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Predicting the Anti-Pulmonary Fibrosis Potential of *Physalis angulata* Compounds A Computational Study

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Abstract

Pulmonary fibrosis is a progressive lung disease characterized by tissue scarring and respiratory decline. Existing treatments have limited efficacy and significant side effects. *Physalis angulata*, a traditional medicinal plant, shows promise for antifibrotic therapy due to its bioactive compounds potentially targeting key fibrotic pathways. This study aims to predict the potential of *Physalis angulata* compounds to PI3K/AKT protein as candidates for antifibrotic therapy. Ten active compounds from *P. angulata* were docked against the PI3K/AKT protein (PDB ID: 2UZT) using AutoDock Vina. Docking was validated by redocking the native ligand. Binding affinities and molecular interactions were analyzed. ADMET properties were predicted via the pkCSM platform to assess pharmacokinetics and toxicity. Myricetrin exhibited the strongest binding affinity (-9.6 kcal/mol), surpassing the native ligand (-9.1 kcal/mol). Other flavonoids, including eriodictyol (-8.9 kcal/mol), naringin (-8.8 kcal/mol), and apigenin (-8.5 kcal/mol), also showed favorable affinities. Critical amino acids involved were Asp184 and Glu121. The redocking RMSD value of 0.893 Å confirmed methodological accuracy. ADMET predictions revealed high intestinal absorption for tangeretin and apigenin, with no mutagenic or hepatotoxic risks, indicating good pharmacokinetic profiles. *Physalis angulata* flavonoids exhibit strong PI3K/AKT binding and favorable pharmacokinetics, supporting their potential as antifibrotic agents.

Keywords: Pulmonary fibrosis: *Physalis angulata*; Molecular docking; PI3K/AKT.

INTRODUCTION

Pulmonary fibrosis is a progressive, chronic interstitial lung disease characterized by the excessive accumulation of fibrotic tissue in the lungs, leading to a steady decline in respiratory function (Mazurek et al., 2025). Among its various forms, Idiopathic Pulmonary Fibrosis (IPF) is the most prevalent and severe, with a reported incidence of 58.7 cases per 100,000 individuals. The disease carries a high mortality rate, with an age-adjusted death rate of 5.4 per 100,000 population in 2017 (Zheng et al., 2022). Although several intrinsic risk factors have been identified, including genetic predisposition, age, sex, and alterations in the lung microbiome, as well as extrinsic factors such as cigarette smoke, environmental exposures, and air pollution, the exact etiology of IPF remains elusive (Zaman & Lee, 2018). Comorbid conditions like gastroesophageal reflux disease, obstructive sleep apnea, diabetes mellitus, and viral infections have also been linked to the disease (Alfaro & Robalo Cordeiro, 2020).

Clinically, patients with pulmonary fibrosis often present with non-specific symptoms such as exertional dyspnea and chronic cough, which can delay diagnosis (Martinez et al., 2017). A detailed clinical history is essential and should include information on environmental exposures, smoking habits, prior treatments, illicit drug use, travel history, and familial cases of lung disease. To aid this process, the German Respiratory Society has developed a standardized patient questionnaire that enhances the accuracy and comprehensiveness of evaluations (Kardos et al., 2020). Diagnostic confirmation typically relies on an integrative assessment involving clinical evaluation, imaging such as high-resolution CT scans, and, in certain cases, histopathological examination (Lee & Song, 2024). Currently, pirfenidone and nintedanib are the only antifibrotic agents approved for IPF management. Although both drugs have demonstrated efficacy in slowing disease progression, their use is often limited by side effects, including gastrointestinal disturbances and hepatotoxicity, necessitating regular liver function monitoring (Glass et al., 2022).

