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Network Pharmacology and Molecular Docking Reveal the Multitarget Antioxidant Potential of Furanoditerpenes from *Arcangelisia flava*

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Abstract: Oxidative stress plays a crucial role in the development of chronic and degenerative diseases due to an imbalance between reactive oxygen species (ROS) production and endogenous antioxidant defenses. *Arcangelisia flava* (Menispermaceae), a traditional medicinal plant widely used in Southeast Asia, is rich in furanoditerpenes with reported antioxidant and anti-inflammatory activities. This study aimed to elucidate the multitarget molecular mechanisms of *A. flava* furanoditerpenes using an integrated network pharmacology and molecular docking approach. Target prediction was performed using the SuperPRED database, while oxidative stress and inflammation-related genes were retrieved from GeneCards. Protein interaction analysis identified ten hub genes, including AKT1, TNF, EGFR, MTOR, and MAPK3, which are primarily involved in redox regulation and inflammatory signaling. Gene Ontology and KEGG pathway enrichment analyses highlighted the PI3K-Akt, MAPK, and NF-κB pathways as key regulatory mechanisms. Molecular docking validation demonstrated that jatrotthizine exhibited strong binding affinity to PI3K (PDB ID: 4HVB; –9.08 kcal/mol), comparable to the native inhibitor, with interactions involving critical catalytic residues. These findings confirm network pharmacology predictions and suggest that A. flava furanoditerpenes exert antioxidant and anti-inflammatory effects by coordinating modulation of the PI3K-Akt-NF-κB signaling axis. This study provides molecular evidence supporting the traditional use of *A. flava* and identifies jatrotthizine as a promising lead compound for further pharmacological development.

Keywords: *Arcangelisia flava*; furanoditerpenes; oxidative stress; network pharmacology; PI3K-Akt.

1. Introduction

Oxidative stress is a fundamental pathological process that underlies the initiation and progression of various chronic and degenerative diseases, including cancer, diabetes mellitus, cardiovascular disorders, and neurodegenerative conditions [1–4]. This condition occurs when the production of reactive oxygen species (ROS) exceeds the capacity of endogenous antioxidant defense systems, leading to molecular damage of lipids, proteins, and nucleic acids [5]. Sustained oxidative stress promotes inflammation, apoptosis, and cellular dysfunction, thereby accelerating tissue injury and disease progression. Consequently, targeting oxidative stress and the underlying redox signaling pathways has emerged as a promising strategy for preventing or alleviating chronic diseases associated with oxidative damage [6].

Natural antioxidants derived from medicinal plants have attracted increasing attention for their ability to modulate multiple biological targets and signaling pathways while causing fewer adverse effects than synthetic antioxidants. Among traditional Southeast Asian medicinal species, *Arcangelisia flava* (L.) Merr. known locally as *Kayu kuning*, Akar kuning, or Tali kuning,r Yellow Wood, is widely used as a traditional remedy for fever, jaundice, malaria, inflammation, and microbial infections [7–13]. Belonging to the Menispermaceae family, *A. flava* has been reported to contain several furanoditerpene compounds such as 6-hydroxyarcangelisin, 2-dehydroarcangelisinol, tinophylol, 6-hydroxyfibleucin, 6-hydroxyfibraurin, and fibreucin. These secondary metabolites possess diverse biological properties, including antioxidants, anti-inflammatory, antifungal, anticancer activities [14–21], wound healing [22], and osteoarthritis [12].

Despite these pharmacological findings, the molecular mechanisms underlying the antioxidant and anti-inflammatory activities of *A. flava* remain poorly characterized. Conventional pharmacological approaches focusing on single targets cannot adequately explain the broad spectrum of activity exhibited by its furanoditerpenes. Recent developments in network pharmacology have introduced a systems-based perspective that integrates bioinformatics, molecular biology, and pharmacology to elucidate the multitarget mechanisms of natural products [7,23]. By mapping compound-target interactions and linking them to disease-associated networks, this approach enables the identification of key targets and pathways that mediate the complex pharmacological effects of phytochemicals.

Therefore, this study employs an integrated *in silico* approach combining network pharmacology and molecular docking to elucidate the multitarget mechanisms of seven furanoditerpenes from *A. flava* in mitigating oxidative stress. Network pharmacology analysis was used to identify potential compound-target interactions and relevant signaling pathways, and molecular docking was performed to validate the predicted interactions at the structural level. Particular attention was given to the PI3K-Akt signaling pathway, a key regulator of redox homeostasis and cellular survival [6,24]. This research provides a systems-level understanding of how *A. flava* furanoditerpenes exert synergistic antioxidant and anti-inflammatory effects, supporting their potential as multitarget therapeutic agents.

