantly rising. Cancer lowers a patient's quality of life, productivity, and financial standing as well as that of their family, the community, and finally, a whole nation.[1] Almost two-thirds of cancer cases worldwide occur in low- and middle-income countries.[2]

In cancer cases, the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and the mammalian target of rapamycin (mTOR) pathway are implicated. Numerous aspects of cell growth and survival in both healthy and sick conditions depend on the PI3K-Akt-mTOR signaling pathways. This method aids in the regulation of survival during cellular stress since tumors grow in an environment that is stressful by nature, marked by low pH, inadequate oxygen and nutrition supply, and both.[3] Akt is identified as a central driver of oncogenesis, necessitating its inhibition to hinder cancer progression.[4]

Cancer therapy is often an intriguing area of research, especially alternative therapy using herbal medicine. Indonesian people have relied on herbal medicine to treat illnesses and maintain health.[5] *Curcuma longa* and *Phyllanthus urinaria* are two plants believed to have anticancer activity. *Curcuma longa* is known as an anti-inflammatory, antioxidant, and anticancer traditional

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herbal remedy.[6-8] *Phyllanthus urinaria*, popularly known as "meniran" in Indonesia, is another plant that demonstrates antiproliferative potential.[9] Various publications cite *Phyllanthus urinaria* as a plant exhibiting anticancer action.[10] *Phyllanthus urinaria* compound action includes activation of PI3K/Akt, MAPKs, and NF-κB signaling.[11]

Continued research into these two plants' potential is necessary to ensure both their safety and efficacy as anticancer medications. "Computational pharmaceutics," a novel discipline, has incorporated big data, artificial intelligence, and multiscale modeling techniques into pharmaceutics, thereby presenting a significant opportunity to revolutionize the delivery of medicine.[12] With this background in mind, this study uses a variety of *in silico* computational approaches, molecular docking research, and machine learning techniques to find putative anticancer compounds in *Curcuma longa* and *Phyllanthus urinaria*. It also cites protein Akt1 as a critical node in the division of cancer cells.

METHODS

Data mining and the extraction of fingerprints

A machine learning algorithm predicted Akt1 protein inhibitors in *Curcuma longa* and *Phyllanthus urinaria* using compound data from the KNApSAcK database.[13] RDKit software extracted molecular structures to generate PubChem fingerprints, consisting of 881 substructures scored binary. Dudedocking compiled a dataset of known Akt1 protein inhibitors and decoy compounds.[14] A machine learning model was trained using active and inactive compounds, with each substructure extracted using RDKit's fingerprint extractor.

Development of machine learning models

Machine learning models were constructed using scikit-learn, a Python toolkit, and code creation and implementation were made with Jupyter Notebook. The receiver operating characteristic (ROC) curve's area under the curve (AUC) was used to assess the models' efficacy. After comparing the random forest (RF), support vector machine, and logistic regression techniques, the model with the highest AUC/ROC score was selected to predict the active chemicals in *Phyllanthus urinaria* and *Curcuma longa*.

Molecular docking and interaction analysis

The PLANTS 1.1 program evaluates each component's possible binding affinities through a molecular docking study. This application finds the lowest energy conformation of the ligand in the binding pocket of the protein using an artificial ant colony. The binding affinity (ΔG) is then determined using Prodigy software, which leverages protein-ligand principles and modifies tiny ligand prediction methods to use atomic interactions rather than residue contacts (https://bianca.science.uu.nl/prodigy/lig).[15]

Druglikeness and absorption, distribution, metabolism, excretion, and toxicity analysis

A commonly used metric for assessing druglikeness is Lipinski's rule of five, which considers four key properties: a maximum of five hydrogen bond donors, 10 or fewer hydrogen bond acceptors, a molecular weight <500 Daltons, and a Log *P* value not exceeding 4.15.[16] To assess the toxicity of each compound, Toxtree software is employed. Toxicity studies are occasionally integrated with assessments of the blood–brain barrier (BBB) and human intestinal absorption to determine the quantity of substances that the gastrointestinal (GI) tract can absorb.