In light of these limitations, interest in plant-based therapies has grown, with *Physalis angulata* emerging as a promising natural candidate. Commonly known as

ciplukan in Indonesia, this plant is traditionally used to treat various ailments, including diabetes, hepatitis, and asthma (Prasetyo & Purwanti, 2024). Pharmacological studies have shown that P. angulata possesses diverse biological activities, such as antioxidant, anti-inflammatory, anticancer, antidiabetic, and antibacterial effects (Fadhli et al., 2023). The plant is well adapted to tropical climates and grows wild across much of Indonesia, making it easily accessible for cultivation and medicinal use (Pillai et al., 2022). Furthermore, subacute toxicity studies have confirmed its safety profile, supporting its suitability for development as a herbal medicinal product. Its wide geographic distribution across Asia, the Americas, Australia, and the Pacific further underscores its global therapeutic potential.

The therapeutic properties of P. angulata are largely attributed to its rich content of withanolide compounds. Recent investigations have identified eight novel withanolides designated withagulides A through H alongside twenty-eight known analogues (Novitasari et al., 2024). Among these, several compounds have shown potent antifibrotic activity, notably by inhibiting COL1A1 gene expression by over 50% (Zhou et al., 2024). One compound, Physalin F, has been found to significantly suppress collagen I and α-SMA expression induced by TGF-β1 in hepatic stellate cells, primarily through inhibition of the PI3K/AKT/mTOR signalling pathway (Wang et al., 2022). This pathway is known to play a central role in cellular proliferation, fibrosis progression, and scar tissue formation. Additionally, the plant exerts anti-inflammatory effects by reducing IL-6 gene expression in TGF-β-induced fibrotic cells, suggesting its potential dual action as both an antifibrotic and anti-inflammatory agent (Wiraswati et al., 2024).

This study aims to explore the antifibrotic potential of *Physalis angulata* through molecular docking analysis, targeting the PI3K/AKT signalling pathway. This pathway is critically involved in the activation of fibrotic cells and the regulation of genes associated with extracellular matrix production and tissue scarring. Through computationally screening the interaction between bioactive compounds from P. angulata and the PI3K/AKT protein complex, the study seeks to identify candidate molecules with high binding affinity that may serve as novel therapeutic agents. The use of molecular docking offers a cost-effective, predictive method for assessing the pharmacological potential of natural compounds prior to in vitro or in vivo validation. Ultimately, this research supports the advancement of plant-based antifibrotic therapies that are safer and potentially more effective than current pharmacological options. It also contributes to the broader scientific understanding of how natural compounds can be leveraged to modulate key fibrotic signalling pathways.

MATERIALS AND METHODS

Prediction of Antifibrotic Activity

The potential antifibrotic activity of *Physalis angulata* active compounds was assessed using the DDI-Pred module of the Way2Drug software. This approach is grounded in the Prediction of Activity Spectra for Substances (PASS) technology, which enables prediction of molecular interactions based on the structural and biological activity relationships of compounds. This method facilitates the evaluation of the likelihood that active compounds interact with molecular targets involved in pulmonary fibrosis, providing an initial indication of their antifibrotic potential (Ananthathandavan & Narayanasamy, 2024).

Receptor and Ligand Preparation

This study utilized the PI3K/AKT protein with PDB ID: 2UZT, obtained from the RCSB Protein Data Bank (https://www.rcsb.org/). This protein was selected based on previous research where it was employed to predict the anti-apoptotic potential of cinnamaldehyde (Fukata et al., 2025). The retrieved protein structure was subsequently repaired to isolate the protein chains and native ligands essential for validation purposes (Utami et al., 2025). This step was carried out using BIOVIA Discovery Studio 2024 to determine the specific protein sequences accurately. The active compounds from *Physalis angulata* served as test ligands in this study, with their chemical structures retrieved from the PubChem database (https://pubchem.ncbi.nlm.nih.gov/). A total of ten compounds were analyzed: rhoifolin (CID 5282150), tangeretin (CID 68077), eriodictyol (CID 440735), catechin (CID 9064), naringin (CID 442428), myricetrin (CID 5281673), kaempferol (CID 5280863), hesperidin (CID 10621), epigallocatechin (CID 72277), and apigenin (CID 5280443) (Ekeke et al., 2019; Nguyen et al., 2021). Nintedanib was included as a reference standard due to its well documented clinical efficacy in slowing disease progression by reducing pulmonary function decline (Kreuter et al., 2021).