2. Materials and Methods

2.1. Material.

This study used seven major furanoditerpenes from *Arcangelisia flava*-6-hydroxyarcangelisin, 2-dehydroarcangelisinol, tinophylol, 6-hydroxyfibleucin, 6-

hydroxyfibraurin, fibreucin, and jatrotthizine, retrieved from the PubChem database. Computational tools included SuperPRED for target prediction, GeneCards for disease-related genes, STRING and Cytoscape for network analysis, ShinyGO for GO and KEGG enrichment, AutoDock 4.2 for molecular docking, Open Babel for ligand conversion, and Discovery Studio for visualization. The PI3K protein structure (PDB ID: 4HVB) was obtained from the RCSB Protein Data Bank. No animal or plant materials were used in this research.

2.2. Methods.

2.2.1. Compound selection and target prediction.

The chemical structures of seven major furanoditerpenes from *Arcangelisia flava*: 6-hydroxyarcangelisin, 2-dehydroarcangelisinol, tinophylol, 6-hydroxyfibleucin, 6-hydroxyfibraurin, fibreucin, and jatrotthizine, were obtained from the PubChem database (https://pubchem.ncbi.nlm.nih.gov). Each compound was converted into a canonical SMILES format and uploaded to the SuperPRED online platform (https://prediction.charite.de) for target prediction. SuperPRED predicts possible human protein targets based on the chemical similarity of ligands to known bioactive molecules [25]. The resulting predicted targets were standardized to official gene names using the UniProt database (https://www.uniprot.org).

2.2.2. Collection of disease-related targets.

To identify disease-associated genes relevant to oxidative stress and inflammation, searches were conducted in the GeneCards database (https://www.genecards.org) using the keywords oxidative stress and inflammation. Gene entries with relevance scores above the median threshold were selected for analysis. The potential therapeutic targets of *A. flava* were determined by identifying overlapping genes between compound-related and disease-related targets using the Venny 2.1 tool (https://bioinfogp.cnb.csic.es/tools/venny/).

2.2.3. Construction and analysis of protein-protein interaction (PPI) network.

Overlapping targets were imported into the STRING database (https://string-db.org) to generate a protein–protein interaction (PPI) network, with Homo sapiens species restriction and a confidence score > 0.7. The resulting network was visualized and topologically analyzed using Cytoscape software (version 3.9.1). Key network parameters, including degree, betweenness centrality, and closeness centrality, were calculated to identify hub genes [26]. The top ten hub genes were selected for further functional enrichment and docking validation.

2.2.4. Gene ontology (GO) and KEGG pathway enrichment analysis.

To elucidate the biological significance of the identified targets, Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analyses were performed using the ShinyGO web server (version 0.77; http://bioinformatics.sdstate.edu/go/). The GO analysis was categorized into three main domains: molecular function (MF), cellular component (CC), and biological process (BP). The KEGG analysis identified the most significantly enriched signaling pathways ($p < 0.05$). The results were visualized using bar and bubble plots generated by ShinyGO and Cytoscape plug-ins. Key pathways associated with oxidative stress regulation, particularly PI3K-Akt, MAPK [27], NF-κB [28,29], and apoptosis, were prioritized for molecular docking analysis.

2.2.5. Molecular Docking Validation

1. Receptor preparation and validation.

Based on KEGG pathway results, the PI3K–Akt signaling pathway was selected for docking validation. The crystal structure of PI3K (PDB ID: 4HVB) was downloaded from the RCSB Protein Data Bank (https://www.rcsb.org). The structure was refined by removing water molecules, adding polar hydrogens, and optimizing the receptor using AutoDock Tools (version 1.5.7). Redocking of the native ligand was performed to validate the docking protocol. The validation criterion was the root mean square deviation (RMSD) between the crystallographic and redocked ligand positions, with RMSD < 2.0 Å indicating reliable docking accuracy [30].

2. Ligand preparation and docking simulation.

All furanoditerpene ligands were converted to PDBQT format using Open Babel software [14,16,31]. Docking simulations were performed using AutoDock [32], employing a grid box centered on the native ligand's binding site. Binding affinity (kcal/mol) was used as the scoring function to assess interaction strengthwith lower values indicating stronger binding [33]. Post-docking analysis, including hydrogen bond identification and interaction visualization, was carried out using Discovery Studio (version 4.5) [34].