Tanimoto similarity for calculating binding site similarity and chemical structure

The potential compounds are fingerprinted for structural similarity assessment with the reference ligand using RDKit in Jupyter Notebook. Molecular docking results involve interaction with protein amino acids, comparing active residue interactions with the reference ligand to gauge similarity using BIOVIA Discovery Studio.

RESULTS

Data mining and the extraction of fingerprints

A total of 180 compounds were obtained from the KNApSAcK database using the keyword *Curcuma longa*, along with 21 compounds from the keyword *Phyllanthus urinaria*. To build a model, a dataset was created from Dudedocking, consisting of 292 active compounds and 800 decoy compounds. After extracting fingerprints using PubChem, the dataset comprised 1092 compounds. Approximately 75% of the dataset was used for training, with the remaining 25% reserved for testing purposes.

Development of machine learning models

After calculating sensitivity, specificity, accuracy, and AUC/ROC score, the RF model is found to be the best fit for the Akt1 dataset.

After developing several machine learning models, a rigorous evaluation process ensued. The RF model emerged

Table 1: The score of each of the three models for Akt1 protein

Model	Accuracy	Sensitivity	Specificity	AUC/ROC score	Cv mean training score	Cv mean testing score
LR	0.985	0.982	0.986	0.9993	1.000	0.978
SVM	0.992	1.000	0.990	0.9997	0.990	0.978
RF	0.992	1.000	0.990	0.9999	1.000	0.979

AUC: Area under the curve, ROC: Receiver operating characteristic curve, RF: Random forest, SVM: Support Vector Machine, LR: Logistic regression, Cv: Cross validation

as the most effective, supported by its superior performance on the training data. To validate this, k-fold cross-validation was utilized, consistently demonstrating strong results for the RF model [Table 1]. The model identified 19 compounds from *Curcuma longa* and 13 from *Phyllanthus urinaria* with potential Akt1 protein inhibitory activity

Molecular docking and interaction analysis

All compounds predicted to inhibit the Akt1 protein underwent analysis using molecular docking software to evaluate their potential binding within the protein's binding pocket. The protein structure of Akt1 (PDB: 3CQW) was utilized, including a reference ligand (PubChem code: 24798742) bound to the protein. Before analyzing the predicted compounds, a redocking process validated the molecular docking software. This involved redocking the reference ligand to the Akt1 protein for 1000 repetitions and calculating the root mean square deviation (RMSD). This step ensured the software accurately replicated, with an ideal RMSD value below or similar to 2 Å.[17]

The redocking process consistently produced RMSD values below 2 Å compared to the reference pose. This confirms the accuracy of the software PLANTS 1.1. Following accuracy validation, the predicted active compounds from the machine learning model underwent molecular docking simulations. The docking score and binding affinity score of selected compounds from *Curcuma longa* and *Phyllanthus urinaria* are presented in Tables 2 and 3.

The results of molecular docking analysis revealed interesting binding affinity trends. Gallic acid from *Phyllanthus urinaria* exhibited a higher binding affinity score compared to the reference ligand. Similarly, in *Curcuma Longa*, caffeic acid, vanillic acid, and vanillin displayed higher binding affinity scores than the reference ligand. Lower scores in this context indicate stronger binding interactions, implying that these specific compounds from *Curcuma longa* may possess enhanced activity. Furthermore, the remaining analyzed compounds demonstrated binding affinity scores lower than the reference ligand, indicating potentially stronger binding interactions.

Table 2: Docking and binding affinity scores (ΔG) for the predicted compounds as inhibitors for Akt1 protein from *Phyllanthus urinaria*

Compound	Docking score	Binding affinity (ΔG) (kcal/mol)
Lintetralin	−60	−9.2
Urinatetralin	−78	−9.8
Virgatusin	−78	−9.8
Gallic acid	−62	−7
Kaempferol	−67	−8.6
Quercetin	−72	−8.58
Quercetin 3-O-alpha-L-rhamnoside	−65	−9.73
Quercetin 3-rutinoside	−55	−10.7
Phyllanthurinolactone	−83	−8.34
Dextrobursehernin	−75	−9.65
Heliobuphthalmin lacton	−88	−9.41
Methyl brevifolincarboxylate	−75	−8.59
Phyllanthin	−71	−9.92
Reference ligand (pubChem id: 24798742)	−79	−7.6

Druglikeness and absorption, distribution, metabolism, excretion, and toxicity analysis

The findings of the analysis of five Lipinski compounds found in both plants are shown here. Two compounds from both of plants were found to fail in Lipinski's rule of five. Quercetin 3-O-alpha-L-rhamnoside and quercetin 3-rutinoside from *Phyllanthus urinaria* [Figure 1]. D-sucrose and trehalose from *Curcuma Longa* [Figure 2].

