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Integrative Network Pharmacology and Molecular Docking Reveal the Mechanism of Myricetin in Targeting Key Proteins for Lung Cancer Therapy

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Abstract: Lung cancer is one of the most prevalent types of cancer. Although current treatments such as immunotherapy, targeted therapy, and chemotherapy provide clinical benefits, they are often associated with serious side effects, including drug resistance. Myricetin has demonstrated promising anticancer properties; however, its underlying biological mechanisms and gene interaction networks related to patient survival remain insufficiently explored. This study employs a network pharmacology approach to investigate the interaction network between myricetin and lung cancer–related targets, followed by molecular docking for validation. The analysis revealed 101 nodes and 207 edges within the protein-protein interaction (PPI) network. Centrality analysis identified six key target proteins, and subsequent KEGG pathway enrichment narrowed these to five key proteins, HSP90AA1, CYP19A1, MAPK14, SRC, and AKR1C3, which are involved in seven critical pathways associated with lung cancer progression. Molecular docking demonstrated that myricetin exhibits stronger binding affinities compared to Gefitinib across all targets, with the most favorable binding energy observed with AKR1C3 (-10.6 kcal/mol) and Gefitinib to AKR1C3 (-9.3 kcal/mol). These findings suggest that myricetin exerts multifaceted anticancer effects by modulating key biological processes, including cell proliferation, angiogenesis, inflammation, oxidative stress, and hormonal signaling. Thus, myricetin has the potential to be developed as a therapeutic agent for lung cancer. Therefore, further in vitro analyses are required to evaluate myricetin's anticancer activity in lung cancer cells, along with gene expression studies and safety assessments in normal cells.

Keywords: myricetin; lung cancer; anticancer; biological processes; mechanism.

1. Introduction

Lung cancer cases are still one of the most prevalent cancers. This is supported by data from Li *et al*. [1], which indicates that among the 2.20 million people diagnosed with lung cancer each year. Similarly, Indonesia has shown a comparable trend, with lung cancer ranking as the third most common cancer in 2020, accounting for 34,783 new cases and 30,843 deaths [2]. Many therapeutic methods, such as immunotherapy, targeted therapy, and chemotherapy, can increase patient life expectancy [3,4]. However, the resulting side effects are still a serious problem, as experienced by NSCLC (non-small cell lung cancer) patients with the highest number of lung cases in the world who experience drug resistance during targeted therapy and immunotherapy treatments [3,5]. Therefore, there is a need for alternative chemopreventive (anticancer) agents to minimize drug side effects in patients by leveraging the potential of natural ingredients in Indonesia.

One natural compound with potential as an alternative chemopreventive agent against lung cancer is myricetin, a flavonoid found in tea, fruit, and other herbal ingredients [3]. Myricetin is known to have antioxidant, anti-inflammatory, and anticancer activities [3,6,7]. This is supported by several studies that have been conducted, such as research by Tao *et al*. [7], which states that myricetin compounds with a concentration of 20 μm are proven safe and do not have toxic effects on HepG2 cells. Furthermore, myricetin compounds at concentrations of 15.6 μm/ml (ABTS assay) and 500 μm/ml (FRAP assay) are reported to exhibit strong antioxidant activity by inhibiting intracellular ROS production [6]. In the cytokine test, myricetin compounds with concentrations of 10-20 μm are reported to be able to regulate TNF-α, IFN-γ, IL-1α, IL-1β, IL-2, and IL-6 levels so that there will be an inhibitory mechanism against the 6 inflammatory mediator compounds [7]. In addition, based on in vitro studies, one of the myricetin-derived compounds, S4-2-2, can induce apoptosis by inhibiting the biological activity of A549 cells through regulation of RE expression and steroid biosynthesis 3].