2.2.6. Integration of network pharmacology and docking analysis.

Finally, results from network pharmacology and molecular docking were integrated to elucidate the multitarget mechanisms of *A. flava* furanoditerpenes. Hub genes and pathways identified in the network model were correlated with molecular docking affinities to confirm the biological relevance of compound–target interactions. Emphasis was placed on the PI3K–Akt, MAPK, and NF-κB signaling pathways, which jointly regulate redox homeostasis, inflammation, and apoptosis.

3. Results and Discussion

3.1. Network pharmacology analysis.

A total of 269 potential protein targets associated with furanoditerpenes from *Arcangelisia flava* were identified using the SuperPRED database. In parallel, 494 inflammation-related genes were retrieved from the GeneCards database. Cross-analysis revealed 191 overlapping genes, indicating a substantial intersection between compound-related targets and inflammation-associated pathways. These shared targets represent potential molecular mediators underlying the antioxidant and anti-inflammatory activities of *A. flava* (Figure 1).

The overlapping genes were subsequently imported into the STRING database to construct a protein–protein interaction (PPI) network. Topological analysis using Cytoscape identified ten hub genes with the highest degree centrality: AKT1, TNF, EGFR, MAPK3, ALB, SRC, JUN, MTOR, ESR1, and CCND1. These hub genes exhibited strong interconnectivity and formed the core regulatory network [35–38].

Functionally, the identified hub genes play critical roles in redox regulation, inflammatory signaling, apoptosis, and cell survival. For example, AKT1 and MTOR are

central regulators of cellular metabolism and antioxidant defense, while TNF and JUN are key mediators of cytokine signaling and reactive oxygen species (ROS) production. In addition, EGFR and SRC are involved in oxidative stress adaptation and cell proliferation [5, 28, 39, 40]. The dense connectivity observed within the PPI network suggests that furanoditerpenes from *A. flava* exert their biological effects through coordinated modulation of multiple interconnected targets rather than a single molecular pathway.

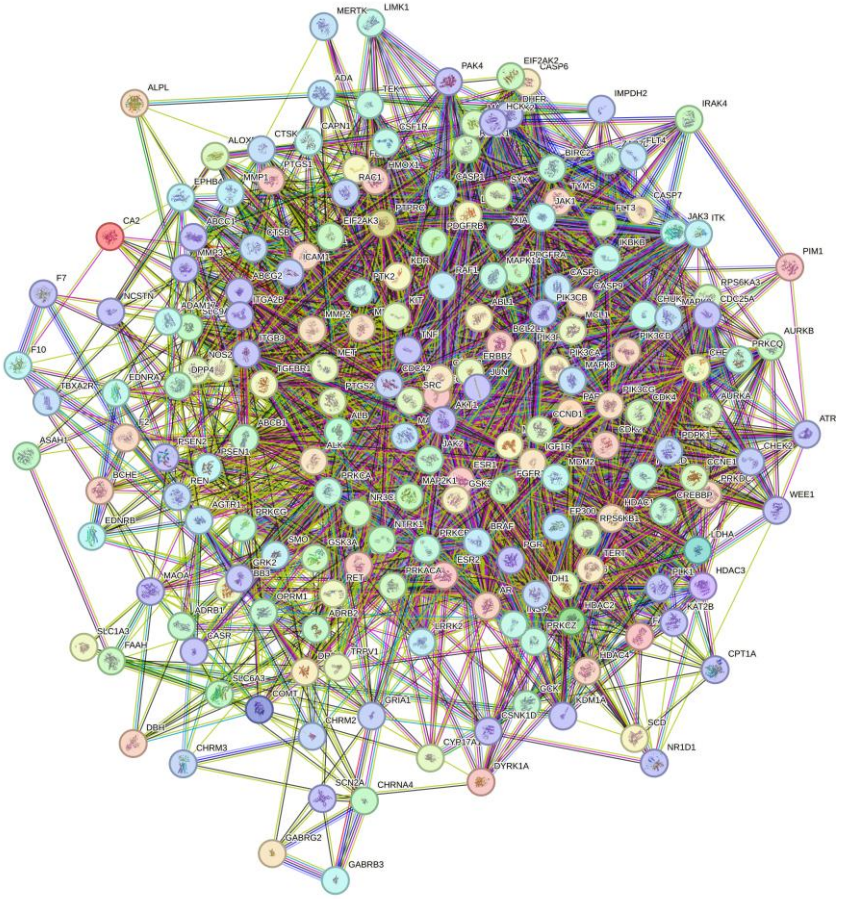


Figure 1. Protein-protein interaction (PPI) network.