According to research, some compounds were predicted to demonstrate high GI absorption and BBB permeation. High GI absorption suggests good oral bioavailability. Similarly, good BBB permeability indicates the ability of drugs to penetrate the BBB and reach their target sites within the brain.[17] Gallic acid was the sole compound from *Phyllanthus urinaria* identified as exhibiting low (Class I) toxicity [Table 4].

Analysis classified three compounds, gitoxigenin, cyclocurcumin, and curcumin, from the *Curcuma longa* group as having high (Class III) toxicity. The remaining compounds were assigned low (Class I) toxicity [Table 5].

Tanimoto similarity for chemical structure and binding site similarity calculation

Tanimoto similarity calculations using Morgan fingerprint did not find any compounds in *Curcuma longa* or *Phyllanthus urinaria* with a structural similarity exceeding 10% to the reference ligand (pubChem id: 24798742) [Tables 6 and 7]. However, amino acid analysis involved in compound binding revealed that at least 50% of the amino acids in selected *Phyllanthus urinaria* compounds exhibited similarity to the amino acid binding site of the reference ligand [Table 6]. Virgatusin displayed the highest binding site similarity (70%) within the *Phyllanthus urinaria* group, while curcumin showed the lowest (20%) in *Curcuma longa*, and vanillin and vanillic acid exhibited 70% similarity [Table 7]. The remaining *Curcuma longa* compounds also showed at least 50% similarity in their binding site amino acids compared to the reference ligand.

Amino acids used in docking poses for selected compounds from *Phyllanthus urinaria* and *Curcuma longa* were about 50% similar to the reference ligand, as shown in Figures 3 and 4. Lintetralin, urinatetralin, virgatusin, phyllanthurinolactone, and phyllanthin in *Phyllanthus urinaria* had higher total hydrogen bond interactions with the protein compared

Table 3: Docking and binding affinity score (ΔG) for the predicted compounds as inhibitors for Akt1 protein from *Curcuma longa*

Compound	Docking score	Binding affinity (ΔG) (kcal/mol)
D-Sucrose	−74	−7.9
Trehalose	−77	−8.0
Caffeic acid	−72	−7.5
Vanillic acid	−61	−7.3
Vanillin	−60	−7.3
3-Hydroxy-1,7-bis (4-hydroxyphenyl)-6-heptene-1,5-dione	−88	−9.15
3,6-Dihydroxy-p-menth-1-en-8-oic acid	−62	−7.67
Gitoxigenin	−72	−10.18
p-Cymene	−61	−7.79
(R)-(-)-alpha-Curcumene	−72	−8.8
(+)-ar-Turmerone	−71	−8.8
p-Cymen-8-ol	−65	−7.7
(+)-ar-Dihydroturmerone	−66	−8.8
alpha-Curcumene	−72	−8.8
Cyclocurcumin	−79	−9.5
(E)-Nuciferol	−80	−8.9
4-[(1S)-1,5-Dimethyl-3-oxo-4-hexen-1-yl]-benzaldehyde	−76	−8.8
beta-Turmerone	−74	−8.9
Curcumin	−74	−9.3
Reference ligand (pubChem id: 24798742)	−79	−7.6