Many studies have been conducted on myricetin compounds, which are stated to have potential as chemopreventive agents, but based on some of these studies, there are still limited explanations regarding interactions between tissues on their biological mechanisms, and there are also limited explanations regarding the regulation of interactions of several genes on the potential survival of patients [8,9]. In the development of new drugs, in silico testing using network pharmacology methods can be a renewable solution. This is in line with the statements from [10,11] that network pharmacology integrates data-based understanding to analyze networks formed by interactions between drugs and potential targets, and that it can also evaluate the effectiveness of a drug on the mechanisms of its biological system [12]. The network pharmacology method consists of several stages to obtain a final result in the form of a potential target protein, after which a further analysis is carried out regarding its expression and its relationship with patient survival rates usinglinical databases [13]. Then, molecular docking analysis is used to validate and model the interaction between the active sitof a compound and the predicted target [4,10].

Previous research by Tianyou *et al*. [14]on the Network Pharmacology study of myricetin as a cardioprotective agent shows that myricetin exerts cardiovascular protective effects by downregulating PTGS2 and MAOB and upregulating MAP2K1 and EGFR. Another study by Ningning *et al*. [15]on the Network Pharmacology of myricetin as an antidiabetic confirmed its efficacy in binding to NOX4 through network pharmacology, molecular docking, in vitro, and in vivo experiments. Previous studies on myricetin using a network pharmacology

approach have mainly focused on its cardiovascular protective and antidiabetic activities. This study systematically explores the molecular mechanisms of myricetin as a therapeutic agent for lung cancer using integrated network pharmacology and molecular docking analyses. The findings of this study are expected to serve as a preliminary step toward the discovery and development of novel therapeutic agents, particularly for the treatment of lung cancer.

2. Materials and Methods

2.1. Acquisition targets myricetin and lung cancer-related genes.

Pharmacological targets of myricetin were predicted using three web-based platforms: SwissTargetPrediction (http://www.swisstargetprediction.ch/), PharmaMapper (https://www.lilab-ecust.cn/pharmmapper/), and TargetNet (http://targetnet.scbdd.com/) with the organism set to Homo sapiens and a probability threshold of ≥0.6 [16–18]. Lung cancer-related genes were obtained from NCBI (https://www.ncbi.nlm.nih.gov/) with the keyword "lung cancer". An online Venn diagram (https://bioinfogp.cnb.csic.es/tools/venny/) was used to identify overlapping targets between Myricetin and lung cancer [19].

2.2. Protein interaction network and key target potential identification.

Overlapping targets were entered into the STRING database (https://string-db.org/, version 12.1) to construct a protein-protein interactions (PPI) network with a confidence score ≥0.7. Only protein–protein interactions with a confidence score >0.7 were selected [20]. The network was then exported and visualized using Cytoscape version 3.10.3 (https://cytoscape.org/) [21]. CytoNCA was used to calculate the network topology parameters, including Degree Centrality (DC), Closeness Centrality (CC), and Betweenness Centrality (BC). Key target proteins were identified based on the average value of each parameter through two stages of screening. The first stage utilized only DC, while the second stage incorporated DC, CC, and BC, applying thresholds based on the average value of each parameter [22].

2.3. Expression analysis and pathway enrichment.

Expression of key target proteins in lung cancer tissues was compared with that in normal tissues using the UALCAN database (http://ualcan.path.uab.edu/) [23]. Genetic functions such as gene ontology (GO), biological processes (BP), cellular components (CC), and molecular functions (MF), as well as KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway analysis, were performed via the DAVID database (https://david.ncifcrf.gov/) with p values <0.05 considered significant [24].

2.4. Molecular docking.

Molecular docking was performed using AutoDock Vina [25]. The 3D structure of the target protein (e.g., SCR: PDB ID 1O42, MAPK14: 6HWT, AKR1C3: 1RY8, CYP19A1, HSP90AA1: 3O0I) was downloaded from the Protein Data Bank (RCSB) (https://www.rcsb.org/). The 3D structure of myricetin was obtained from PubChem (https://pubchem.ncbi.nlm.nih.gov/) [26]. Protein structures were prepared using AutoDock Tools by removing water molecules, adding polar hydrogens, incorporating non-polar hydrogens, and adding Gasteiger charges [27]. Ligands were also modified and converted to .pdbqt format. Docking was performed with an exhaustiveness parameter = 8. Grid box size

and coordinates were determined based on known ligand binding sites. Validation was performed by re-docking the native crystal ligand on each protein, and the RMSD value had to be < 2 Å [28]. Interaction results were analyzed using BIOVIA Discovery Studio Visualizer 2021.

