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RESEARCH ARTICLE

Docking-Based Virtual Screening of Bisbenzylisoquinoline Derivatives from *Stephania* Genus Against Hepatocellular Carcinoma

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ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common and aggressive subtypes of liver cancer. It has a poor prognosis, a high rate of recurrence and shows limited response to current therapies. In order to combat this condition, the use of natural products as multitarget anticancer agents is gaining momentum. In this study, we investigated the medicinal value of bisbenzylisoquinoline (BBI) alkaloids from the Stephania genus via an integrative in silico approach. Due to their improved pharmacokinetic profiles and expected low toxicity, we chose 11 BBI derivatives. Network pharmacology analysis revealed 334 overlapped targets between the compounds and HCC. Functional enrichment indicated that the PI3K-Akt signaling pathway was essential in HCC progression. In addition, protein-protein interaction (PPI) network construction and topological analysis identified AKT1 and PI3K as hub proteins. Molecular docking simulations found that isotrilobine had the highest binding affinity towards both AKT1 (−10.5 kcal/mol) and PI3K (−9.9 kcal/mol), compared to that of the reference drug sorafenib. These findings indicated a possible involvement of BBI compounds in modulating key oncogenic pathways relevant to tumor growth and metastasis. Taken together, this study unveils isotrilobine as a promising lead compound and provides a mechanistic rationale for the further exploration of Stephania-derived BBI alkaloids as potential HCC therapeutics.

Keywords: Bisbenzylisoquinolines, Hepatocellular carcinoma, Molecular docking, Network pharmacology, Stephania

Introduction

Hepatocellular carcinoma (HCC) is the most prevalent type of liver cancer and one of the leading causes of cancer-related mortality globally.[1,2] Despite advancements in therapies such as surgical resection, transarterial chemoembolization, tumor ablation, and liver transplantation, survival remains poor. That's because tumors typically return and resist chemotherapy.[3] Oral targeted therapies, such as sorafenib and levantinib, have led to improved clinical outcomes; however, these agents are not without side effects or the development of drug resistance.[4] This demonstrates that we should always seek new avenues for treating diseases. The use of natural compounds as anticancer agents has attracted attention owing to their varied bioactive properties and lower toxicity,[5–7] significantly impacting modern

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drug discovery in the context of Traditional Chinese Medicine (TCM), which plays a significant role by highlighting the potential existence of plant-based anticancer compounds. *Stephania* is a genus of the Menispermaceae family. It has long been known to help with pain and swelling. Now it is receiving more attention as it may be able to help treat cancer.[8–10] Among its bioactive constituents, bisbenzylisoquinoline (BBI) alkaloids stand out for their promising anticancer properties, particularly in inducing apoptosis and blocking the cell cycle in many types of cancers.[11–13] Nonetheless, the molecular mechanisms that enable their therapeutic effects against HCC remain insufficiently understood. This study utilized network pharmacology to elucidate the primary molecular mechanisms and therapeutic targets of BBI derivatives from *Stephania* in the context of HCC, with the objective of advancing drug discovery efforts.[14] A molecular docking analysis was performed to evaluate the binding affinity of critical target molecules to prospective HCC inhibitors, offering additional computational validation.[15] Computational approaches markedly diminish the time and expense related to drug development when contrasted with traditional drug discovery methods.[16] We also looked at the pharmacokinetic properties and safety profile of BBI derivatives by testing their GI absorption, drug-likeness, and LD_{50} toxicity.[17] By integrating these approaches, this current study establishes a mechanistic basis for the anticancer potential of BBI alkaloids and lays the groundwork for further *in vitro* and *in vivo* validation.

Materials and methods

Selection of bisbenzylisoquinoline derivatives from Stephania genus and toxicity prediction

BBI compounds were retrieved from relevant literature and screened using PASS Online (http://www.pharmaexpert.ru/passonline/, Institute of Biomedical Chemistry, Russia). SMILES representation of each compound was obtained from PubChem (PubChem). Selected compounds were further evaluated using SwissADME (SwissADME, version 2023.2, Swiss Institute of Bioinformatics) to predict gastrointestinal (GI) absorption and drug-likeness. Toxicity prediction was performed using ProTox 3.0 (ProTox-3.0-Prediction of TOXicity of chemicals, Charité – Universitätsmedizin Berlin). Only compounds exhibiting high gastrointestinal (GI) absorption and favorable drug-likeness properties were selected for further analysis.

Target identification: Bisbenzylisoquinoline derivatives from Stephania genus

Target prediction in this study was conducted using 3 databases. In Swiss Target Prediction (SwissTargetPrediction, Swiss Institute of Bioinformatics) and Similarity Ensemble Approach (SEA) (SEA Search Server, Brian Shoichet Laboratory, UCSF), each compound was entered in SMILES format and limited to the species *Homo sapiens*. In the Comparative Toxicogenomics Database (CTD) (The Comparative Toxicogenomics Database | CTD, MDI Biological Laboratory), targets were identified using compound names. The resulting targets were compiled and defined as BBI-related targets.

Identification of HCC-related targets

We got HCC-associated targets from GeneCards (GeneCards-Human Genes | Gene Database | Gene Search, version 5.12, The Weizmann Institute of Science) and OpenTargets (Home-Open Targets, version 23.11, Open Targets Consortium). GeneCards gave information about both the genome and how it works, while Open Targets ranks targets based on evidence from multiple omics and the literature. Overlapping targets from both databases were selected as HCC-related genes.

