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Molecular Docking and Toxicity Prediction of *Artocarpus heterophyllus* Compounds as Anti-Pancreatic Cancer Agents

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ABSTRACT

Background: Pancreatic cancer is a highly aggressive cancer with increasing incidence and poor survival rates. Current therapies like gemcitabine show limited efficacy and cause significant toxicity. Natural compounds from Artocarpus heterophyllus have demonstrated diverse pharmacological properties, including anticancer potential, making them promising candidates for alternative treatments.

Objective: This study aims to evaluate the anti-pancreatic cancer potential of *Artocarpus heterophyllus* compounds targeting PPARγ using molecular docking and toxicity prediction.

Research methods: The PPARγ protein (PDB ID: 3U9Q) was prepared and refined for docking simulations. Six compounds from *A. heterophyllus* and gemcitabine were docked using AutoDock Vina to assess binding affinities. Interaction profiles were visualized to identify key residues involved. Toxicity parameters including hepatotoxicity, carcinogenicity, and immunotoxicity were predicted using ProTox-3 to evaluate safety profiles.

Results: Quercetin exhibited the strongest binding affinity –7.6 kcal/mol, surpassing gemcitabine –5.4 kcal/mol and native ligand decanoic acid –5.8 kcal/mol. Myricetin and cintriamide also showed favorable binding energies –5.9 and –7.0 kcal/mol. Quercetin and myricetin had low predicted toxicity, including non-hepatotoxic and non-mutagenic profiles, supported by previous hepatoprotective evidence. Cintriamide displayed strong binding but raised immunotoxicity concerns. Artocarpesin and licoflavone C showed weaker binding yet low toxicity. Key interactions involved residues Ser289, Cys285, and Phe363, critical for ligand stability.

Conclusion: *Artocarpus heterophyllus* compounds, especially quercetin and myricetin, demonstrate promising anticancer activity against pancreatic cancer with favorable safety profiles.

Keywords*: Artocarpus heterophyllus; Pancreatic cancer; PPARγ; Molecular docking; Toxicity prediction*

INTRODUCTION

Pancreatic cancer, particularly pancreatic ductal adenocarcinoma (PDAC), represents one of the most aggressive malignancies with a notably poor prognosis (Park et al., 2021). Although its incidence remains lower than that of many other cancers, the rate of new cases continues to rise by approximately 0.5% to 1% annually. Alarmingly, pancreatic cancer is projected to become the second leading cause of cancer related deaths by the year 2030 (Park et al., 2021) This high mortality rate is primarily attributed to late-stage diagnosis, as most patients present with advanced or metastatic disease at the time of detection. Various risk factors have been implicated in the development of pancreatic cancer, including family history, tobacco use, chronic pancreatitis, obesity, diabetes mellitus, and exposure to specific environmental chemicals (McGuigan et al., 2018). Moreover, genetic mutations such as those in BRCA2, CDKN2A, and KRAS play a pivotal role in pancreatic carcinogenesis (Stefanoudakis et al., 2024). The absence of reliable early detection methods further complicates disease management, underscoring the critical need for preventive strategies and a deeper understanding of modifiable risk factors.

Due to its non-specific symptoms and lack of effective screening tools, this cancer is often diagnosed at an advanced stage. Current diagnostic approaches rely on imaging modalities such as computed tomography (CT) and magnetic resonance imaging (MRI), typically followed by histopathological confirmation through biopsy (McGuigan et al., 2018). Therapeutic interventions for unresectable or metastatic commonly include gemcitabine, a chemotherapeutic agent that has served as a standard first-line treatment (Jiang et al., 2022). While gemcitabine can modestly extend survival, its overall therapeutic efficacy remains limited, with most patients experiencing only temporary responses. Additionally, treatment is frequently accompanied by adverse effects including fatigue, neutropenia, nausea, and hepatic toxicity (Huai et al., 2019). In recent years, scientific interest has increasingly focused on the role of peroxisome proliferator-activated receptor gamma (PPARγ) in pancreatic cancer (Zhang et al., 2015). PPARγ is often overexpressed in pancreatic tumor tissues and has been associated with advanced disease stages and poorer clinical outcomes. Intriguingly, PPARγ activation has also been linked to chemoresistance, particularly against gemcitabine and 5-fluorouracil (Zhang et al., 2015).