3. Results and Discussion

3.1. Identification of myricetin target slices and lung cancer.

The anticancer activity of myricetin attracts attention because of its ability to inhibit cancer cell growth, trigger apoptosis (programmed cell death), inhibit angiogenesis (the formation of new blood vessels that support tumor growth), and also have an inhibitory effect on metastasis.

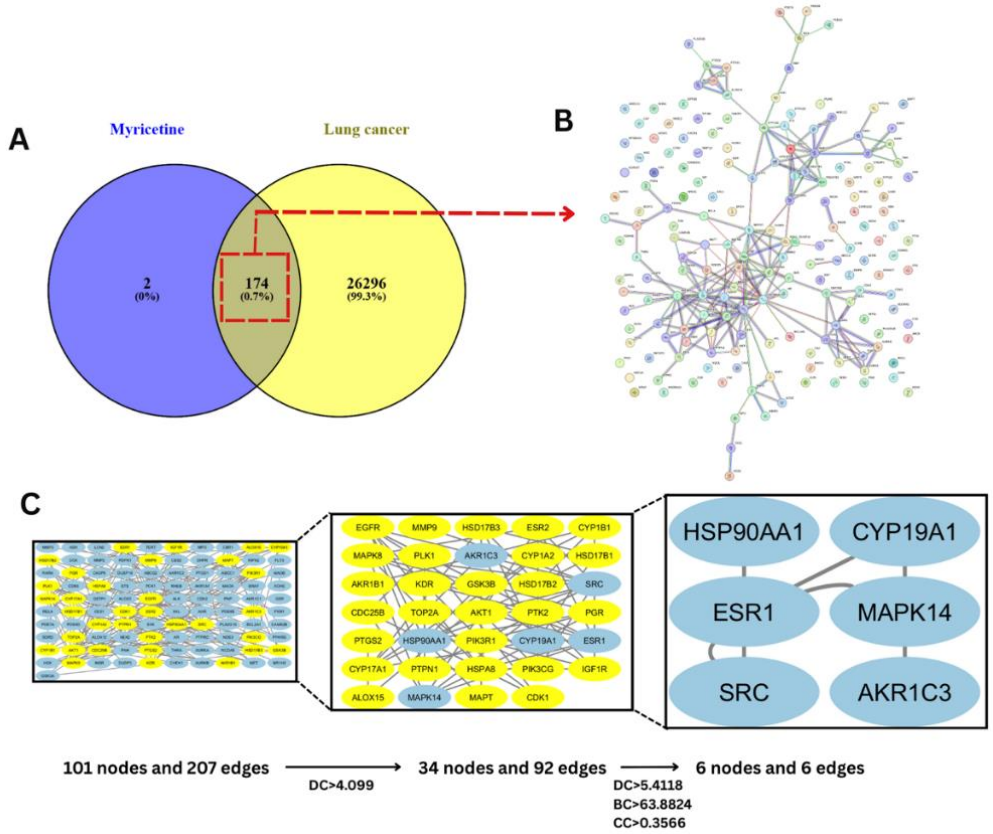


Figure 1. (A) Venn diagram of myricetin and lung cancer target; **(B)** Protein-protein interactions network using STRING; **(C)** Analysis CytoNCA.

This process allows cancer cells to spread to other parts of the body. In a study conducted by Devi *et al*. [29], myricetin has been reported to interact with several key proteins involved in cellular signaling pathways, including protein kinase B (Akt), Fyn, MEK1, and the JAK1–STAT3 (Janus kinase–signal transducer and activator of transcription 3) pathway. Through these interactions, myricetin contributes to the inhibition of neoplastic transformation in cancer cells. Furthermore, myricetin (DT2.1) has been shown to target mitochondria and to induce multiple forms of programmed cell death across various cancer cell types. A study conducted by Shijie *et al*. [30] stated that in lung cancer cell lines A549 and H1299, when combined with radiotherapy, myricetin increased apoptosis by increasing caspase-3 expression, and reduced cell survival and proliferation relative to radiotherapy alone. By combining genes from various databases (TargetNet, PharmMapper, SwissTargetPrediction,

NCBI, and GeneCard) and removing duplicate genes, 26,471 proteins associated with lung cancer were found. Figure 1A illustrates the overlap between proteins associated with lung cancer and the predicted targets of myricetin, revealing 58 proteins that are involved in lung cancer pathogenesis.