3.2. Gene ontology enrichment analysis.

Gene Ontology (GO) enrichment analysis was conducted to clarify the biological roles of the overlapping targets identified from the network pharmacology analysis. The targets were classified into three GO categories: Biological Process (BP), Molecular Function (MF), and Cellular Component (CC).

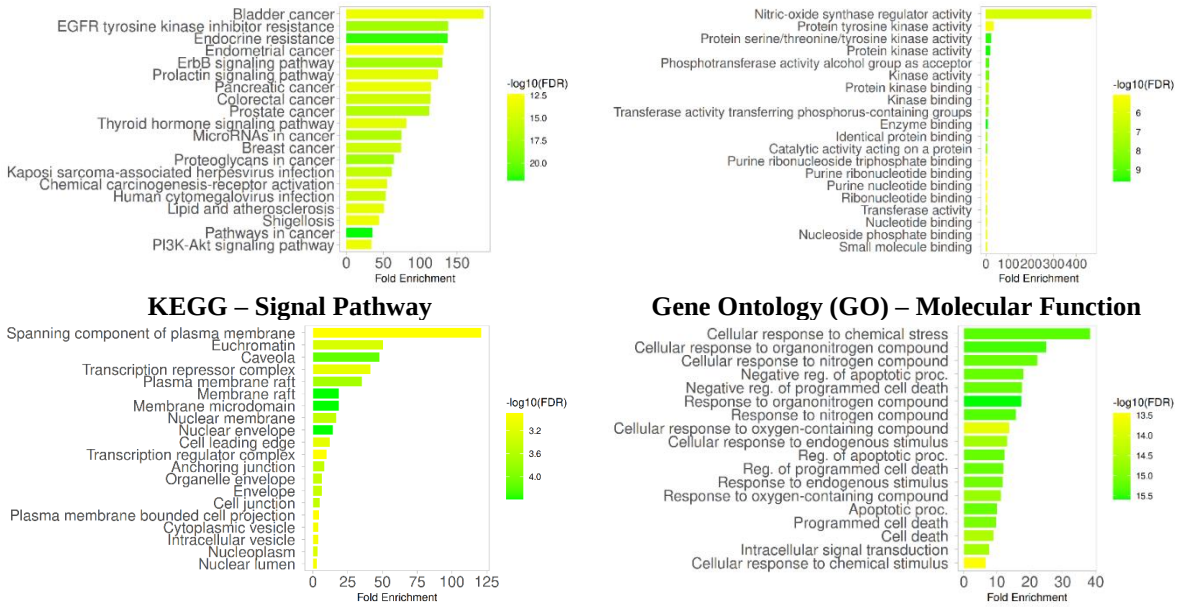
In the Biological Process (BP) category, the most significantly enriched terms were related to response to oxidative stress, regulation of apoptosis, inflammatory response, and cell survival (Figure 2). These processes are closely associated with redox homeostasis and inflammatory regulation, supporting the antioxidant and anti-inflammatory potential of *the furanoditerpenes of Arcangelisia flava*[7].

The Molecular Function (MF) analysis showed that the targets were mainly involved in protein binding, kinase activity, and ATP binding. This indicates that the bioactive compounds may influence phosphorylation-dependent signaling pathways, which play an important role in oxidative stress signaling and inflammation [6,24].

For the Cellular Component (CC) category, the enriched targets were primarily localized in the cytoplasm, nucleus, and mitochondria. The presence of targets in mitochondrial

compartments is particularly relevant, as mitochondria are a major source of reactive oxygen species and a key site for redox regulation [24,29,41–43].

Overall, the GO enrichment results suggest that *A. flava* furanoditerpenes regulate oxidative stress and inflammation by coordinating effects across multiple biological processes, molecular functions, and cellular locations. These findings are consistent with the multitarget characteristics of plant-derived bioactive compounds and support the subsequent pathway and docking analyses.