Artocarpus heterophyllus (jackfruit), a tropical plant widely utilized in traditional medicine, has recently garnered attention in biomedical research due to its diverse array of bioactive compounds (Fayazuddin et al., 2023). Various parts of the plant including its fruit, seeds, leaves, and wood have demonstrated multiple health benefits, such as glycemic control in diabetes, lipid profile improvement, anti-atherosclerotic activity, and antiviral, antidiarrheal, and antiplatelet properties (Nilakandhi et al., 2023; Soni et al., 2024). Additionally, the presence of dietary fiber, antioxidants, and phenolic compounds supports digestive and immune health (Ranasinghe et al., 2019). Notably, several phytochemicals found in jackfruit, such as saponins, flavonoids, and artocarpesin, exhibit anticancer potential through mechanisms involving the inhibition of cancer cell proliferation and angiogenesis (Tripathi et al., 2023).

Given its pharmacologically active constituents, *Artocarpus heterophyllus* holds promise not only as a functional food but also as a potential source for novel anticancer therapies. As a result, PPARγ is emerging as a potential therapeutic target, with the possibility of overcoming drug resistance and enhancing treatment efficacy. This study aims to investigate the potential of *Artocarpus heterophyllus* derived compounds as therapeutic agents against pancreatic cancer, specifically through in silico approaches targeting PPARγ, with the goal of addressing chemoresistance and improving treatment outcomes.

RESEARCH METHODS

Methods Receptor and Ligand Preparation

This study employed the Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) protein, retrieved from the RCSB Protein Data Bank with PDB ID: 3U9Q (https://www.rcsb.org/). The selected structure has been previously utilized in studies exploring its interaction potential with pancreatic cancer-related ligands (Purnama et al., 2021). Prior to molecular docking, the protein was refined to remove all non-essential molecules such as water, native ligands, and cofactors. Protein chain isolation and structure correction were carried out using PyMOL to ensure specificity of the target region. Active compounds from Artocarpus altilis were selected as test ligands. Their 3D structures were downloaded from PubChem (https://pubchem.ncbi.nlm.nih.gov/) using the following Compound IDs: Gemcitabine (60750, as control), Cintriamide (6154037), Artocarpesin (399491), Myricetin (5281672), Quercetin (5280343), and Licoflavone C (10246505) (Sharma et al., 2015; Yuniarti et al., 2025)

Molecular Docking Simulation

Validate the docking protocol using redocking procedure was conducted using the native ligand. This step is essential to assess the reliability of the docking method, with a root mean square deviation (RMSD) value below 2 Å considered acceptable. Lower RMSD values indicate higher accuracy and reproducibility. The grid box dimensions (X, Y, Z) were determined based on the native ligand's binding site to ensure precise alignment during docking (Farid et al., 2025). Molecular docking simulations were conducted using AutoDock Vina through the PyRx interface. Ligand and receptor files were converted to the PDBQT format using the Open Babel tool within PyRx, which also performed energy minimization to ensure the ligands adopted their most stable conformations. All test ligands were docked using the same grid box parameters defined during the redocking process. The primary output metric was binding affinity (kcal/mol), with lower values indicating stronger predicted interactions between the ligand and the protein target (Farid et al., 2025).

Visualization of Interactions

Redocking results were evaluated by calculating RMSD based on the superimposition of ligand poses before and after docking using PyMOL and Biovia Discovery Studio (Farid 2025). Amino acid interactions were visualized using Biovia Discovery Studio, allowing for detailed analysis of hydrogen and non-hydrogen interactions between the ligands and receptor residues (Lestariningrum et al., 2024).

Toxicity Prediction

Toxicity profiles of the test compounds were predicted using the ProTox-3 platform (https://tox.charite.de/protox3/), utilizing the canonical SMILES format of each compound

as input. The parameters analyzed included toxicity class, hepatotoxicity, carcinogenicity, immunotoxicity, mutagenicity, and cytotoxicity (Banerjee et al., 2024).

RESULTS AND DISCUSSION

RESULTS

The docking simulation, the defined grid box was centered at coordinates x = 1.02, y = 0.32, z = 23.20 with dimensions of 9.65 Å along the x-axis, 9.57 Å along the y-axis, and 8.78 Å along the z-axis. These parameters were selected to ensure the identification of optimal ligand conformations within the active site. The root mean square deviation (RMSD) value of 1.35 Å indicated reliable stability and reproducibility of the docking outcomes.