3.2. Target identification of myricetine and its intersection with lung cancer.

The Protein-Protein Interactions (PPI) of 174 major targets of myricetin and lung cancer were analyzed using STRING (Figure 1B). The topological characteristics of this PPI network include 101 nodes and 207 edges. In the first step, DC was used to filter out target nodes with degrees greater than the average of all degrees (>4.099), and 34 nodes and 92 edges were obtained. In the second step, three parameters (DC, BC, CC) were selected to identify the main targets that play an important role in lung cancer by filtering nodes along the best-connected paths to the entire network. Based on the average values of DC, BC, and CC, they are 5.4118, 63.8824, and 0.3566, respectively. From STRING and Cytoscape analyses using Cyto-NCA parameters, 6 main proteins are implicated in lung cancer: HSP90AA1, CYP19A1, ESR1, MAPK14, AKR1C3, and SRC (Figure 1C).

HSP90 plays an important role in regulating oncogenes, apoptosis, and chemotherapy resistance [31]. In lung cancer cells, HSP90 plays a role in stabilizing protein kinases such as EFG, BRAF, HER2, and ALK receptors [32]. CYP19A1 plays an important role in cancer initiation and progression. Research by Chan *et al*. [33] evaluated the association between CYP19A1 gene polymorphisms and lung cancer risk in the Chinese Han population, the results showed that three SNPs (rs28757157, rs3751592, and rs59429575) of CYP19A1 were associated with an increased risk of lung cancer, especially in individuals under 60 years of age, women, smokers, and alcohol drinkers [33]. AKR1C3 promotes cell growth and metastasis, thereby driving drug resistance by inducingMT and angiogenesis in small-cell lung cancer [34]. Overexpression of AKR1C3 functions as an oncogenic factor, which promotes proliferation, invasion, and metastasis of carcinoma cells, and correlates with an unfavorable prognosis in patients. Therefore, inhibiting AKR1C3 has shown strong efficacy in suppressing tumor progression and overcoming treatment resistance, especially in lung cancer [35]. A related study of p38MAPK (MAPK14) in mouse cancer models showed that p38MAPK suppresses lung and liver tumor formation *in vivo* [36,37]. However, enhanced p38MAPK activation and overexpression in various cancers, including lung tumors, have been reported in some cases, correlating with the occurrence of poor prognosis [38]. The activity of SRC and its downstream effectors, such as STAT3 and FAK, is often found to be elevated in NSCLC tissues. Moreover, inhibition of SRC in EGFR-dependent NSCLC cell lines can lead to the cessation of growth signaling and induction of apoptosis [39]. Based on the research of [40], it is explained that high ESR1 mRNA expression is associated with improved survival in metastatic NSCLC patients. In two separate cohorts, patients with high ESR1 expression had a longer median overall survival (OS) compared to patients with low ESR1 expression. The results of the study are in line with the results of the expression analysis in Figure 2A showing that ESR1 has low expression in lung cancer in this study, so if ESR1 is targeted as a lung cancer therapy, namely through the mechanism of inducing or increasing ESR1 expression, it will have a great opportunity as a target therapy for lung cancer [40].