KEGG – Signal Pathway **Gene Ontology (GO) – Molecular Function**

Gene Ontology (GO) – Cellular Component **Gene Ontology (GO) – Biological Process**

Figure 2. Gene ontology *A. flava*.

3.3. KEGG pathway analysis.

Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway enrichment analysis was performed to identify key signaling pathways associated with the overlapping targets identified in the network pharmacology analysis. The results revealed several pathways significantly enriched for oxidative stress and inflammatory regulation.

Among these pathways, the PI3K-Akt signaling pathway emerged as the most prominent, highlighting its central role in maintaining redox homeostasis and promoting cell survival [27]. Activation of this pathway is known to enhance antioxidant defense mechanisms and suppress excessive inflammatory responses. In addition, the MAPK and NF-κB signaling pathways were also significantly enriched, both of which are closely involved in oxidative stress responses, inflammation, and apoptosis [24,44].

Other enriched pathways, including apoptosis and VEGF signaling, further support the involvement of these targets in regulating cell survival, tissue repair, and adaptive responses under oxidative conditions [29]. Collectively, the KEGG pathway analysis (Figure 3) indicates that Arcangelisia flava furanoditerpenes exert their antioxidant and anti-inflammatory effects by coordinating the modulation of multiple interconnected signaling pathways, particularlyI3K–Akt, MAPK, and NF-κB [45].

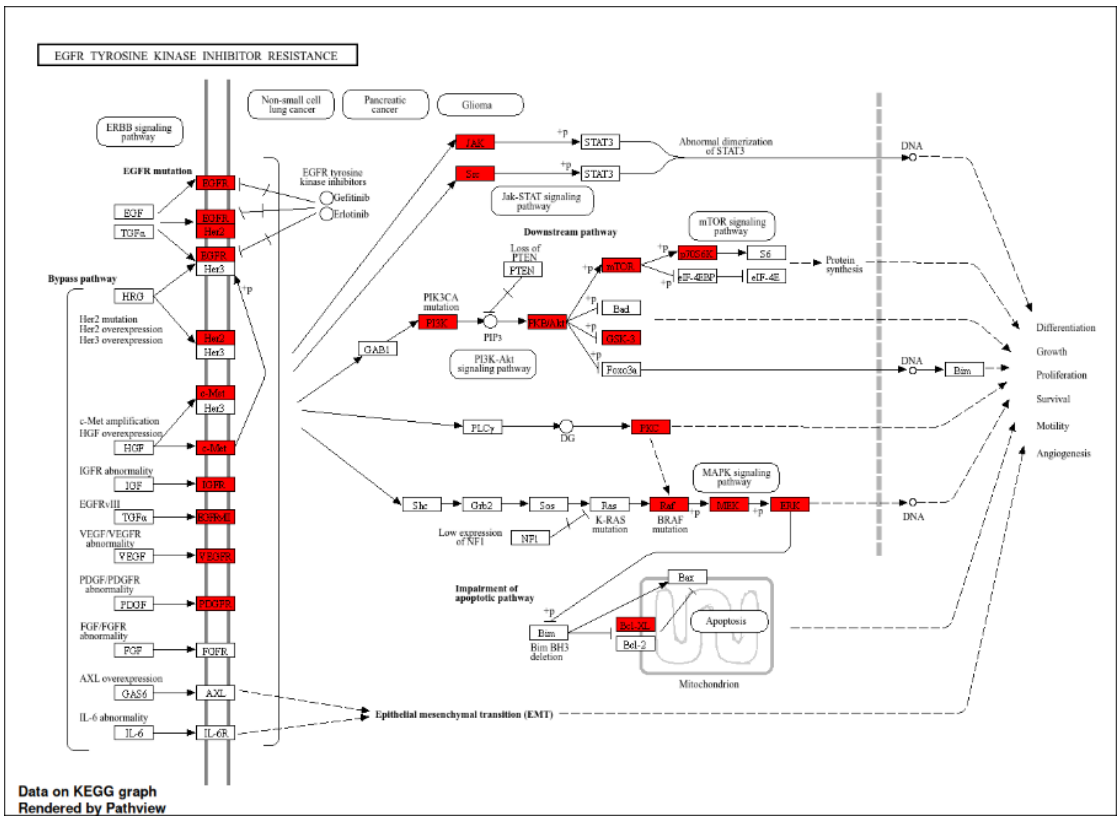


Figure 3. KEGG pathway analysis.