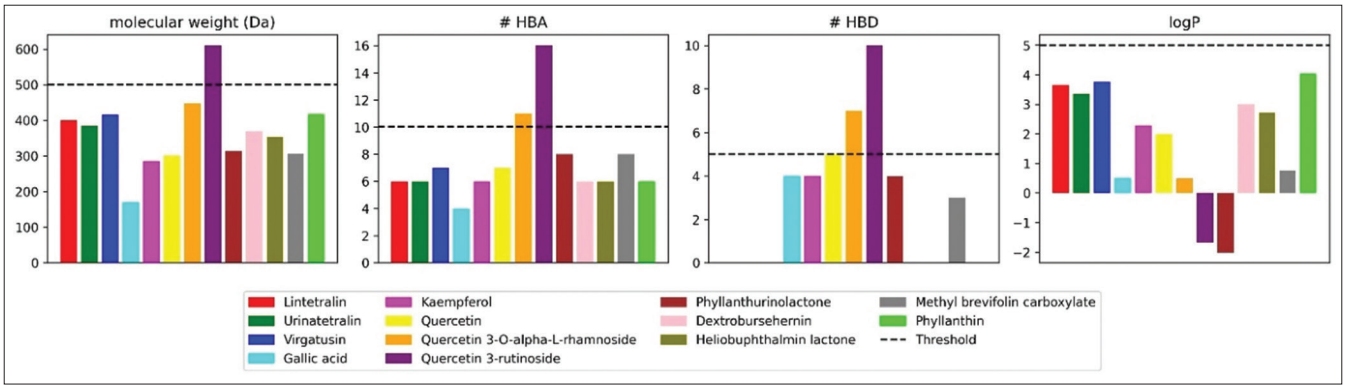

Figure 1: Lipinski rule of five for selected compound from *Phyllanthus urinaria*. HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, logP: Partition coefficient

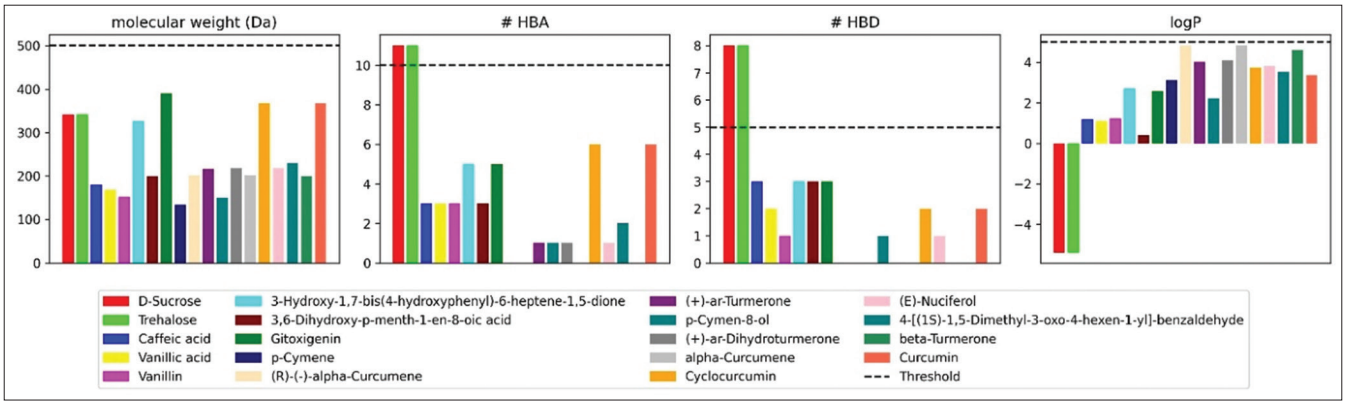

Figure 2: Lipinski rule of five for selected compound from *Curcuma longa.* HBA: Hydrogen bond acceptor, HBD: Hydrogen bond donor, logP: Partition coefficient

Table 4: Absorption, distribution, metabolism, excretion and toxicity prediction of predicted ligand inhibitor for Akt1 protein from *Phyllanthus urinaria*