The molecular docking results for seven tested ligands are summarized in Table 1. Among them, quercetin demonstrated the most favorable binding affinity with a binding energy of -7.6 kcal/mol, suggesting the strongest interaction with the target protein. Cintriamide followed closely with a binding energy of –7.0 kcal/mol. Myricetin and licoflavone C each exhibited binding energies of –5.9 kcal/mol. In comparison, the native ligand decanoic acid showed a binding energy of –5.8 kcal/mol, slightly stronger than that of the positive control drug, gemcitabine –5.4 kcal/mol. Artocarpesin displayed the weakest interaction, with a binding energy of –2.0 kcal/mol, indicating the lowest affinity for the target protein.

TABLE 1. Docking Simulation Results

Compound	Binding Energy	Amino Acids Hydrogen Bonds	Amino Acids Non-Hydrogen Bonds
	-5.8	Ser 289	Phe 363, Phe 282, Cys 285, Ile 281, Phe 260, His 449
Gemcitabine	-5.4	Ser 289, Tyr 327	Phe 363, His 323, His 449, Met 364, Cys 285
Cintriamide	-7.0	Ser 289, Phe 360, Tyr 327	Phe 282, Phe 363, Leu 453, His 323, His 449, Met 364, Cys 285
Artocarpesin	-2.0	Gln 286	Phe 363, Ile 281, Cys 285, Leu 356, Met 364, Leu 453, Leu 469, Tyr 473, His 323, His 449
Myricetin	-5.9	Ser 289, Phe 282, Ala 278, Met 364	Phe 363, His 449, Cys 285
Quercetin	-7.6	Phe 360, Cys 285	Phe 363, Met 364, His 449
Licoflavone c	-5.9	His 449, Tyr 473, Cys 285	Phe 363, Met 364, His 449, Cys 285, Tyr 473, Leu 465, Phe 282, Leu 469, Leu 453

Hydrogen bonding analysis revealed that residues Ser289 and Cys285 were frequently involved in ligand interactions, underscoring their relevance in ligand-protein complex stability. Ser289 formed hydrogen bonds with five out of the seven ligands, while Cys285 was engaged in both hydrogen and non-hydrogen interactions with nearly all compounds tested. Regarding non-hydrogen interactions, Phe363 consistently interacted with all ligands, identifying it as a key residue in ligand recognition. Additionally, His449, Met364, and

Cys285 were present in the interaction profiles of six out of the seven ligands, reinforcing their significant roles in the binding process.

TABLE 2. Toxicity Prediction

Compound	1	2	3	4	5	6
Gemcitabine	4	Active (0.93)	Inactive (0.52)	Inactive (0.79)	Inactive (0.81)	Inactive (0.94)
Cintriamide	4	Inactive (0.57)	Active (0.56)	Active (0.93)	Inactive (0.57)	Inactive (0.62)
Artocarpesin	5	Inactive (0.70)	Inactive (0.69)	Active (0.76)	Inactive (0.63)	Inactive (0.81)
Myricetin	3	Inactive (0.69)	Active (0.68)	Inactive (0.86)	Active (0.51)	Inactive (0.99)
Quercetin	3	Inactive (0.69)	Active (0.68)	Inactive (0.87)	Active (0.51)	Inactive (0.99)
Licoflavone c	5	Inactive (0.70)	Inactive (0.69)	Inactive (0.93)	Inactive (0.63)	Inactive (0.81)

1: Toxicity Class, 2: Hepatotoxicity, 3: Carcinogenicity, 4: Immunotoxicity, 5: Mutagenic, 6: Cytotoxic

Based on Protox III analysis in table 2, gemcitabine and cintriamide fall under toxicity class 4, with gemcitabine showing potential hepatotoxicity and cintriamide displaying carcinogenic and immunotoxic risks. Myricetin and quercetin, both in class 3, are flagged for carcinogenicity and mutagenicity but are otherwise non-toxic. Artocarpesin and licoflavone c, classified as class 5, show low overall toxicity, though artocarpesin may have some immunotoxic potential.