3.4. Molecular docking.

An initial receptor screening was conducted on 19 protein targets representing major oxidative stress-related pathways identified through KEGG analysis, including PI3K-Akt, MAPK, NF-κB, VEGF, and apoptosis pathways. Each target was docked with representative *Arcangelisia flava* compounds (berberine and jatrotthizine) and their native inhibitors to compare binding affinities (ΔG). The docking results showed binding energies ranging from –3.6 to –11.6 kcal/mol, with eight receptors exhibiting strong affinities (ΔG ≤ –8.0 kcal/mol): MEK (3E8N), PI3K (5JHB), PKC (1XJD), VEGFR (2QU5), JAK (2B7A), RAF (1UWH), BCL-XL (3ZK8), and C-MET (3LQ8). Notably, the PI3K-jatrotthizine (–9.11 kcal/mol) and MEK-berberine (–9.34 kcal/mol) complexes displayed binding energies comparable to their native inhibitors, indicating that these furanoditerpenes can effectively stabilize the catalytic sites of redox-sensitive kinases.

To refine target selection, the eight top-performing receptors were subjected to a second-stage docking analysis using both berberine and jatrotthizine. Among all evaluated targets, PI3K (PDB IDs: 4HVB and 5JHB) showed the most stable and reproducible interactions. Jatrotthizine exhibited strong binding to PI3K (4HVB; –9.08 kcal/mol), comparable to the native inhibitor (–10.38 kcal/mol), whereas berberine showed markedly weaker binding (–2.56 kcal/mol). This difference suggests that the structural features of jatrotthizine enable optimal accommodation within the PI3K catalytic cleft and promote favorable hydrogen bonding and hydrophobic interactions with key residues, including Asp836, Leu838, and Tyr867. Taken together, these findings support PI3K as the most biologically and structurally relevant target for further mechanistic analysis and highlight jatrotthizine as a promising multitarget compound involved in oxidative stress regulation (Table 1).

Table 1. Free binding energy of *A.flava* with various genes/proteins.

No.	Compound	Protein	PDB ID	ΔG (Kcal/mol)
1	Berberin	EGFR	1I18	-6,73
2	Jatrotthizine	EGFR	1I18	-6,09
3	Inhibitor 1I18	EGFR	1I18	-5,50
4	Jatrotthizine	PKC	1XJD	-7,83
5	Berberin	PKC	1XJD	-7,44
6	Inhibitor 1XJD	PKC	1XJD	-11,88
7	Jatrotthizine	Src	1Y57	-6,63
8	Berberin	Src	1Y57	-6,60
9	Inhibitor 1Y57	Src	1Y57	-10,51
10	Berberin	VEGFR	2QU5	-8,85
11	Jatrotthizine	VEGFR	2QU5	-8,15
12	Inhibitor 2QU5	VEGFR	2QU5	-11,62
13	Berberin	IGFR	3I18	-7,71
14	Jatrotthizine	IGFR	3I18	-7,41
15	Inhibitor 3I18	IGFR	3I18	-11,01
16	Berberin	PDGFR	3MJG	-4,98
17	Jatrotthizine	PDGFR	3MJG	-4,17
18	Native ligand of 3MJG	PDGFR	3MJG	-3,67
19	Jatrotthizine	PI3K	4HVB	-9,08
20	Berberin	PI3K	4HVB	-2,56
21	Native ligand of 4HVB	PI3K	4HVB	-10,38
22	Berberin	PI3K	5JHB	-7,84
23	Native ligand of 5JHB	PI3K	5JHB	-7,53
24	Jatrotthizine	PI3K	5JHB	-6,79
25	Native ligand of 7F7W	JAK	7F7W	-8,55
26	Berberin	JAK	7F7W	-7,75
27	Jatrotthizine	JAK	7F7W	-7,74

Validation of the docking protocol was performed by redocking the native ligand into the PI3K binding site, yielding an RMSD value below 2.0 Å, which confirms the reliability of the docking parameters. The native inhibitor of PI3K (PDB ID: 4HVB) [46] exhibited the strongest binding affinity (–10.38 kcal/mol) and formed multiple stabilizing interactions, including hydrogen bonds with Lys 745, Gly 857, and Asp 790, as well as extensive hydrophobic contacts with residues such as Trp 812, Ile 831, Leu 838, Ile 879, Ile 881, Val 882, Ala 885, Met 953, Tyr 867, and Ile 963 (Table 2). Additional π–σ interactions involving Ser530, Arg120, and Tyr355 further stabilized the ligand within the catalytic pocket, providing a reliable benchmark for evaluating the tested compounds [47,48].