Molecular Docking Simulation

A crucial step in this study involved validating the docking methodology through a redocking procedure to confirm its accuracy. Redocking evaluates whether the docking protocol can accurately reproduce the native ligand's binding pose within the protein-ligand complex. This assessment is quantified by calculating the Root Mean Square Deviation (RMSD) between the docked and original ligand positions, with values below 2 Å considered acceptable. Lower RMSD values correspond to higher docking precision. Besides validation, redocking aids in defining the grid box's center coordinates (X, Y, Z) and dimensions for subsequent specific docking runs, referencing the native ligand's position in the crystal structure (Farid et al., 2025). Docking simulations were performed using AutoDock

Vina integrated within PyRx software. Prior to docking, ligand and receptor files were converted to the PDBQT format using Open Babel, which also facilitated energy minimization to ensure that both ligand and receptor conformations were energetically favorable. Docking results were evaluated based on binding affinity values, with lower affinities indicating stronger ligand-protein interactions and potential biological activity (Farid et al., 2025).

Visualization of Docking Results

Redocking outcomes were analyzed by calculating RMSD values to assess the congruence between docked ligand positions and their native conformations. Additionally, three dimensional overlap visualization of ligands before and after docking was performed using PyMOL to observe positional deviations (Farid et al., 2025). Further interaction analysis between ligands and amino acid residues within the receptor binding site was conducted using BIOVIA software, enabling detailed characterization of the types and strengths of molecular interactions formed (Farid et al., 2025).

Pharmacokinetic and Toxicity Predictions

Pharmacokinetic and toxicity properties of the tested compounds were predicted using ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters via the pkCSM online platform (https://biosig.lab.uq.edu.au/pkcsm/prediction). For this analysis, each compound's Canonical SMILES notation was obtained from the PubChem database. Key parameters evaluated included intestinal absorption percentage, blood-brain barrier (BBB) permeability, central nervous system (CNS) permeability, substrate specificity for cytochrome P450 enzymes CYP2D6 and CYP3A4, total clearance rate (log ml/min/kg), renal organic cation transporter 2 (OCT2) substrate status, as well as toxicity profiles including Ames mutagenicity and hepatotoxicity potential (Utami et al., 2025).

RESULTS AND DISCUSSION

Results

The PASS Online analysis revealed that several compounds from *Physalis angulata* possess predicted pharmacological activities related to lung fibrosis and lung cancer. Notably, myricetrin had the highest predicted activity (Pa = 0.479) for antineoplastic effects in lung cancer, while also showing moderate potential for cystic fibrosis treatment (Pa = 0.273). Rhoifolin exhibited Pa values of 0.478 and 0.306 for lung cancer and cystic fibrosis, respectively, indicating dual relevance in antifibrotic and antineoplastic contexts. Apigenin and kaempferol both demonstrated moderate activity predictions for cystic fibrosis and small cell lung cancer, while hesperidin showed a Pa of 0.405 for general lung cancer. Tangeretin and naringin also displayed potential with Pa values consistently near or above the 0.3 threshold across multiple lung cancer types. These findings suggest that multiple flavonoids from P. angulata may interact with targets relevant to fibrosis and neoplastic lung conditions (Ananthathandavan & Narayanasamy, 2024).

Redocking was conducted using the receptor file to validate the accuracy of the docking method. The grid box was defined with center coordinates at X = 21.580, Y = 7.910, and Z = 35.577, and dimensions of 14.153 Å (X), 10.807 Å (Y), and 4.976 Å (Z). The evaluation yielded an RMSD value of 0.893 Å based on the alignment of 27 atoms, confirming that the predicted ligand conformation closely resembled the original pose (Farid et al., 2025). This indicates that the docking protocol was valid and reliable. The determined grid parameters were subsequently used for the main docking simulations.