Construction and analysis of the Protein–Protein Interaction (PPI) network

The common targets between BBI-related and HCC-related genes were identified through Venny 2.1 (Venny 2.1.0). The intersected genes were then uploaded into STRING (STRING: functional protein association networks, version 11.5, Swiss Institute of Bioinformatics) with a confidence score $\geq$ 0.9 to construct the PPI network. Furthermore, the network was analyzed using Cytoscape 3.10.2, and hub genes were identified using the CytoHubba plugin based on topological parameters such as degree, betweenness centrality (BC), and closeness centrality (CC). The top 3 hub proteins were selected for docking analysis.

Functional enrichment and pathway analysis

All intersected targets were analyzed for Gene Ontology (GO) terms and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment using DAVID (DAVID Functional Annotation Bioinformatics Microarray Analysis, NIH/NCI). Results were categorized into biological process (BP), molecular function

Table 1. ADME and toxicity prediction of 11 filtered active components.

Compounds	Molecular weight	GI absorption	Druglikeness	Plasma Protein Binding	Predicted Toxicity Class	Predicted LD_{50} (mg/Kg)
Cepharanoline	592.7 g/mol	High	Yes	81,0362	4	1190
Cepharanthine	606.7 g/mol	High	Yes	80,58489	4	1190
Hypoepistephanine	592.7 g/mol	High	Yes	88,26509	4	1190
Oxyacanthine	608.7 g/mol	High	Yes	73,28471	4	1190
Stebisimine	590.7 g/mol	High	Yes	95,69549	4	1190
Fangchinoline	608.7 g/mol	High	Yes	71,38013	4	1190
Isotetrandrine	622.7 g/mol	High	Yes	75,32017	4	1190
Obamegine	594.7 g/mol	High	Yes	67,1433	4	1190
(–)-Tetrandrine	622.7 g/mol	High	Yes	72,22052	4	1190
(+)-Tetrandrine	622.7 g/mol	High	Yes	72,22052	4	1190
Isotrilobine	576.7 g/mol	High	Yes	4,539854	4	1190

(MF), and cellular component (CC). Visualization of enriched results was performed using SRPlot (SRplot-Science and Research online plot).

Ligand and protein preparation

The 3-dimensional (3D) structures of target proteins were retrieved from the RCSB PDB database (RCSB PDB: Homepage), while ligand structures were downloaded from PubChem.

Docking validation

In this study, the docking grid box was defined based on the coordinates of the native ligand from the target PDB structure. Docking validation was performed through redocking, and the root mean square deviation (RMSD) was calculated. A grid box was considered valid when the RMSD value was < 2 Å.[18]

Molecular docking analysis

Molecular docking was conducted using AutoDock Vina 1.2.5 (AutoDock Vina, The Scripps Research Institute) to assess the binding affinities of selected BBI compounds and sorafenib against the prioritized protein targets. Binding interactions were visualized and analyzed using Discovery Studio Visualizer (version 2021, Dassault Systèmes).

Results and discussion

Chemical candidates of Bisbenzylisoquinoline compounds from Stephania and toxicity prediction

A literature search initially identified 165 BBI derivatives, which were filtered to 17 compounds derived specifically from the *Stephania* genus. This selection was based on previous pharmacological studies. Further screening using PASS Online and SwissADME identified 11 compounds with predicted anticancer potential, high gastrointestinal (GI) absorption, and favorable drug-likeness profiles, as presented in Table 1. GI absorption was an important pharmacokinetic parameter that reflected a compound's potential for oral bioavailability, while drug-likeness assessed its suitability as an orally active therapeutic agent.[19] Testing the candidates for toxicity to ensure they are both safe and effective[20] was also a major part of this process. For evaluating potential hazardous effects, acute oral toxicity served as an initial criterion.[21] The Globally Harmonized System (GHS) was used to classify toxicity. It put compounds into six groups based on their LD_{50} values, as explained in ProTox-II. These classes included Class 1 (extremely toxic, $LD_{50} \leq 5$ mg/kg), Class 2 (highly toxic, $5 < LD_{50} \leq 50$), Class 3 (moderately toxic, $50 < LD_{50} \leq 300$), Class 4 (mildly toxic, $300 < LD_{50} \leq 2000$), Class 5 (potentially hazardous, $2000 < LD_{50} \leq 5000$), and Class 6 (non-toxic, $LD_{50} > 5000$).[22] In this classification system, a higher class number means that the substance is less toxic when eaten. The filtered BBI derivatives were predicted to exhibit an LD_{50} value of approximately 1190 mg/kg, placing them in Class 4 (mildly toxic). However, additional studies focusing on chronic and long-term toxicity were required to validate these in silico results.

Target identification: Bisbenzylisoquinoline derivatives from the Stephania genus

Network pharmacology offers an integrated approach to elucidating drug mechanisms and identifying therapeutic targets by constructing complex models that explore interactions among biological systems, drugs, and diseases.[23,24] In this study, the potential targets of BBI derivatives were predicted using SwissTargetPrediction, CTD, and SEA databases. After the removal of duplicate entries, a total of 456