Among the furanoditerpenes evaluated, jatrotthizine showed the highest binding affinity to PI3K (–9.08 kcal/mol), closely approaching that of the native inhibitor. Jatrotthizine formed stable hydrogen bonds and hydrophobic interactions with key catalytic residues, including Asp 836, Leu 838, Asp 841, Tyr 867, and Met 953, which are critical for PI3K activity (Table 2). This interaction profile suggests the formation of a stable ligand–receptor complex. It supports the potential of jatrotthizine to inhibit PI3K activity and downstream Akt phosphorylation, thereby contributing to the regulation of redox homeostasis. In contrast, ligands such as fibleucin and pacybasin exhibited weaker binding affinities (–3.70 and –3.08 kcal/mol), indicating lower interaction stability with the PI3K active site [39,49].

Table 2. Free binding energy of *A.flava* with 4HVB.

No	Ligand	Energy	Interaction
1	Native ligand	-10.38	H bonds (Lys 745, Gly 857, Asp 790), Asp 694; Trp 812; Ile 831; Leu 838; Ile 879; Ile 881; Val 882; Ala 885; Met 953; Tyr 867; Ile 963, and pi sigma bond (Ser 530, Arg 120, and Tyr 355)
2	Jatrotthizine	-9.08	Trp 812; Glu 880; Ile 881; Val 882; Ala 885; Asp 836; Leu 838; Asp 841; Tyr 867; Cys 869; Ile 879; Val 882; Met 953; Ile 963
3	1-3-hidroksi-berberine	-6.60	Met 804; Trp 812; Thr 866; Tyr 867; Ile 879; Lys 890; Met 953; Ile 963; Asp 964
4	Fibleucin	-3.70	Arg 982; Trp 1086

No	Ligand	Energy	Interaction
5	Tenuifolin	-3.42	Glu 981; Asn 1085; Trp 1086; His 1089
6	Pacybasin	-3.08	Glu 981; Arg 982
7	2a,3a-epoxy-2,3,7,8a-tetrahydroPenianthic acidmethylester	-2.87	Glu 981; Arg 982; Asn 1085; Trp 1086
8	Berberin	-2.56	Arg 982; Glu 981
9	Thalifendiane	-2.48	Glu 981; Asn 1085; Trp 1086
10	Palmatine	-2.44	Glu 981; Arg 982; Val 1074; Lys 1078
11	p-hydroxy benzaldehyde	-2.37	Glu 981; Arg 982; Lys 1087
12	dehydrocorydalmine	-2.25	Arg 982; Asn 1085; Glu 981; Leu 1088
13	Pycnarrhine	-2.12	Glu 981; Arg 982; Val 1074
14	Limacine	-1.99	Glu 981; Arg 982; Val 1074; Lys 1078

1,3-Hydroxyberberine demonstrated moderate binding affinity (–6.60 kcal/mol), interacting with residues such as Met 804, Trp 812, Thr 866, Tyr 867, Ile 879, and Met 953. Although biologically relevant, this interaction was weaker than that of jatrotthizine, likely because fewer hydrogen-bonding interactions occur within the catalytic pocket. Other furanoditerpenes showed only limited peripheral interactions, resulting in low binding stability. Overall, the observed affinity hierarchy-jatrotthizine (strong) > 1,3-hydroxyberberine (moderate) >> other furanoditerpenes (weak) reflects structural differences influencing hydrogen bonding and π–π stacking capabilities. Notably, the strong affinity of jatrotthizine exceeds the –6.0 kcal/mol threshold commonly considered biologically significant in in silico screening, supporting its potential as a lead compound. These docking results provide structural validation of the network pharmacology predictions, particularly highlighting PI3K, AKT1, and MTOR as central targets involved in oxidative stress and inflammatory regulation.

3.5. Integration of network pharmacology and docking findings.

Integration of network pharmacology and molecular docking analyses provides a coherent understanding of the multitarget mechanisms of *the furanoditerpenes from Arcangelisia flava*. Network pharmacology identified several hub genes, including AKT1, MTOR, TNF, and MAPK3, which are centrally involved in oxidative stress regulation and inflammatory signaling pathways. These findings suggest that the bioactive compounds act through interconnected signaling networks rather than a single molecular target.