PubChem_id	Compound name	GI absorption	BBB	Creamer	Carcinogenicity
11361584	Lintetralin	High	Yes	High (Class III)	Alert for nongenotoxic carcinogenicity
11760779	Urinatetralin	High	Yes	High (Class III)	Alert for nongenotoxic carcinogenicity
10549813	Virgatusin	High	Yes	High (Class III)	Alert for nongenotoxic carcinogenicity
370	Gallic acid	High	No	Low (Class I)	Negative
5280863	Kaempferol	High	No	High (Class III)	Negative
5280343	Quercetin	High	No	High (Class III)	Negative
5280459	Quercetin 3-O-alpha-L-rhamnoside	High	No	High (Class III)	Negative
5280805	Quercetin 3-rutinoside	Low	No	High (Class III)	Negative
10957981	Phyllanthurinolactone	Low	No	High (Class III)	Negative
15941633	Dextrobursehernin	High	Yes	High (Class III)	Alert for nongenotoxic carcinogenicity
11002708	Heliobuphthalmin lactone	High	Yes	High (Class III)	Alert for nongenotoxic carcinogenicity
441161352	Methyl brevifolincarboxylate	High	No	High (Class III)	Negative
358901	Phyllanthin	High	Yes	High (Class III)	Alert for nongenotoxic carcinogenicity

GI: Gastrointestinal, BBB: Blood–brain barrier

Table 5: Absorption, distribution, metabolism, excretion, and toxicity prediction of predicted ligand inhibitor for Akt1 protein from *Curcuma longa*

PubChem_id	Compound name	GI absorption	BBB	Creamer	Carcinogenicity
689043	Caffeic acid	High	No	Low (Class I)	Negative
8468	Vanillic acid	High	No	Low (Class I)	Negative
1183	Vanillin	High	Yes	Low (Class I)	Alert for genotoxic carcinogenicity
91307775	3-Hydroxy-1,7-bis-(4-hydroxyphenyl)-6-heptene-1,5-dione	High	No	Low (Class I)	Negative
91451640	3,6-Dihydroxy-p-menth-1-en-8-oic acid	High	No	Low (Class I)	Negative
348482	Gitoxigenin	High	No	High (Class III)	Negative
7463	p-Cymene	Low	Yes	Low (Class I)	Negative
442360	(R)-(-)-alpha-curcumene	Low	No	Low (Class I)	Negative
160512	(+)-ar-Turmerone	High	Yes	Low (Class I)	Alert for genotoxic carcinogenicity
14529	p-Cymen-8-ol	High	Yes	Low (Class I)	Negative
1.63E+08	(+)-ar-Dihydroturmerone	High	Yes	Low (Class I)	Negative
92139	alpha-Curcumene	Low	No	Low (Class I)	Negative
69879809	Cyclocurcumin	High	No	High (Class III)	Alert for genotoxic carcinogenicity
6429177	(E)-Nuciferol	High	Yes	Low (Class I)	Negative
73318873	4-[(1S)-1,5-Dimethyl-3-oxo-4-hexen-1-yl]-benzaldehyde	High	Yes	Low (Class I)	Alert for genotoxic carcinogenicity
11063457	beta-Turmerone	Low	No	Low (Class I)	Negative
969516	Curcumin	High	No	High (Class III)	Negative

GI: Gastrointestinal, BBB: Blood–brain barrier

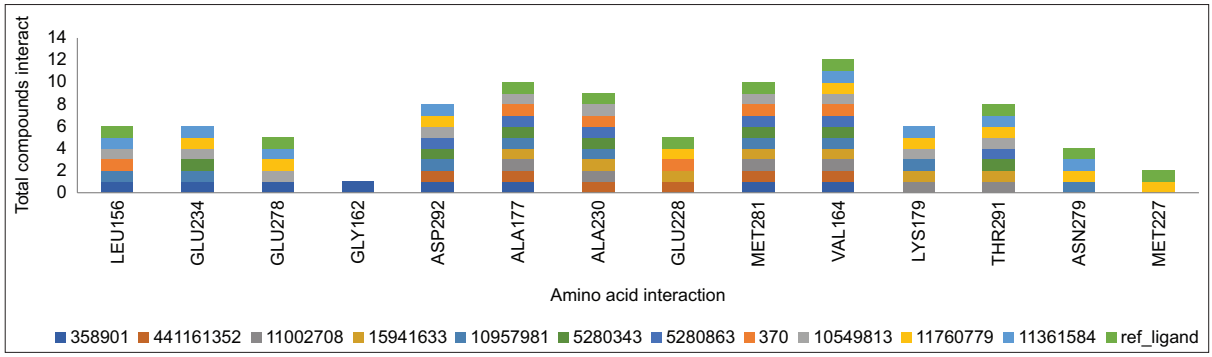

Figure 3: Amino acid in protein used in docking poses for selected compound from *Phyllanthus urinaria*