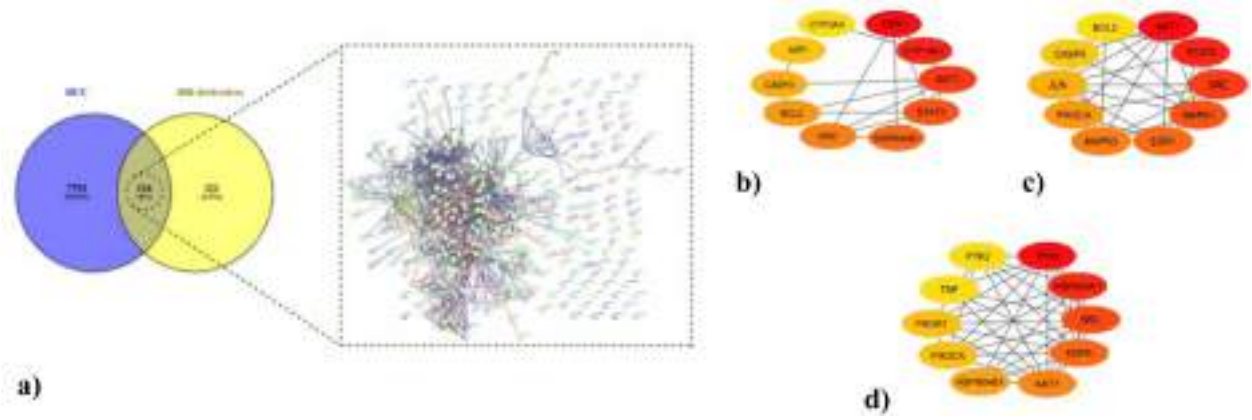


Fig. 1. Venn diagram of overlapping targets for BBI (456 targets) and HCC (8127 targets), (b) PPI network diagram of common targets (334 targets), (c) top 10 of topology degree centrality in Cytoscape, (d) top 10 of topology betweeennes in Cytoscape, (e) top 10 of topology closeness in Cytoscape.

filtered targets associated with BBI compounds were identified.

Identification of HCC-related targets

Using "*hepatocellular carcinoma*" as the primary keyword, HCC-related target genes were retrieved from the GeneCards and OpenTargets databases. After filtering for duplicates and consolidating overlapping entries, a total of 8,127 HCC-related genes were identified.

Construction and analysis of the Protein–Protein Interaction (PPI) network

A comparative analysis of BBI-related and HCC-related targets revealed 334 intersecting genes, which were regarded as potential therapeutic targets of *Stephania*-derived BBI compounds in HCC. These overlapping genes were illustrated in the Venn diagram, as shown in Fig. 1. To analyze their protein–protein interaction patterns, the intersected targets were uploaded into the STRING database. Subsequently, the resulting PPI network was imported into Cytoscape for topological analysis and visualization. A weighted "compounds–targets–pathways" network was constructed, and the top 10 hub genes were prioritized based on network metrics.

The color intensity of the nodes in the visualization showed how important each gene was in relation to the others. Darker nodes meant that the gene had a bigger impact on the network.[25] A higher degree value meant that the node was more important to the network. Betweenness centrality also measured how much a node acted as a bridge in the network, which could have affected how information moves. Finally, closeness centrality told us how well a node interacted with all the other nodes, which gives us an idea of how well it could control things.[26,27]

Functional enrichment and pathway analysis

We performed a Gene Ontology (GO) enrichment analysis to ascertain the relationships among the identified genes and their corresponding GO terms.[28] The most common BP terms were mostly about apoptosis, while the MF analysis showed a big rise in RNA binding. When it came to CC, the target genes were mostly found in the cytosol. These results demonstrated that the selected genes were significantly implicated in cancer-related processes, such as aberrant cell proliferation and dysfunctional metabolism, and that they may exert effects via various biological pathways.

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was conducted to predict the involvement of these targets in known signaling pathways. KEGG utilized curated datasets of well-characterized proteins to delineate their functions within interconnected biological networks.[28] Fig. 2 shows that the pathways that were most significantly enriched were cancer, apoptosis, hepatitis B, and especially the PI3K-Akt signaling pathway. Among these, the PI3K-Akt signaling pathway has emerged as a central mechanism implicated in HCC progression, indicating its potential as a therapeutic target. Prior research indicated that the activation of this pathway facilitated both the proliferation and metastasis of HCC cells.[29,30] Based on these results, PI3K and AKT1 were chosen as the main receptor targets for the next molecular docking simulations with the candidate BBI compounds.

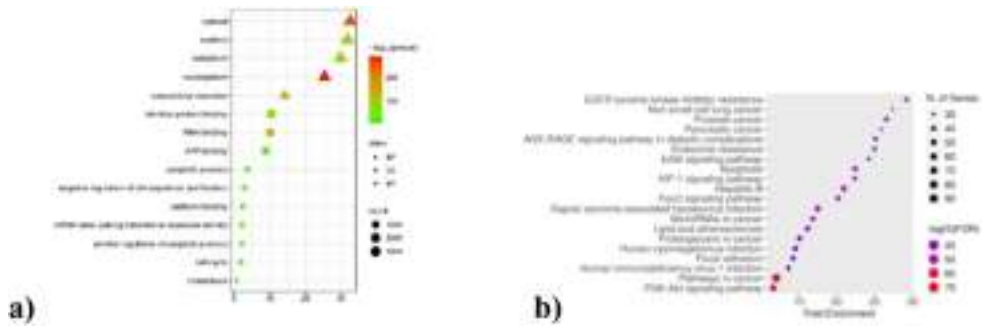


Fig. 2. The diagram of a) GO analysis, b) KEGG analysis.

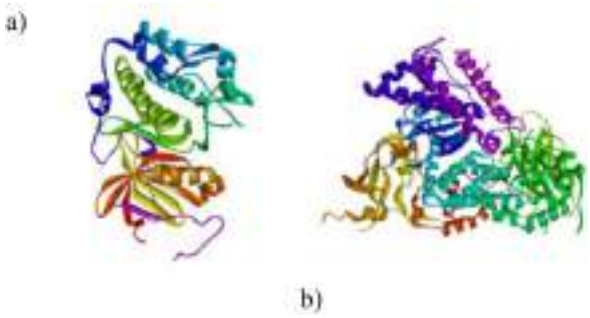


Fig. 3. 3D Structure after preparation of, a) AKT1 protein (PDB ID: 4GV1), b) PI3K protein (PDB ID: 3DBS).