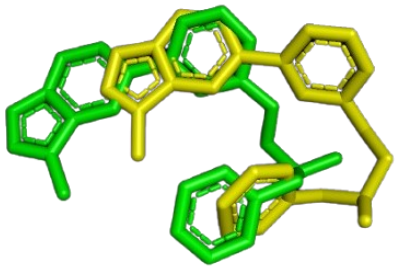

Figure 1. Native ligand before (green) and after (yellow) redocking.

Molecular docking simulations produced varied binding affinity values for the tested compounds against the PI3K/AKT target. Myricetrin exhibited the strongest binding affinity at -9.6 kcal/mol, surpassing even the native ligand at -9.1 kcal/mol. Other compounds such as eriodictyol (-8.9 kcal/mol), naringin (-8.8 kcal/mol), epigallocatechin (-8.6kcal/mol), apigenin (-8.5 kcal/mol), and kaempferol (-8.3 kcal/mol) also demonstrated strong interactions. Conversely, compounds like hesperidin (-4.8 kcal/mol) and rhoifolin (-4.9 kcal/mol) showed the weakest binding affinities. The reference drug nintedanib showed a positive binding energy of +1.73 kcal/mol, which may suggest poor binding affinity under these docking parameters.

Table 1. Docking scores and amino acid interactions.

Compound	ΔG (kcal/mol)	Hydrogen Bonding Amino Acids	Non-Hydrogen Bonding Amino Acids
Native Ligand	-9.1	Arg18, Thr51	Val57, Ala70, Leu173, Asp184, Met120, Lys72
Rhoifolin	-4.9	Asp184, Lys72, Asn171, Gly50, Ser53	Val57, Leu173, Ala70, Val123, Leu49, Met120, Lys72
Tangeretin	-8.2	Glu121, Thr51, Lys72	Val57, Leu173, Ala70, Val123, Met120, Asp184, Arg18
Eriodictyol	-8.9	Lys72, Glu121, Thr51	Val57, Ala70, Leu173, Val104, Met120, Thr183, Asp184, Arg18
Catechin	-8.2	—	Val57, Leu173, Ala70, Asp184
Naringin	-8.8	Glu127, Val123, Leu49, Asp184, Ser53	Val57, Ala70, Leu173, Lys72, Asn171, Leu49, Asp184
Myricetrin	-9.6	Glu121, Glu170, Asp184, Asn171, Gly50	Val57, Ala70, Leu173, Tyr330
Kaempferol	-8.3	Glu121, Asp184	Val57, Ala70, Leu173, Thr183, Asp184
Hesperidin	-4.8	Glu121, Val123, Lys72, Asp184	Val57, Leu173, Gly50, Thr183
Epigallocatechin	-8.6	Glu121, Tyr330, Leu49, Glu127, Arg18, Thr51	Val57, Ala70, Leu173, Gly50
Apigenin	-8.5	Glu121, Gly50	Val57, Leu173, Ala70, Met120, Val104, Thr183
Nintedanib	+1.73	Asp264, Thr299	—

The docking results also identified key amino acid residues involved in the interactions. Non-hydrogen bonding interactions were most commonly observed with residues Val57, Leu173, and Ala70 across nearly all ligands. In terms of hydrogen bonding, Asp184, Glu121, and Lys72 were among the most frequently engaged residues. Notably, Asp184 formed hydrogen bonds with eight of the eleven tested ligands, highlighting its importance in ligand recognition.

Table 2. Predicted ADMET profiles of selected compounds.

Compound	Absorption (%)	BBB Penetration	CNS Penetration	CYP3A4 Substrate	Clearance	AMES Toxicity	Hepatotoxicity
Rhoifolin	24.3	-1.702	-4.798	No	-0.005	No	No
Tangeretin	98.5	-1.026	-3.011	Yes	0.780	No	No
Eriodictyol	74.7	-0.827	-3.142	No	-0.013	No	No
Catechin	68.8	-1.054	-3.298	No	0.183	No	No
Naringin	25.8	-1.600	-4.773	No	0.318	No	No
Myricetrin	43.3	-1.811	-4.376	No	0.303	No	No
Kaempferol	74.3	-0.939	-2.228	No	0.477	No	No
Hesperidin	31.5	-1.715	-4.807	No	0.211	No	No
Epigallocatechin	54.1	-1.377	-3.507	No	0.328	No	No
Apigenin	93.3	-0.734	-2.061	No	0.566	No	No