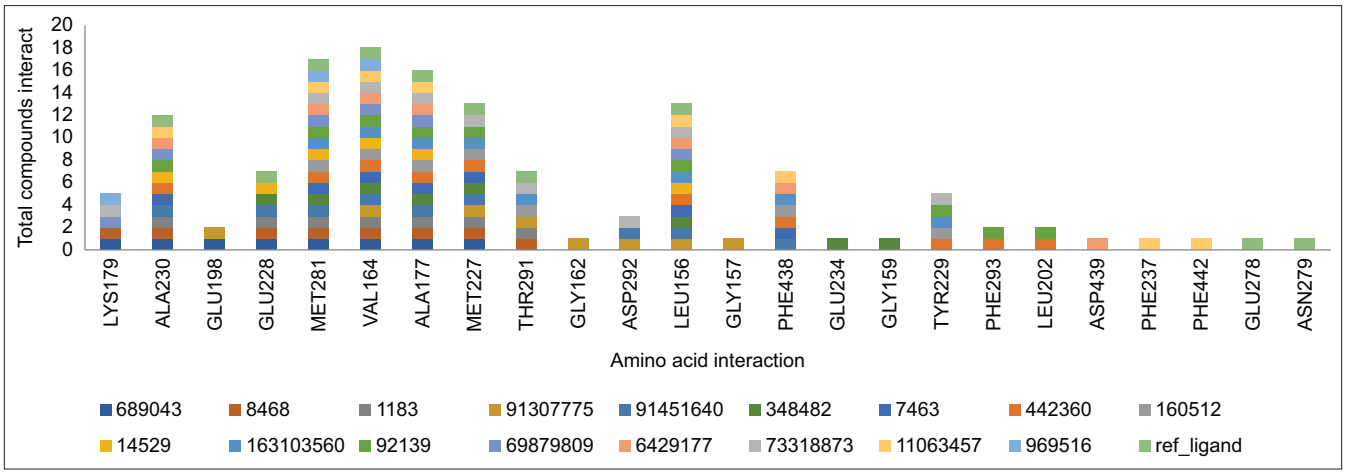

Figure 4: Amino Acid in protein used in docking poses for selected compound from *Curcuma longa*

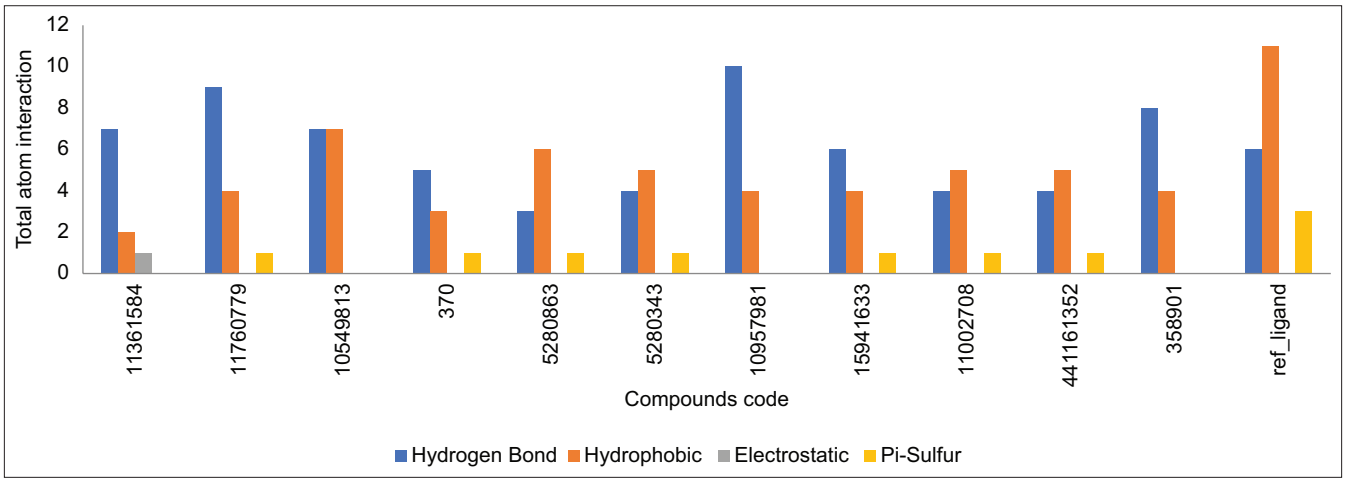

Figure 5: Calculated total interaction between selected ligand in *Phyllanthus urinaria* compared to reference ligand with protein Akt1