3.3. GO and KEGG analysis.

GO analysis was conducted based on the analysis of three ontologies, namely biological process (BP), molecular function (MF), and cellular component (CC) of five main targets. The results were filtered based on statistical significance (p-value < 0.05), yielding 20 Biological Process (BP), 10 Cellular Component (CC), and 10 Molecular Function (MF) entries. From both the Gene Ontology (GO) and KEGG pathway analyses, only the top ten results were selected and presented as the final data in Table 1. Furthermore, the KEGG pathway analysis initially identified 10 pathways. However, upon further investigation of their relevance to lung cancer, only 7 pathways were found to be associated. These include Endocrine resistance, Estrogen signaling pathway, Proteoglycans in cancer, Chemical carcinogenesis – receptor activation, Chemical carcinogenesis – reactive oxygen species, Ovarian steroidogenesis, and the VEGF signaling pathway. Endocrine resistance pathway, based on Feifei *et al*. [41], used the TyG-BMI index to assess insulin resistance and found it to be a risk factor for NSCLC in the Chinese population [41]. Then another study involving 29,133 Finnish men showed that elevated levels of insulin resistance were associated with an increased risk of lung cancer [42]. So the Endocrin resistance pathway can be one of the pathways in the development of cancer therapy from myricetin compounds [43]. The estrogen receptor alpha (ERα) pathway plays a role in lung carcinogenesis, mainly through activation by carcinogens such as NNK (N-nitrosamine). This activation involves the CYP1B1 enzyme and the ERK/MAPK pathway, which promoteung cancer cell proliferation [44].

Serglycin (SRGN), an intracellular proteoglycan, has been increasingly recognized for its involvement in cancer progression. In non-small cell lung cancer (NSCLC), SRGN has been shown to promote a malignant phenotype through a CD44-dependent mechanism. Clinically, elevated SRGN expression is associated with poor prognosis in patients with primary lung adenocarcinoma, indicating its potential value as a prognostic biomarker. The mechanism by which SRGN proteoglycan promotes NSCLC cell migration is through binding of its GAG motif to CD44, which induces Rho-family GTPase-mediated cytoskeletal reorganization and facilitatesRC-mediated focal adhesion turnover, leading to increased cell migration [45]. This is in line with this study: the target protein in the Proteoglycans pathway is SRC, which is associated with increased cell migration. In addition, myricetin compounds also have a relationship with the ovarian steroidogenesis pathway involving AKR1C3 and CYP19A1. The results of this study are in line with research by Marija and Tea [46] on the ovarian steroidogenesis pathway, involving key enzymes such as CYP11A1, CYP17A1, CYP19A1 (aromatase), HSD3B2, and HSD17B1, which convert cholesterol into active steroid hormones. Some of these enzymes are also expressed in lung tissue, allowing the local synthesis of steroid hormones that can influence the microenvironment of lung tumors [46]. Furthermore, the VEGF signaling pathway is not only an important angiogenic factor but also an environmental immunomodulator.

Table 1. Top 10 KEGG pathway classification targets.

KEGG Pathways	%	Count	p-value	Genes
Prolactin signaling pathway	50	3	6,72E-04	SRC, MAPK14, ESR1
Endocrine resistance	50	3	0,001302	SRC, MAPK14, ESR1
Estrogen signaling pathway	50	3	0,002551	HSP90AA1, SRC, ESR1
Fluid shear stress and atherosclerosis	50	3	0,002624	HSP90AA1, SRC, MAPK14
Proteoglycans in cancer	50	3	0,005422	SRC, MAPK14, ESR1
Chemical carcinogenesis - receptor activation	50	3	0,006009	HSP90AA1, SRC, ESR1
Lipid and atherosclerosis	50	3	0,006063	HSP90AA1, SRC, MAPK14
Chemical carcinogenesis - reactive oxygen species	50	3	0,006681	SRC, AKR1C3, MAPK14

KEGG Pathways	%	Count	p-value	Genes
Ovarian steroidogenesis	33,3	2	0,030104	AKR1C3, CYP19A1
VEGF signaling pathway	33,3	2	0,034671	SRC, MAPK14