Based on ADMET prediction using the PKCMS tool, most compounds from *Physalis angulata* showed good intestinal absorption, except for Rhoifolin (24.3%) and Naringin (25.8%), which fell below the 30% threshold. Tangeretin exhibited the highest absorption rate (98.5%), followed by Apigenin (93.3%) and Kaempferol (74.3%) (Ramadhan et al., 2024). All ten compounds were predicted to have poor blood–brain barrier (BBB) permeability, with values below -1, particularly Myricetrin (-1.811) and Hesperidin (-1.715). Only Apigenin (-2.061) and Kaempferol (-2.228) approached the CNS permeability threshold. None of the compounds were substrates for CYP2D6 or OCT2, while only Tangeretin was predicted as a CYP3A4 substrate. All compounds were classified as non-mutagenic and non-hepatotoxic. In terms of clearance, Tangeretin (0.78 log ml/min/kg) and Apigenin (0.566) had the highest predicted elimination rates (Utami et al., 2025).

Discussion

The results of the docking analysis provide insight into the molecular interactions between active compounds from *Physalis angulata* and the PI3K/AKT protein, a critical signalling pathway implicated in fibrosis progression. The high binding affinity observed in compounds like myricetrin and eriodictyol suggests a strong and potentially biologically relevant interaction, comparable or even superior to the native ligand. These findings support the hypothesis that certain flavonoids may inhibit PI3K/AKT activity and thus interfere with fibrotic signalling mechanisms.

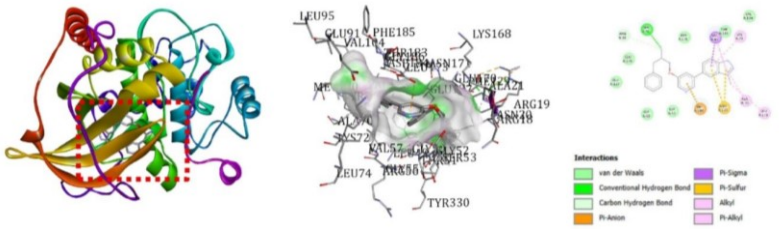

Figure 2. 3D structure of PI3K/AKT protein (PDB ID: 2UZT) with binding site.

The frequent appearance of Val57, Leu173, and Ala70 in non-polar interactions implies the presence of a conserved hydrophobic pocket that stabilizes the ligand through van der Waals and hydrophobic interactions. This structural feature may contribute significantly to the overall binding strength of the tested ligands. Moreover, the consistent involvement of polar residues such as Asp184 and Glu121 in hydrogen bonding highlights their central role in mediating strong and specific ligand-receptor interactions. Asp184's ability to act as both a donor and acceptor enhances its versatility and reactivity, potentially serving as a critical anchor point in the binding site.