Table 6: Tanimoto similarity and Interaction fingerprint similarity of structure selected compound from *Phyllanthus urinaria* with reference ligand (pubChem id: 24798742)

Compounds_ID	Tanimoto similarity (%)	Interaction fingerprint similarity (%)
358901	3	50
11361584	5	50
11760779	5	60
10549813	5	70
370	4	60
5280863	6	50
5280343	6	50
10957981	6	60
15941633	5	60
11002708	6	50
441161352	8	50

to the reference ligand despite showing lower total hydrophobic interactions. Dextrobursehernin showed a similar total number of hydrogen bond interactions with the reference ligand [Figure 5]. Conversely, no compounds in curcumin exhibited higher total hydrogen bond interactions with the ligand compared to the reference ligand. However, after calculating hydrophobic interactions, beta-turmerone, (+)-ar-Dihydroturmerone, alpha-curcumene, and (R)-(-)-alpha-curcumene showed higher total hydrophobic interactions compared to the reference ligand [Figure 6].

The reference ligand may possess a lower number of hydrogen or hydrophobic bonds. However, it compensates with three pi-sulfur interactions, the strongest type of interaction listed. While some compounds in *Phyllanthus urinaria* and *Curcuma longa* also exhibit pi-sulfur interactions, the number is lower compared to the reference ligand. This suggests that natural compounds might have fewer pi-sulfur interactions. However, Lintetralin from *Phyllanthus urinaria* and vanillic acid, cyclocurcumin, and curcumin from *Curcuma longa* exhibit electrostatic interactions, the second strongest interaction type. These electrostatic interactions could potentially contribute to tight binding of the natural compounds to the protein target.[18]

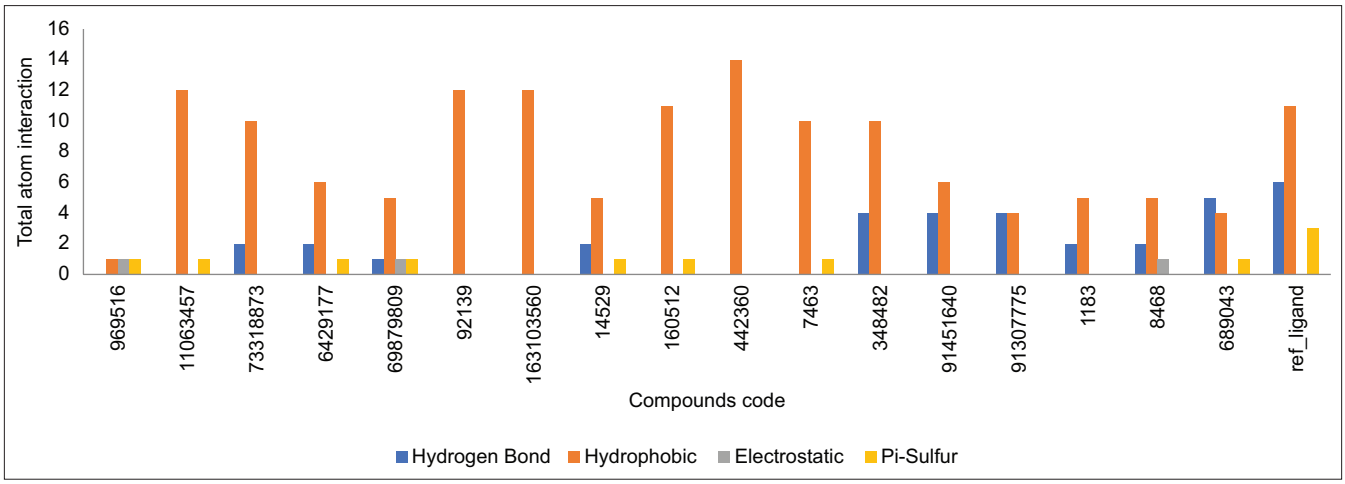

Figure 6: Calculated total interaction between selected ligand in *Curcuma longa* compared to reference ligand with protein Akt1