Molecular docking results further supported these predictions by demonstrating strong and stable interactions between jatrotthizine and PI3K, a key upstream regulator of the PI3K–Akt signaling pathway. The high binding affinity of jatrotthizine for PI3K and its interactions with critical catalytic residues indicate a direct inhibitory potential that may subsequently modulate downstream targets such as AKT1 and MTOR. This convergence of systems-level prediction and structural validation highlights PI3K as a central molecular node linking redox regulation and inflammation [6,24,27].

Overall, the combined analyses confirm that *A. flava* furanoditerpenes exert antioxidant and anti-inflammatory effects by coordinating modulation of the PI3K–Akt, MAPK, and NF-κB pathways. This integrative approach strengthens the biological relevance of the findings and supports the identification of jatrotthizine as a promising multitarget compound for further pharmacological investigation.

3.6. Biological implications.

The integrated network pharmacology and molecular docking results provide important biological insights into the antioxidant and anti-inflammatory potential of *the furanoditerpenes of Arcangelisia flava*. The identification of PI3K–Akt, MAPK, and NF-κB pathways as central regulatory axes suggests that these compounds modulate oxidative stress and inflammation through coordinated regulation of cell survival, redox balance, and cytokine signaling.

The strong interaction between jatrotthizine and PI3K highlights a potential molecular mechanism by which *A. flava* may suppress excessive reactive oxygen species (ROS) production and downstream inflammatory responses. By modulating PI3K activity and Akt phosphorylation, jatrotthizine may enhance endogenous antioxidant defenses while limiting pro-inflammatory signaling, thereby contributing to redox homeostasis.

These findings provide a molecular basis for the traditional use of *A. flava* in treating inflammatory and oxidative stress–related conditions. Moreover, the multitarget characteristics observed in this study reflect the synergistic nature of phytochemical mixtures, suggesting that the combined effects of furanoditerpenes may be more effective than single-compound actions. Although the results are based on in silico analyses, they offer a strong rationale for future experimental validation, including in vitro and in vivo studies, to further explore the therapeutic potential of *A. flava* and its bioactive constituents.

4. Conclusions

This study revealed that furanoditerpenes derived from *Arcangelisia flava* exhibit potent multitarget antioxidant and anti-inflammatory activities by modulating key signaling pathways, particularly PI3K-Akt, MAPK, and NF-κB. Network pharmacology identified ten hub genes: AKT1, TNF, EGFR, MTOR, SRC, JUN, ESR1, CCND1, ALB, and MAPK3, closely associated with redox regulation and inflammatory responses. Molecular docking validation confirmed that Jatrotthizine displayed strong binding affinity to PI3K (PDB ID: 4HVB; –9.08 kcal/mol), suggesting its ability to stabilize redox-sensitive kinases and inhibit downstream signaling. These results provide mechanistic insights supporting the traditional use of *A. flava* as an antioxidant and anti-inflammatory agent. The findings highlight Jatrotthizine as a promising lead compound for further pharmacological and in vivo evaluations. Future research should focus on experimental validation, pharmacokinetic profiling, and formulation development to translate these computational insights into therapeutic applications.

Author Contributions

Conceptualization, Y.R.Y. and E.S.S.; methodology, Y.R.Y. and K.D.; software, J.E.M.; validation, Y.R.Y., K.D., and D.O.; formal analysis, F.T. and J.E.M.; investigation, Y.R.Y. and K.D.; resources, F.T.; data curation, J.E.M. and D.O.; writing—original draft preparation, Y.R.Y. and E.S.S.; writing—review and editing, E.S.S. and K.D.; visualization, J.E.M.; supervision, E.S.S.; project administration, E.S.S.; funding acquisition, Y.R.Y. All authors have read and agreed to the published version of the manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Not applicable.

Data Availability Statement

The data presented in this study are available on request from the corresponding author. All datasets used in this research, including protein structures (PDB IDs: 1I18, 1XJD, 1Y57, 2QU5, 3I18, 3MJG, 4HVB, 5JHB, and 7F7W), gene targets, and compound structures, were obtained from publicly available databases such as the Protein Data Bank (http://www.rcsb.org), SuperPRED (https://prediction.charite.de), UniProt (https://www.uniprot.org), GeneCards (https://www.genecards.org), STRING (https://string-db.org), and KEGG (https://www.kegg.jp). No proprietary data were generated or used in this study.

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Conflicts of Interest

The authors declare no conflict of interest.

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