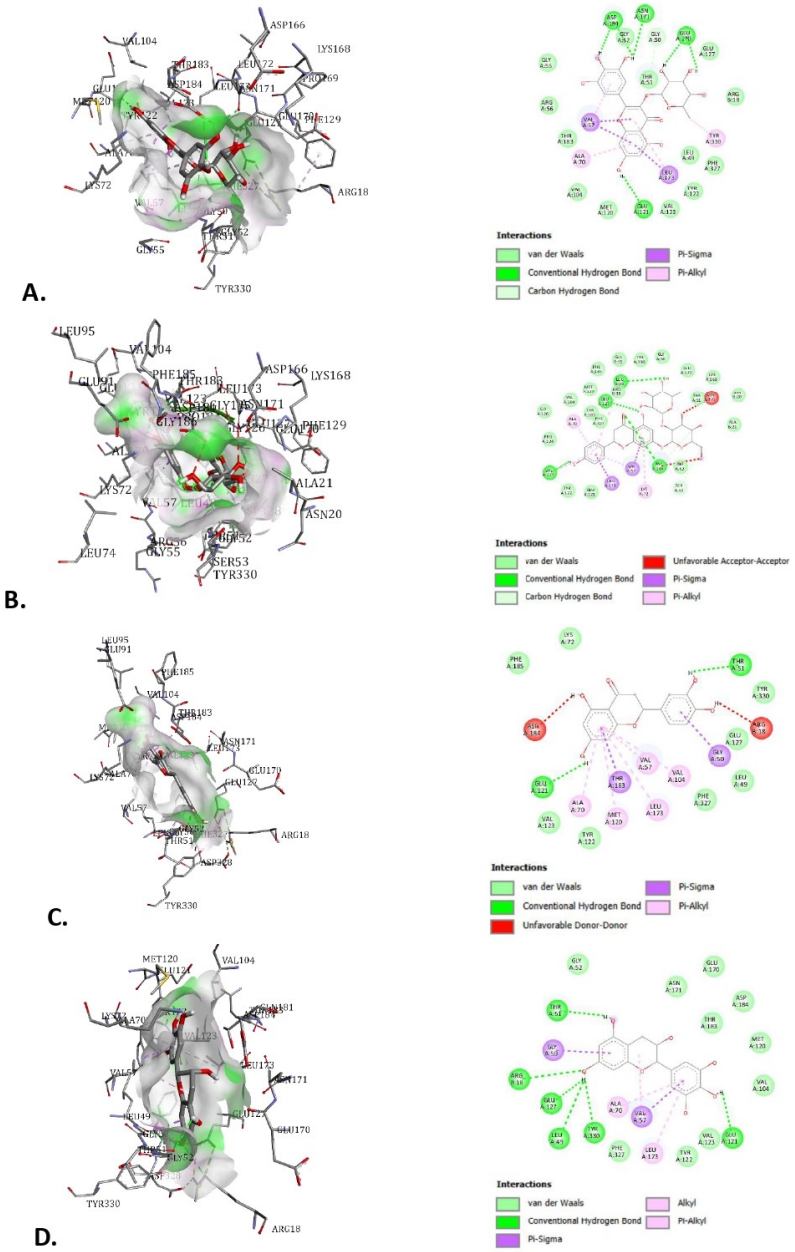

Figure 3. Binding pocket interactions of (A) Myricetrin, (B) Eriodictyol, (C) Naringin, and (D) Epigallocatechin with AKT.

The results suggest that bioactive compounds from *Physalis angulata* may have therapeutic potential for pulmonary fibrosis by targeting pathways shared with lung cancer, such as fibroblast proliferation and extracellular matrix accumulation through modulation of TGF-β/Smad and NF-κB signalling (Fan et al., 2023). Compounds like myricetrin and rhoifolin showed high predictive activity values, indicating strong antifibrotic potential, while apigenin and kaempferol, despite slightly lower scores, have been shown to suppress key fibrosis markers such as α-SMA and fibronectin (B. Ke et al., 2018). Hesperidin and tangeretin also demonstrated promising anti-inflammatory and antiproliferative effects that may slow fibrosis progression (Fan et al., 2023). The overlap between antifibrotic and antineoplastic activities highlights the molecular parallels between fibrosis and cancer, especially involving EMT and abnormal cell growth (Vithalkar et al., 2025). This supports the use of network pharmacology as a useful approach to explore multi-target and multi-component therapies, which are better suited for complex diseases like pulmonary fibrosis where single-target drugs often fall short (Liu et al., 2021; Nogales et al., 2022). Consequently, myricetrin, rhoifolin, and kaempferol emerge as promising candidates for further research and development as natural anti-fibrotic agents (H. L. Ke et al., 2024).