Table 7: Tanimoto similarity and Interaction fingerprint similarity of structure selected compound from *Curcuma longa* with reference ligand (pubChem id: 24798742)

Compounds_ ID	Tanimoto similarity (%)	Interaction fingerprint similarity (%)
689043	3	60
8468	3	70
1183	3	70
91307775	3	40
442360	3	60
160512	3	50
163103560	3	60
92139	3	60
6429177	3	50
73318873	3	60
11063457	3	50
14529	4	60
969516	4	20
91451640	4	70
348482	5	60
69879809	5	50
7463	6	60

DISCUSSION

This study highlights the widespread use of traditional medicine in Indonesian civilization for health management and treatment, revealing a critical knowledge gap in the safety and efficacy of medicinal plants. This lack hinders evidence-based practices and raises concerns about potential adverse effects. *Curcuma longa* and *Phyllanthus urinaria* exemplify this gap, with their precise beneficial compounds unidentified. Using a machine learning approach, potential AKT1 protein inhibitors were predicted from *Curcuma longa* and *Phyllanthus urinaria*. *In silico* methods were employed for investigation, with compound selection from public databases and fingerprint generation using RDKit. The RF model proved the most effective in predicting active compounds.[19,20]

The predicted active compounds underwent molecular docking analysis to evaluate their binding interactions with target proteins. However, interpreting the results requires caution, as higher binding affinity scores may signify weaker interactions. Gallic acid from *Phyllanthus urinaria* and certain compounds (caffeic acid, vanillic acid, and vanillin) from *Curcuma longa* showed particularly high scores, warranting further investigation as potential drug candidates.

The adherence of identified compounds to Lipinski's rule of five provided valuable insights. However, several compounds from both plants violated the rule (e.g., quercetin derivatives, D-sucrose, and trehalose), potentially limiting their oral bioavailability.[16] Future studies could explore alternative administration routes or structural modifications to enhance their drug-like properties. *Phyllanthus urinaria* compounds, including lintetralin, urinatetralin, virgatusin, dextrobursehernin, heliobuphthalmin lactone, and phyllanthin, were predicted to have good GI absorption and BBB permeability, crucial for oral drugs to reach target sites.[18]

This study explored the binding mechanisms of natural products from *Phyllanthus urinaria* and *Curcuma longa* in comparison to a reference ligand. While the reference ligand showed a profile with more pi-sulfur interactions, the natural compounds revealed alternative binding strategies, showcasing the complexity of protein-ligand interactions. Interestingly, natural products compensated for the lack of pi-sulfur bonds with electrostatic interactions, suggesting tight binding with the protein target. These findings emphasize the importance of considering various intermolecular interactions in protein-ligand binding evaluation. Despite the insights provided, the study's

reliance on computational methods presents limitations, necessitating validation through *in vitro* and *in vivo* studies. Nonetheless, this research contributes to understanding natural product binding strategies and encourages further investigation for evidence-based natural therapies.

CONCLUSION

This study explored natural products from *Phyllanthus urinaria* and *Curcuma longa* as Akt1 protein inhibitors, addressing their limited scientific understanding despite extensive traditional use. Using an *in silico* approach, promising compounds were identified through machine learning and molecular docking. However, interpreting docking results is crucial, as higher affinity scores may indicate weaker protein interactions. Lipinski's rule of five analysis highlighted potential limitations for some compounds, suggesting oral bioavailability challenges. Understanding alternative binding strategies of natural products compared to traditional drugs is vital for evaluating protein-ligand interactions. This study lays the groundwork for further research, prioritizing *in vitro* and *in vivo* assays to validate activities and safety profiles, contributing to evidence-based natural therapies, and enhancing our understanding of protein-ligand interactions.

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Nil.

Conflicts of interest
There are no conflicts of interest.

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