DISCUSSION

Discussion The selection of Peroxisome Proliferator-Activated Receptor Gamma (PPARγ), with PDB ID: 3U9Q, as the molecular target in this study was based on its central role in the transcriptional regulation of genes involved in lipid and glucose metabolism, as well as cellular differentiation. PPARγ has been implicated in the pathophysiology of several diseases, including pancreatic cancer, type 2 diabetes, and various metabolic disorders (Malapaka et al., 2012). The crystal structure of 3U9Q, representing the ligand-binding domain of PPARγ at a high resolution of 1.52 Å, provides a robust platform for detailed analysis of ligand interactions (Figure 1). Notably, the presence of a co-crystallized ligand, decanoic acid, offers a useful natural reference point for evaluating the relative binding affinity of other compounds. The protein was expressed in Escherichia coli without any mutations, thereby preserving its native conformation and increasing the biological relevance of the docking results. Given its established involvement in tumor biology and chemoresistance, PPARγ is a strategic and relevant target for drug development.

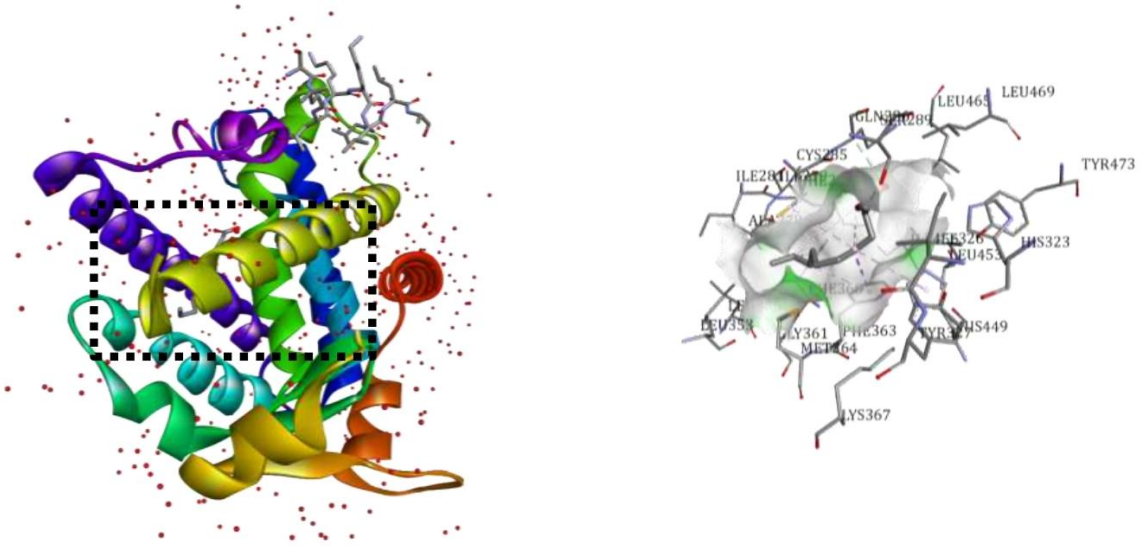

FIGURE 1. 3D Crystal of PPARγ Protein (PDBID 3U9Q)

Molecular docking serves as an essential preliminary approach in drug discovery, enabling the evaluation of ligand binding affinity and interaction profiles with the target protein. In this study, binding energy was used as a primary metric to assess ligand affinity. Among the compounds tested, quercetin exhibited the strongest interaction with PPARγ, with a binding energy of –7.6 kcal/mol. This value not only surpassed that of the native ligand decanoic acid –5.8 kcal/mol but also exceeded the binding affinity of gemcitabine –5.4 kcal/mol, the current standard therapy for pancreatic cancer. These findings highlight quercetin's potential as a promising candidate for further development as an alternative therapeutic agent.

Cintriamide also demonstrated substantial binding affinity –7.0 kcal/mol and engaged in a broad range of interactions with key residues such as Phe363, His449, Met364, and Cys285. These interactions suggest a highly stable and specific ligand-protein complex (Purnama et al., 2021). Myricetin and licoflavone C, both with binding energies of –5.9 kcal/mol, exhibited comparable or slightly superior affinities to the native ligand. Although their binding energies were lower than those of quercetin and cintriamide, both compounds formed extensive hydrogen and non-hydrogen interactions, indicating that ligand orientation and the number of involved residues also play significant roles in pharmacological evaluation.

Residue level interaction analysis revealed consistent binding patterns. Ser289 and Cys285 were the most frequently involved in hydrogen bonding, crucial for stabilizing ligand orientation within the active site. Ser289 participated in hydrogen bonds with five out of the seven ligands, underscoring its importance in initial ligand recognition. Cys285 was found to contribute to both hydrogen and hydrophobic interactions, reinforcing its role in complex stability. Phe363 emerged as the only residue involved in non-hydrogen interactions across all ligands, suggesting its strategic location within the binding pocket and its critical function in ligand recognition (Purnama et al., 2022). Additionally, His449 and Met364 were present in the interaction profiles of six ligands, further affirming their biological relevance in ligand binding (Figures 2 and 3).