Further analysis of the lung cancer target proteins associated with myricetin revealed their involvement in key biological pathways. The VEGF receptor signaling pathway, mediated by SRC and MAPK14, underscores myricetin's potential to inhibit angiogenesis, a hallmark of tumor progression [47]. The negative regulation of Hippo signaling and inflammatory responses suggests myricetin may suppress abnormal cell proliferation and immune responses. Additionally, the activation of ROS metabolic processes, involving AKR1C3 and MAPK14, supports the idea that myricetin not only acts as an antioxidant but may also induce controlled oxidative stress to promote cancer cell death [35]. The involvement of ESR1 and HSP90AA1 in the estrogen response pathway suggests potential hormonal modulation, particularly in hormone-responsive lung cancer subtypes such as lung adenocarcinoma. These results suggest that myricetin acts through a multitarget mechanism that modulates proliferation, angiogenesis, inflammation, oxidative stress, and hormonal signaling [47].

Table 2. Top 5 gen ontology.

Pathways	%	Count	p-value	Genes
Biological Process				
Vascular endothelial growth factor receptor signaling pathway	33,3	2	0.007933218205	SRC, MAPK14
Negative regulation of hippo signaling	33,3	2	0.0061462629	SRC, MAPK14
Negative regulation of the inflammatory response to antigenic stimulus	33,3	2	0.006912415918	SRC, MAPK14
Positive regulation of the reactive oxygen species metabolic process	33,3	2	0.008953180888	AKR1C3, MAPK14
Response to estrogen	33,3	2	0.01454799084	ESR1,HSP90AA1,
Molecular Function				
Enzyme binding	50	3	0.003639290928	SRC, MAPK14, ESR1
Protein phosphatase binding	33,3	2	0.02264795078	HSP90AA1, MAPK14
Nuclear estrogen receptor binding	33,3	2	0.01060353527	SRC, ESR1
Nitric-oxide synthase regulator activity	33,3	2	0.001297959439	HSP90AA1,ESR1
ATPase binding	33,3	2	0.02213782393	SRC, ESR1
Cellular Component				
Dendritic growth cone	33,3	2	0.002162317205	HSP90AA1, SRC
Cytosol	83,3	5	0.02220943532	HSP90AA1, SRC, AKR1C3, MAPK14, ESR1
Cytoplasm	83,3	5	0.02670474957	HSP90AA1, SRC, AKR1C3, MAPK14, ESR1
Secretory granule lumen	33,3	2	0.02805470173	HSP90AA1, MAPK14

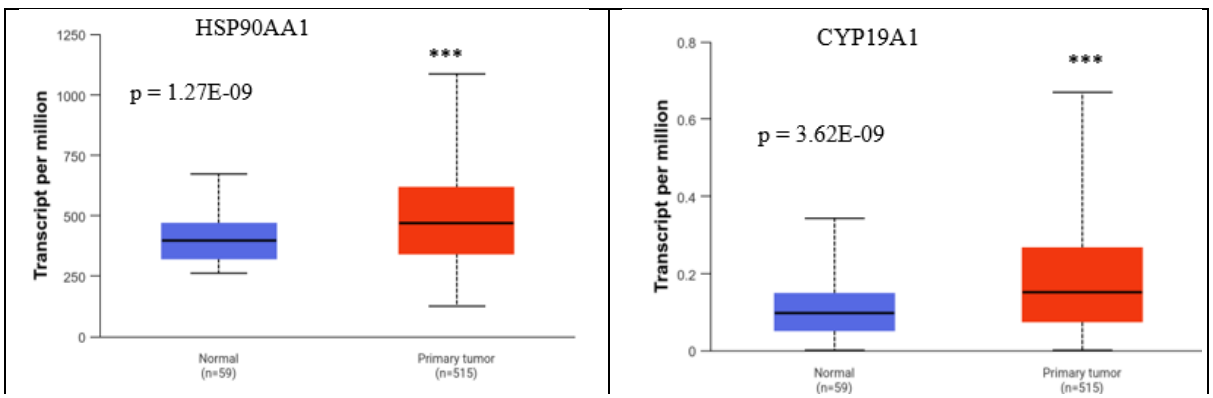
Based on Table 2, the results of the gene ontology analysis of molecular function show that myricetin target compounds exhibit dominant activity in enzyme binding, including the SRC, MAPK14, and ESR1 genes. This interaction reinforces the role of myricetin in inhibiting key enzymes involved in cancer cell proliferation signaling [48]. Protein kinase activity suggests the potential importance of modulating signaling pathways such as MAPKs, which are involved in lung cancer progression [49]. The nuclear estrogen receptor binding pathway involving ESR1 and SRC suggests that myricetin also interacts with nuclear hormone receptors that play an important role in estrogen-dependent lung cancer subtypes, especially in women [50]. The pathway with the highest significance value was nitric oxide synthase regulatory activity, involving HSP90AA1 and ESR1, indicating a role for myricetin in regulating NO levels, whichre closely associated with oxidative stress, angiogenesis, and resistance to