Table 2. Configured grid boxes were used.

Protein	X	Y	Z	RMSD	Binding affinity
4GV1	–20.286	3.748	11.736	0.991	–10.9
3DBS	26.857	62.441	22.401	0.898	–10.3

Ligand and protein preparation

Molecular docking is a well-known in silico method for predicting interactions between ligands and receptors. It provides a rapid and effective approach to understanding how drugs bind to their target receptors.[31,32] In this study, the three-dimensional structures of the selected compounds were used to simulate molecular interactions and determine the optimal binding conformations,[33] as illustrated in Fig. 3, which presents the prepared 3D structures of the target proteins, AKT1 (PDB ID: 4GV1) and PI3K (PDB ID: 3DBS), prior to docking analysis.

Docking validation

The Protein Data Bank provided the crystallographic structures of AKT1 and PI3K, with PDB IDs 4GV1 (resolution: 1.49 Å) and 3DBS (resolution: 2.8 Å), respectively. For docking simulations, a grid box that was 40 × 40 × 40 Å was used. The control RMSD values, which are shown in Table 2, were less than 2.0 Å, which is the accepted limit for docking accuracy.[34]

Table 3. Binding affinity between AKT1 and PI3K protein and test compounds.

	Binding Affinity (kcal/mol)	
Compounds	4GV1	3DBS
Native ligand	–10.9	–10.3
Cepharanoline	–10.0	–8.8
Cepharanthine	–9.8	–8.9
Hypoepistephanine	–9.7	–9.2
Oxyacanthine	–9.5	–9.1
Stebisimine	–9.9	–8.2
Fangchinoline	–9.5	–8.8
Isotetrandrine	–9.6	–9.6
Obamegine	–8.6	–8.6
(–)-Tetrandrine	–9.0	–9.5
(+)-Tetrandrine	–9.1	–9.3
Isotrilobine	–10.5	–9.9
Sorafenib	–10.1	–8.3

The results confirmed that the docking protocol was correct, which meant that the next simulations with the test compounds could go ahead.

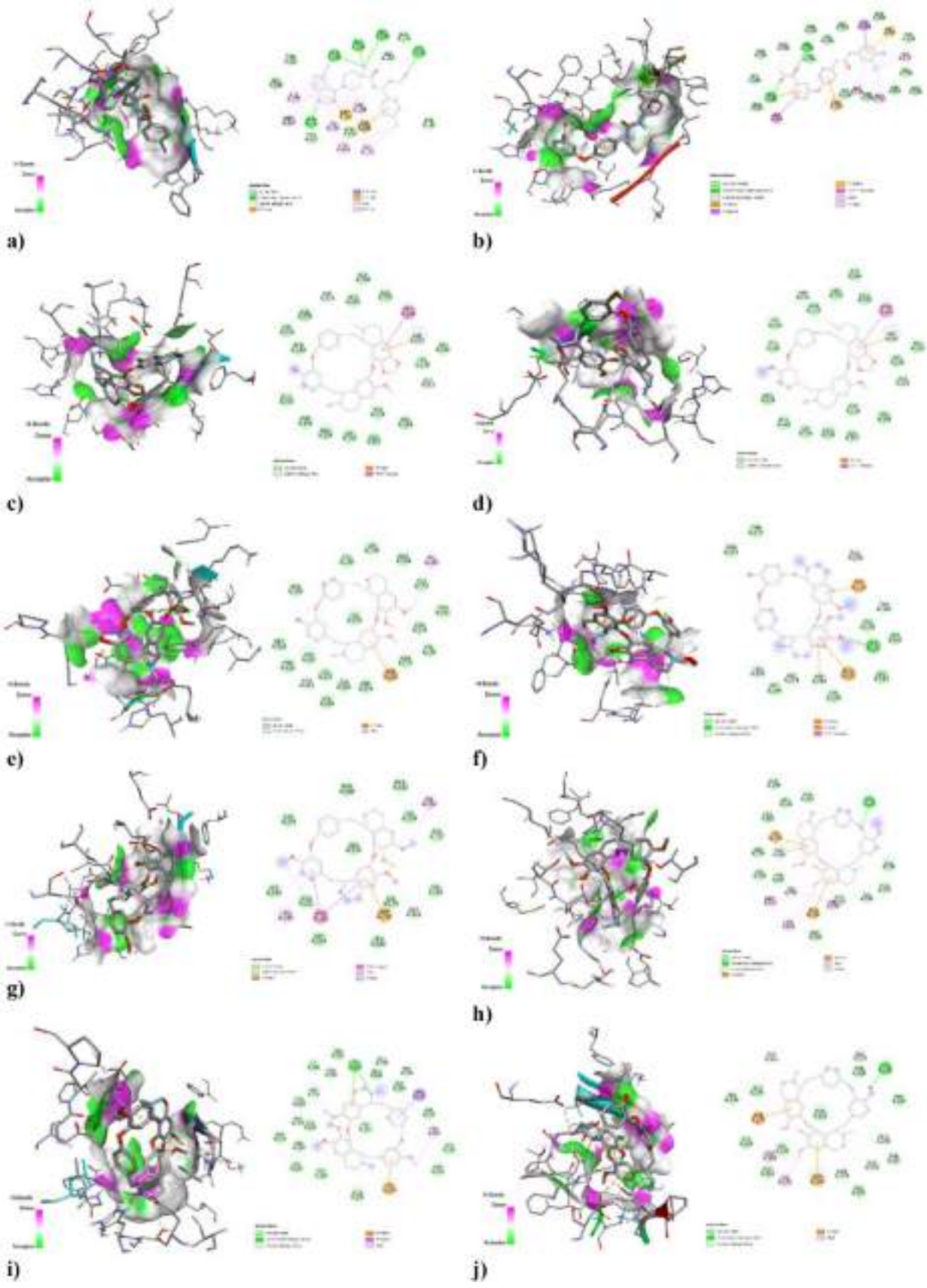
Results of docking analysis

Table 3 shows the results of molecular docking for the AKT1 protein. They showed that several test compounds had strong interactions with the target protein, with binding affinities between –9.0 and –10.5 kcal/mol. Isotrilobine had the strongest binding affinity (–10.5 kcal/mol), which suggests that it

Table 4. Interaction of amino acid residues produced in AKT1 protein and PI3K protein with test compounds.