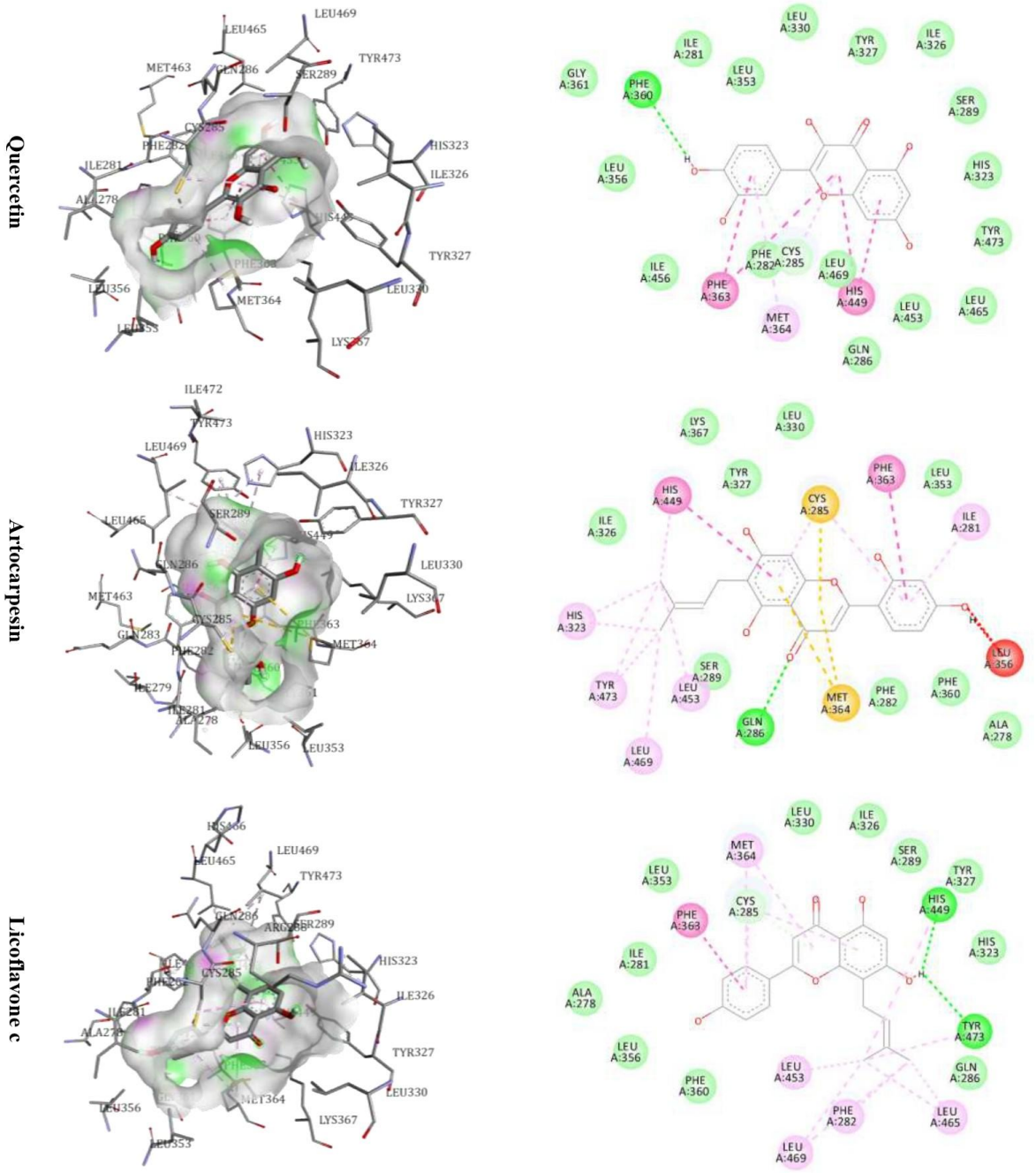

FIGURE 2. Visualization of The Best Pose Docking Results and Amino Acid Interactions