Multiple in vivo and in vitro studies have consistently demonstrated the antifibrotic potential of *Physalis angulata* (Ciplukan), supporting the molecular docking results presented in this study. Wiraswati et al. (2024) reported that ethanol extract of P. angulata significantly reduced fibrosis scores and serum levels of IL-6, TGF-β1, and KL-6 in a bleomycin-induced pulmonary fibrosis mouse model. These biological outcomes are consistent with the docking findings, where flavonoid compounds such as myricetrin, eriodictyol, and hesperidin exhibited strong binding affinities and interacted with key residues including Asp184, Glu121, and Lys72 associated with fibrotic and inflammatory pathways. A fibroblast model confirmed that P. angulata ethanol extract inhibited cell migration and downregulated IL-6 and HIF-1α expression in TGF-β-induced 3T3-L1 cells, which supports the proposed anti-inflammatory and anti-fibrogenic mechanism of the docked ligands (Rohmawaty et al., 2021).

Further molecular validation was provided by Imaduddin et al. (2024), who demonstrated that P. angulata extract significantly downregulated fibrosis-related genes such as Nox4, Mmp8, and Klf4 in a bleomycin-induced mouse model. These gene targets are central to oxidative stress response and extracellular matrix remodeling mechanisms possibly modulated via the observed ligand-residue interactions in silico. Complementary liver fibrosis studies also support P. angulata's systemic antifibrotic activity. Bestari et al. (2023) and Rohmawaty et al. (2023) observed improvements in liver histopathology, ALT, and cholesterol levels in NAFLD models, while Rohmawaty et al. (2021) reported reduced fibrosis scores and serum transaminase levels in CCl_4-induced liver fibrosis rats treated with the plant extract. Taken together, these findings demonstrate that the consistent interaction of docked flavonoids with polar and hydrophobic residues particularly Asp184, Glu121, and Val57 may underlie the extract's observed antifibrotic efficacy, thus reinforcing P. angulata's therapeutic promise across multiple fibrotic disease models.

The ADMET profiles indicate that several *Physalis angulata* compounds, particularly Tangeretin and Apigenin, possess favorable pharmacokinetic characteristics, including high intestinal absorption and relatively fast systemic clearance (Farid et al., 2025). However, poor BBB and CNS permeability across all compounds may limit their central nervous system effects, suggesting a more localized or peripheral antifibrotic action (Utami et al., 2025). The absence of CYP2D6 and OCT2 interactions reduces the risk of metabolic and renal toxicity, enhancing their safety profile. Notably, the lack of AMES toxicity and hepatotoxicity predictions across all compounds further supports their potential as safe therapeutic candidates. Overall, the pharmacokinetic properties strengthen the viability of these bioactive agents especially Tangeretin, Apigenin, and Kaempferol for further development as anti-fibrotic treatments with minimal systemic toxicity.

This study is limited by its reliance on in silico predictions, which, while informative, do not fully replicate the complexity of biological systems. The docking results and ADMET simulations require further validation through experimental assays, such as in vitro tests on lung fibroblasts or in vivo models of pulmonary fibrosis. Additionally, the pharmacokinetic predictions need to be confirmed by actual bioavailability and toxicity studies. Future research should focus on elucidating the specific molecular mechanisms of promising compounds like myricetrin and apigenin, particularly their influence on the pathway and fibrotic markers. Such investigations will be essential to assess their therapeutic relevance and advance them as potential candidates for natural anti-fibrotic drug development.

CONCLUSIONS

Several bioactive compounds from *Physalis angulata*, particularly myricetrin (ΔG = -9.6 kcal/mol), apigenin (-8.5 kcal/mol), and eriodictyol (-8.9 kcal/mol), demonstrated strong binding affinities to the PI3K/AKT protein and interacted with key residues like Asp184 and Glu121, suggesting potential antifibrotic activity. ADMET predictions indicated favorable absorption and safety profiles, especially for tangeretin and apigenin. These findings highlight the therapeutic promise of *P. angulata* flavonoids in targeting fibrotic pathways.

Further in vitro and in vivo studies are needed to validate their mechanisms and efficacy as multi target agents for pulmonary fibrosis treatment.

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Authors' Contributions: MF and AAK designed the in-silico study. NDO and SR conducted the computational analyses. DA processed and analyzed the data. MF and WAR drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Competing Interests: The authors declare that there are no competing interests.

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