	Interaction					
	AKT1 Protein			PI3K Protein		
Ligand	Hydrogen Bond	Hydrophobic interaction	Others	Hydrogen Bond	Hydrophobic interaction	Others
Native ligand	A: GLU 234* A: GLU 278* A: THR 291 A: LYS 276* A: ALA 230 A: GLY 157*	A: MET 227* A: LEU 156* A: LEU 181* A: ALA 177* A: LYS 179* A: VAL 164* A: ASP 292* A: MET 281*		A: GLN 846 A: GLU 880* A: HIS 658*	A: LEU 865*	A: HIS 295*
Sorafenib	A: GLU 191 A: GLY 294	A: ASP 292* A: MET 281	A: PHE 161 A: VAL 164* A: ALA 177 A: MET 227* A: LEU 156*	A: ASN 634 A: PHE 497 A: GLN 391 A: GLN 388 A: LYS 104 A: SER 594	A: ILE 828	A: ASP 632 A: GLN 629 A: PRO 563 A: PHE 635 A: LYS 591 A: PRO 590
Cepharanoline	A: ASP 292* A: ASP 274 A: GLY 162		A: PHE 161	A: ASN 688	A: LEU 195 A: VAL 202	A: ARG 687 A: ASP 653 A: GLU 652
Cepharanthine	A: ASP 292* A: ASP 274 A: GLY 162		A: PHE 161	A: ASN 688	A: LEU 195 A: VAL 202 A: PRO 200	A: ARG 687 A: ASP 653 A: GLU 652
Hypoepiste- phanine	A: GLU 191	A: ASP 292*	A: VAL 164*	A: ASN 299 A: HIS 295*	A: LEU 865*	A: ARG 690
Oxyacanthine	A: ASP 292* A: ASP 274 A: LEU 295 A: PHE 161 A: THR 160 A: GLU 278*	A: LYS 276* A: GLU 191		A: ASP 653	A: LEU 195 A: PRO 200	A: ARG 687 A: GLU 652
Stebisimine	A: GLY 162	A: ASP 292*	A: LEU 295 A: PHE 161 A: VAL 164	A: LYS 320 A: VAL 188	A: PRO 193 A: VAL 318	A: ASP 316
Fangchinoline	A: ASP 292* A: GLY 162 A: LYS 158 A: LYS 276	A: LYS 179* A: GLU 234	A: MET 281 A: LEU 156 A: VAL 164	A: ARG 687 A: ASP 653 A: GLU 649	A: VAL 202 A: PRO 200 A: PRO 286	
Isotetrandrine	A: ASP 292* A: GLY 162 A: THR 195 A: LYS 179* A: GLU 198 A: HIS 194	A: LYS 276*	A: LEU 295 A: PRO 313	A: HIS 295* A: PRO 866	A: ARG 849 A: LEU 657 A: LEU 865* A: PHE 694	A: LYS 298 A: HIS 658* A: TRP 201
Obamegine	A: GLY 311 A: GLY 159 A: LYS 158 A: GLU 278* A: GLU 234* A: ASN 279	A: ASP 292* A: ASP 274	A: LEU 181* A: LYS 179*	A: PRO 200 A: VAL 202 A: SER 190 A: GLU 652	A: LEU 195	A: ASP 653
(–)-Tetrandrine	A: ASP 292* A: GLU 268 A: GLU 234	A: LYS 276*	A: PHE 442 A: PHE 236	A: PRO 866 A: TYR 787	A: HIS 658* A: ARG 690 A: ARG 849	A: HIS 295* A: TRP 292 A: PHE 694 A: LEU 657 A: PHE 698
(+)-Tetrandrine	A: ASP 279 A: ASN 274 A: GLU 278*	A: LYS 276*	A: PHE 161 A: LEU 295 A: CYS 310	A: GLU 826 A: ARG 277	A: GLU 880*	A: LEU 865* A: LEU 791 A: LYS 883
Isotrilobine	A: GLU 278* A: GLU 234* A: LEU 156*	A: ASP 292 * A: LYS 276*	A: VAL 164* A: MET 281*	A: LEU 864 A: LYS 298	A: GLU 880* A: ARG 690 A: ARG 849 A: GLU 852	A: LEU 865* A: HIS 295* A: HIS 658* A: TYR 867 A: PHE 694

*Residues from the native ligand were retained in test compounds.