The strong docking affinities observed for several bioactive compounds derived from Artocarpus heterophyllus support previous findings indicating its anticancer potential. A recent study by Dewi et al., (2025) reported that ethanol extracts of A. heterophyllus leaves (AHEE) exhibited significant antiproliferative effects on cervical cancer and triple-negative breast cancer cells. These effects were attributed to the presence of flavonoids, alkaloids, and tannins, which inhibited cell viability, migration, and colony formation in both 2D and 3D cultures. Furthermore, AHEE was shown to enhance the efficacy of chemotherapeutic agents such as doxorubicin and cisplatin, suggesting that its constituents may target cellular proliferation and survival pathways relevant to drug-resistant cancers like pancreatic adenocarcinoma.

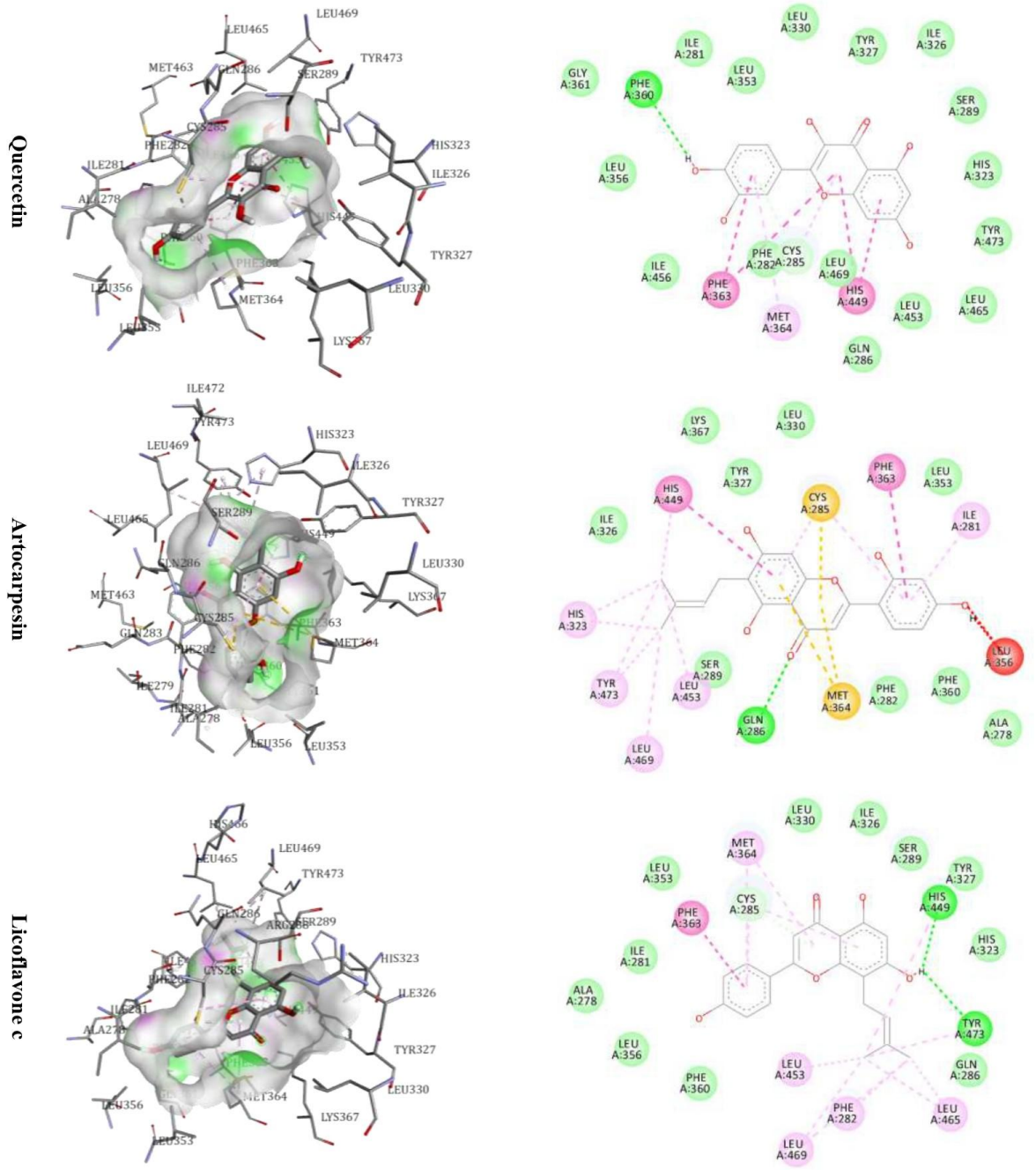

FIGURE 3. Visualization of The Best Pose Docking Results and Amino Acid Interactions