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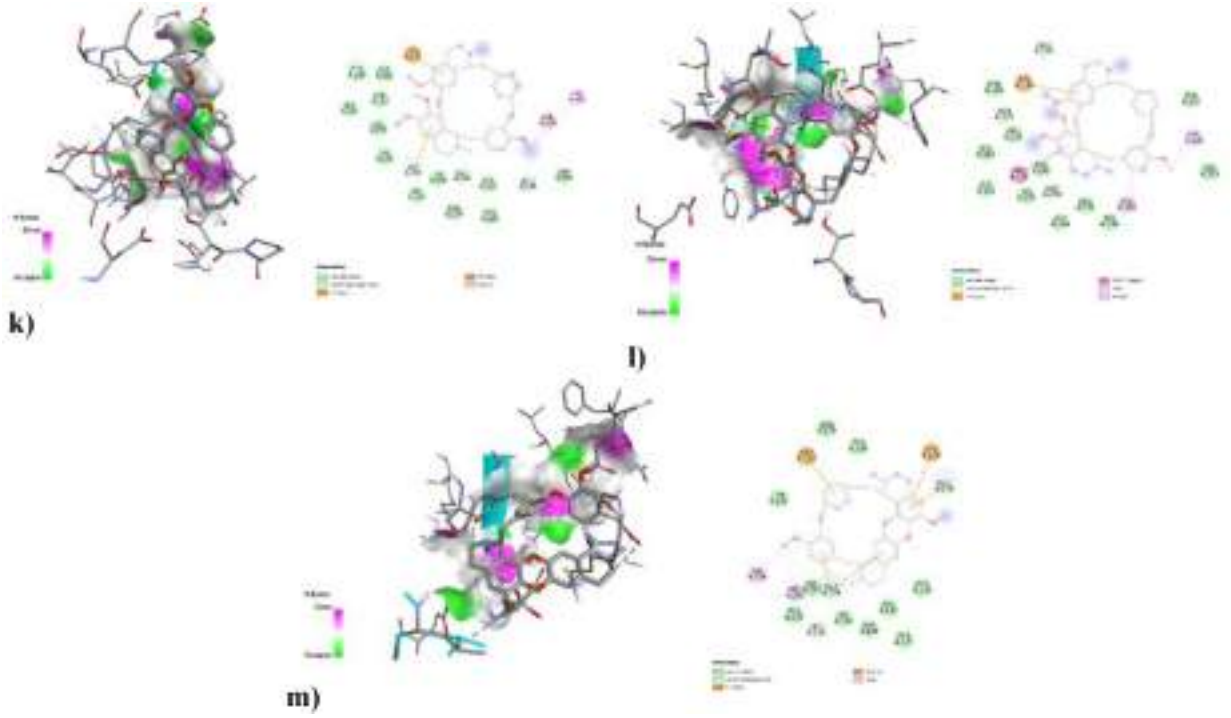

Fig. 4. 3D and 2D visualization of docking results with AKT1 protein, a) native ligand, (b) sorafenib, (c) cepharanoline, (d) cepharanthine, (e) hypoepistephanine, (f) oxyacanthine, (g) stebisimine, (h) fangchinoline, (i) isotetrandrine, (j) obamegine, (k) (–)-tetrandrine, (l) (+)-tetrandrine, and (m) isotrilobine.

could be a strong AKT1 inhibitor. The reference compound, sorafenib, exhibited a binding affinity of –10.1 kcal/mol, marginally lower than that of isotrilobine. In the same way, docking studies against the PI3K protein showed binding affinities between –8.6 and –9.9 kcal/mol. Isotrilobine consistently exhibited the most advantageous binding affinity (–9.9 kcal/mol), surpassing sorafenib, which demonstrated a diminished binding affinity of –8.3 kcal/mol.

These binding energy values showed how stable the ligand–protein complexes were. Lower (more negative) energy values meant that the interactions were stronger and better. These kinds of stable interactions were usually linked to a higher inhibitory potential. [35,36]

Table 4 showed how each ligand interacted with the AKT1 and PI3K proteins. Conventional hydrogen bonds and hydrophobic interactions were the most common types of interactions that were seen. Molecular docking analysis for AKT1 showed that isotrilobine kept all of the active site residues of the native ligand. This suggests that the binding pattern is very stable. But the docking results for PI3K showed that not all of the test compounds kept the same amino acid interactions as the native ligand. Isotrilobine showed the best retention of active site residues, which shows that it has a strong and specific binding affinity. The reference drug sorafenib, on the other hand, did not have any amino acid interactions with the native ligand in the PI3K complex. This suggests that there may be a different way that it binds that needs to be looked into further.

Fig. 4 displayed both 3D and 2D representations of AKT1 protein in association with the native ligand, the pharmaceutical agent sorafenib, and 11 BBI derivatives originating from the Stephania genus. The dashed magenta and green lines show the hydrogen bonds between the hydrogen donor and acceptor groups of the ligand and the amino acid residues in the protein's active site [37] interact with each other. Also, hydrophobic interactions, which are shown as white-shaded areas around the ligand, which shows that nonpolar residues were involved in binding to the ligand. These interactions helped to stabilize the complex, and more hydrophobic contact usually means better binding stability. [38] Earlier research [39] demonstrated that the knockout of the AKT1 gene markedly diminished HCC cell proliferation and migration, underscoring its function as a pivotal oncogene in HCC progression and differentiation.

Fig. 5 showed both 3D and 2D visualizations of PI3K protein complexes, including the native ligand, the commercial drug sorafenib, and 11 BBI derivatives from the *Stephania* genus. The white-shaded

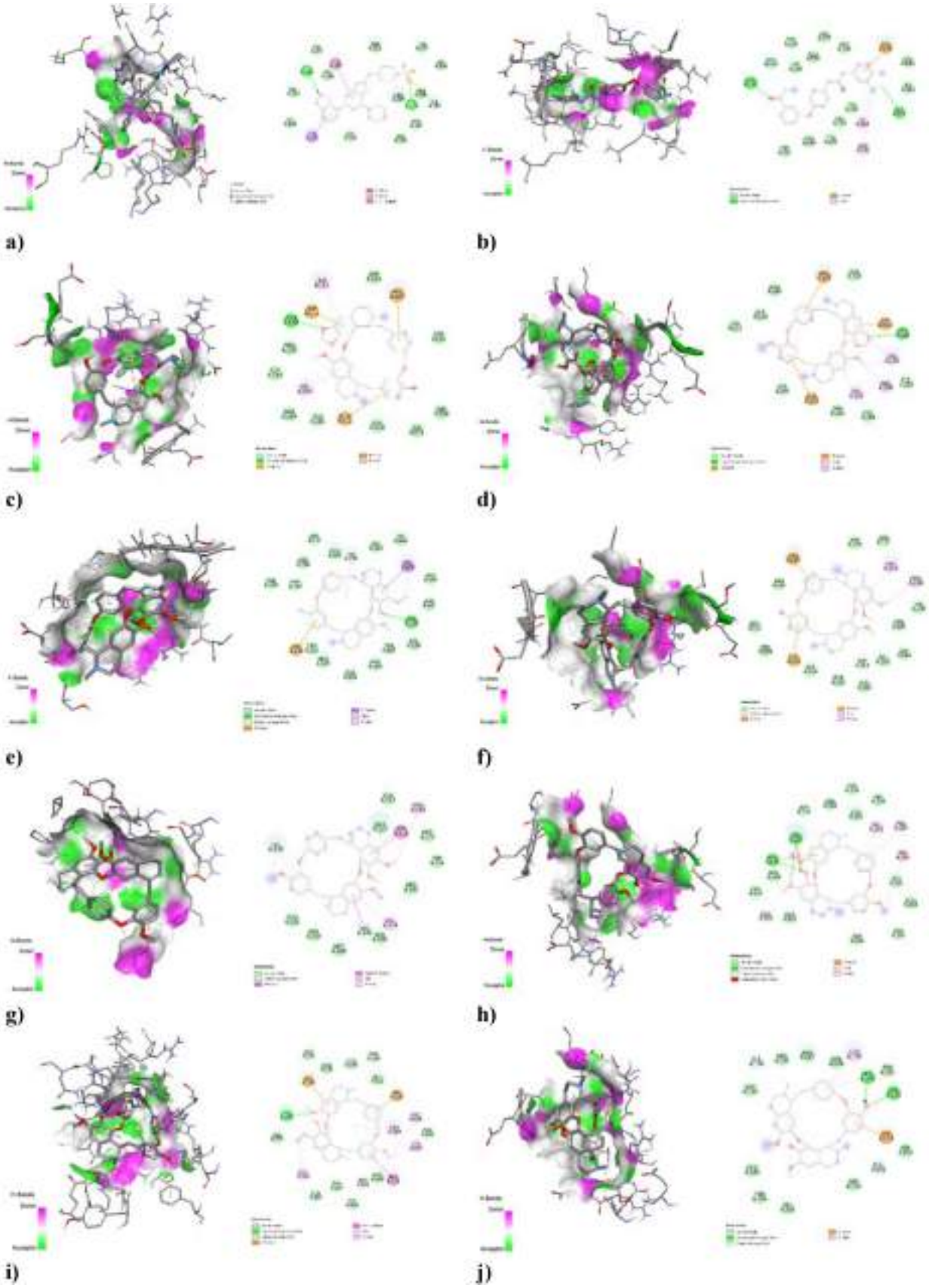

Fig. 5. Continued.

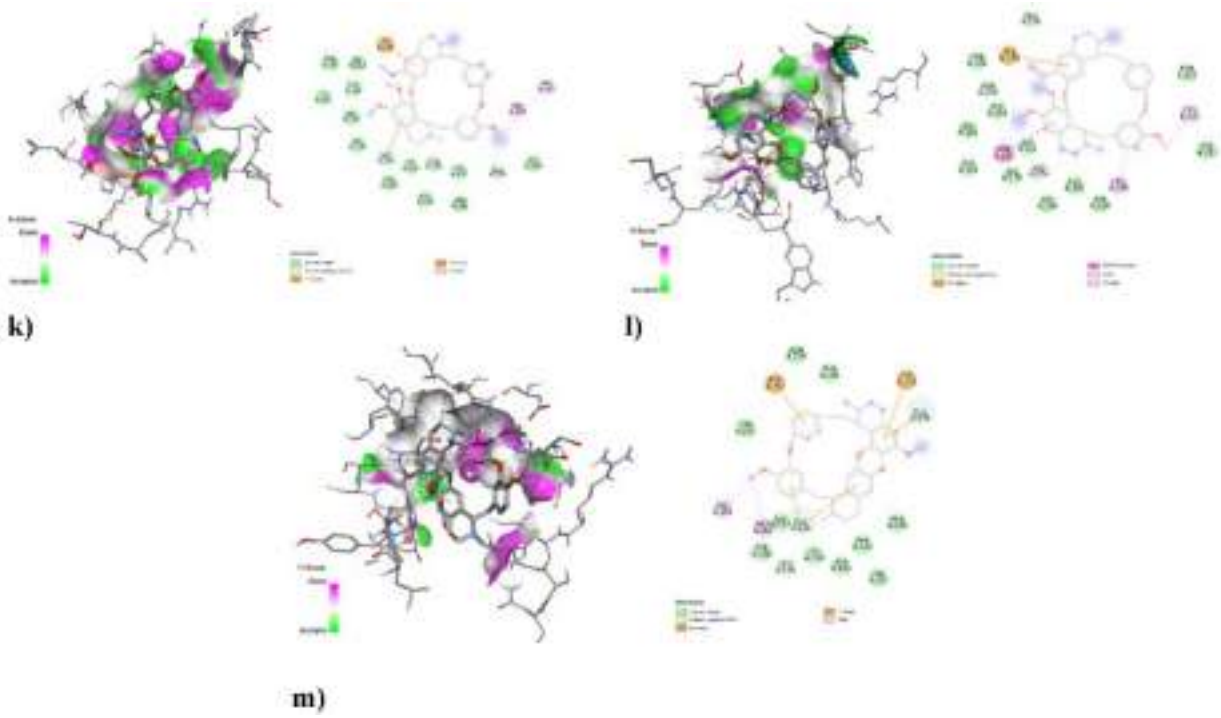

Fig. 5. 3D and 2D visualization of docking results with PI3K protein, a) native ligand, (b) sorafenib, (c) cepharanoline, (d) cepharanthine, (e) hypoepistephanine, (f) oxyacanthine, (g) stebisimine, (h) fangchinoline, (i) isotetrandrine, (j) obamegine, (k) (–)-tetrandrine, (l) (+)-tetrandrine, and (m) isotrilobine.