Additional evidence from Morrison et al., (2021) indicated that artocarpin, a flavonoid specific to the Artocarpus genus, can inhibit CYP2C9, an enzyme involved in drug resistance and carcinogen metabolism. This inhibition was associated with reduced expression of the proliferation marker PCNA and pro-inflammatory cytokines in animal models, which are often upregulated in the tumor microenvironment of pancreatic cancer. Moreover, research by Mardianingrum et al., (2023) demonstrated that prenylated flavonoids from A. heterophyllus exhibited strong binding affinity toward VEGFR2, a key angiogenic receptor, based on docking and molecular dynamics simulations. Considering the reliance of pancreatic tumors on angiogenesis and survival pathways such as VEGF and COX-2, these findings align with those of Mutiyani and Nuriliani (2024), who reported gene expression suppression by A. heterophyllus-derived compounds. Collectively, these studies support the

therapeutic potential of these phytochemicals and validate the relevance of the docking results obtained in the present investigation.

The liver, as the central organ for xenobiotic metabolism, is particularly vulnerable to drug-induced toxicity, making hepatotoxicity a critical parameter in early drug safety evaluation (Hosack et al., 2023). Among the tested compounds, Gemcitabine showed the highest predicted hepatotoxicity (0.93), aligning with its known clinical profile. Although its use in pancreatic cancer is well-established, Gemcitabine exhibits poor tumor selectivity and accumulates systemically (Beutel & Halbrook, 2023). Its hepatotoxicity, although rare, can be severe and rapid, leading to cholestasis or acute liver failure, as demonstrated in a fatal case reported by previous studies. In contrast, Myricetin and Quercetin were predicted as non-hepatotoxic (0.69), supported by extensive in vivo studies showing their hepatoprotective effects via antioxidant, anti-inflammatory, and Nrf2-mediated pathways (Turedi, 2023).

Similarly, Artocarpesin and Licoflavone C exhibited inactive hepatotoxic profiles (0.70), although direct hepatic studies are limited. Artocarpesin's anti-inflammatory and MAPK-modulating properties suggest a low risk to liver tissue (Kwon et al., 2022). Licoflavone C also demonstrated no systemic toxicity in vivo, particularly in Galleria mellonella larvae models, indicating a favorable safety margin at therapeutic doses (Ozanique et al., 2024). These findings reinforce the potential of natural flavonoids as low-risk alternatives in therapeutic development.

With respect to carcinogenicity, Myricetin and Quercetin displayed moderate predicted risk (0.68), though substantial evidence points to their chemopreventive roles. Myricetin induces apoptosis and autophagy through endoplasmic reticulum stress and regulates pro-survival pathways in hepatocellular carcinoma (Ji et al., 2022; Rahmani et al., 2023), while Quercetin counteracts the genotoxic effects of aflatoxin B1 by attenuating oxidative stress and inflammation (Dai et al., 2024). On the other hand, Gemcitabine, Artocarpesin, and Licoflavone C were predicted to be non-carcinogenic ($\leq$0.69), which aligns with the mechanistic profile of Gemcitabine as a nucleoside analog that disrupts DNA synthesis without being intrinsically carcinogenic (Beutel & Halbrook, 2023). Although data are still limited, the anti-inflammatory and antiviral actions of Artocarpesin and Licoflavone C support their safety and therapeutic potential (Gao et al., 2025; Kwon et al., 2022).

Regarding immunotoxicity, Cintriamide stood out as the only compound with high predicted risk (0.93), underscoring the need for further immunological evaluation before advancing its therapeutic application. In contrast, Myricetin, Quercetin, Artocarpesin, and Licoflavone C were predicted to be non-immunotoxic. Notably, Myricetin was shown to reduce immune stress by suppressing NF-κB and MAPK signaling (Rahmani et al., 2023), while Quercetin has demonstrated immune-balancing effects and protective action against immunotoxic agents such as cyclophosphamide and aflatoxin B1 (Dai et al., 2024). Though direct immunotoxic studies on Artocarpesin are sparse, its role in inhibiting platelet aggregation suggests regulatory rather than suppressive immune activity (Kwon et al., 2022). Licoflavone C also showed no immunotoxic effects in vivo and may even support antiviral immune responses (Gao et al., 2025).