areas around the ligands show hydrophobic interactions. These happen because non-polar solutes don't dissolve well in water.[40,41] These interactions were crucial for preventing dissociation of the ligand–protein complexes. The mechanism of the PI3K signaling pathway is extremely important for tumor initiation and development because it regulates the process of growth and apoptosis.[42] Importantly, this pathway dysregulation was significantly correlated with the metastatic behavior of HCC.[43]

Conclusion

In conclusion, this study illustrates the critical function of multicellular signaling pathways in the advancement of HCC, underscoring their potential as therapeutic targets. The selected compounds' good pharmacokinetic and toxicological profiles suggest that they could be used to make drugs. Isotrilobine exhibits the highest binding affinity to AKT1 and PI3K, suggesting its potential as a therapeutic candidate. These findings establish a basis for subsequent in vitro and in vivo investigations to confirm the efficacy and clarify the mechanisms of Stephania-derived BBI alkaloids in the context of HCC.

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Authors' declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images that are not ours have been included with the necessary permission for republication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Authors signed on ethical considerations' approval.
- Ethical Clearance: The project was approved by the local ethical committee at Universitas Sumatera Utara, Medan 20155, Indonesia.

Authors' contributions statement

This manuscript was created in collaboration with all authors: A.S. conceptualized the study, designed the methodology, performed network pharmacology and molecular docking, analyzed the results, and drafted the manuscript. D.S. validated docking results and assisted in data visualization. P.A.Z.H. curated data and conducted statistical analysis. J.M.K. supported software utilization and troubleshooting. S.B.W. edited and finalized the manuscript. C.Y.M. supervised the research and reviewed the manuscript. All authors approved the final version.

Data availability

The data used in this study are publicly available from online databases. The three-dimensional structures of the ligands were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/), while the protein structures of AKT1 (PDB ID: 4GV1) and PI3K (PDB ID: 3DBS) were retrieved from the RCSB Protein Data Bank (https://www.rcsb.org/). All data generated or analyzed during this study are included in this published article. Additional data supporting the findings of this study are available from the corresponding author upon reasonable request.

Funding statement

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الفحص الافتراضي القائم على الإرساء لمشتقات (Bisbenzylisoquinoline) من جنس (Stephania) ضد سرطان الخلايا الكبدية

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الخلاصة

يُعدّ سرطان الخلايا الكبدية (Hepatocellular Carcinoma, HCC) أحد أكثر الأنواع شيوعًا وعدوانية من سرطان الكبد. يتميز هذا المرض بسوء الإنذار، وارتفاع معدل النكس، والاستجابة المحدودة للعلاجات الحالية. ومن أجل مواجهة هذه الحالة، يزداد الاهتمام باستخدام المنتجات الطبيعية كعوامل مضادة للسرطان متعددة الأهداف. في هذه الدراسة، قمنا بالتحقيق في القيمة العلاجية لقلويدات البيسبنزيل إيزوكينولين (Bisbenzylisoquinoline, BBI) المشتقة من جنس ستيفانيا (Stephania) باستخدام نهج تكاملي حاسوبي (in silico). ونظرًا لخصائصها الدوائية الحركية المحسّنة وتوقع انخفاض سميتها، تم اختيار 11 مشتقًا من BBI. أظهر تحليل علم الأدوية الشبكي (Network Pharmacology) وجود 334 هدفًا مشتركًا بين المركبات وسرطان الخلايا الكبدية. كما أشار تحليل الإثراء الوظيفي إلى أن مسار الإشارة PI3K-Akt (PI3K-Akt signaling pathway) يلعب دورًا أساسيًا في تطور المرض. بالإضافة إلى ذلك، كشف بناء شبكة تفاعل البروتين-البروتين (Protein-Protein Interaction, PPI) والتحليل الطوبولوجي عن أن بروتيني AKT1 وPI3K يمثلان بروتينات محورية. وأظهرت محاكاة الإرساء الجزيئي (Molecular Docking) أن مركب الإيزوتريلوبين (Isotrilobine) يمتلك أعلى ألفة ارتباط تجاه كل من AKT1 (−10.5 kcal/mol) وPI3K (−9.9 kcal/mol)، مقارنةً بالدواء المرجعي سورافينيب (Sorafenib). تشير هذه النتائج إلى احتمال مشاركة مركبات BBI في تنظيم المسارات الورمية الرئيسية المرتبطة بنمو الأورام وانتشارها. وبشكل عام، تكشف هذه الدراسة عن الإيزوتريلوبين كمركب واعد، وتوفر تفسيرًا آليًا يدعم المزيد من استكشاف قلويدات BBI المشتقة من جنس ستيفانيا كعلاجات محتملة لسرطان الخلايا الكبدية.

الكلمات المفتاحية: بيسبنزيل إيزوكينولين (Bisbenzylisoquinolines)، سرطان الخلايا الكبدية، الإرساء الجزيئي، علم الأدوية الشبكي ، ستيفانيا (Stephania).