In terms of mutagenicity, Myricetin and Quercetin were near the predictive threshold (0.51 and 0.54), but extensive biological data demonstrate their DNA-protective roles. Both

flavonoids counteract mutagenic agents and promote genomic stability through antioxidative and anti-inflammatory mechanisms (Ji et al., 2022; Rahmani et al., 2023). Quercetin's safety has also been confirmed through sub-chronic exposure studies in mice (Cunningham et al., 2022). Conversely, Gemcitabine, Artocarpesin, and Licoflavone C had lower predicted mutagenicity (≤0.63). Although Gemcitabine interferes with DNA replication as part of its therapeutic effect, caution is advised due to its potential genotoxicity at high or repeated exposures (Beutel & Halbrook, 2023). While no direct genotoxicity studies have been conducted on Artocarpesin or Licoflavone C, their flavonoid structures, rich in antioxidant elements, suggest a protective role in maintaining DNA integrity (Kwon et al., 2022; Ozanique et al., 2024)

Cytotoxicity predictions classified all tested compounds as low risk, with Myricetin and Quercetin showing the highest safety (0.99). Both compounds selectively induce apoptosis in cancer cells without affecting healthy tissues, primarily through ER stress activation and inhibition of proliferative signals (Xiong et al., 2024). Artocarpesin, although less studied, has not shown any cytotoxic effects in published data and likely supports cellular balance through its anti-inflammatory mechanisms (Kwon et al., 2022). Licoflavone C also demonstrated no cytotoxicity in vivo and may act selectively against virus-infected cells, highlighting its therapeutic potential (Ozanique et al., 2024). In contrast, Gemcitabine, while predicted to be non-cytotoxic (0.94), is clinically recognized for its broad myelosuppressive and antiproliferative effects on both malignant and healthy dividing cells, thus requiring targeted delivery strategies to minimize systemic damage (Beutel & Halbrook, 2023).

Integrating the molecular docking and toxicity findings reveals a compelling profile for quercetin, which not only exhibited the strongest binding affinity to the target protein –7.6 kcal/mol but also demonstrated a favorable safety profile in toxicity assessments, showing non-hepatotoxic, non-mutagenic, and non-cytotoxic predictions alongside experimentally supported hepatoprotective and immunomodulatory effects. Similarly, myricetin, with moderate binding energy –5.9 kcal/mol, aligns well with its low toxicity profile and selective anticancer activity. In contrast, although cintriamide showed strong binding affinity –7.0 kcal/mol, its predicted immunotoxicity and carcinogenicity raise significant safety concerns, highlighting the importance of balancing binding potency with toxicity risk. Artocarpesin, despite its low toxicity profile, demonstrated the weakest binding –2.0 kcal/mol, suggesting limited therapeutic potential unless modified or used in combination. These findings underscore quercetin and myricetin as promising lead compounds with both effective target engagement and minimal toxicity, whereas compounds like cintriamide warrant further toxicological validation despite favorable docking results

This study is limited by its reliance solely on in silico molecular docking methods, which, while valuable for predicting ligand protein interactions, do not account for the full complexity of biological systems, such as bioavailability, metabolism, and cellular uptake. The absence of in vitro or in vivo validation restricts the ability to confirm the actual pharmacological activity and safety profiles of the compounds studied. Additionally, the dynamic behavior of protein-ligand complexes over time was not explored through molecular dynamics simulations, which could provide deeper insights into interaction stability. Future research should involve experimental validation using cell-based assays and animal models to evaluate the anticancer efficacy of promising compounds such as quercetin and cintriamide. Incorporating pharmacokinetic and toxicity profiling, as well as exploring

structure activity relationships, will also be critical in advancing these natural compounds toward potential therapeutic applications.

CONCLUSION

Compounds derived from Artocarpus heterophyllus exhibit promising characteristics as anti-pancreatic cancer agents. Quercetin and myricetin, in particular, demonstrated strong binding affinity to PPARγ and favorable toxicity profiles, including hepatoprotective and non-cytotoxic effects. Although cintriamide showed high affinity, its potential immunotoxicity warrants further evaluation. Overall, A. heterophyllus phytochemicals represent viable candidates for further development in pancreatic cancer therapeutics.

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