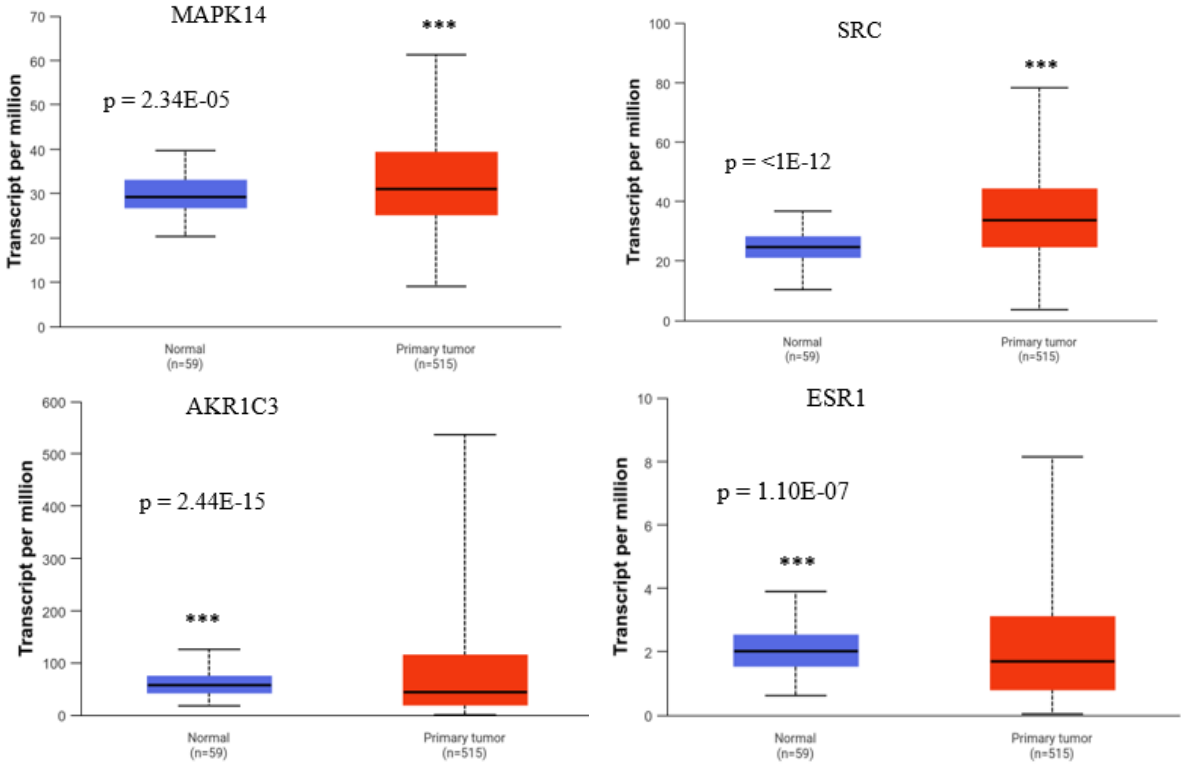
apoptosis [47]. The ATPase binding ability suggests possible inhibition of cellular energy pump activity, which plays a role in drug resistance and substrate transport, which is an important target in multiresistant cancer therapy [51]. This combination of molecular functions suggests that myricetin has a broad spectrum of activity against strategic lung cancer targets.

Cellular components (Table 2) revealed that myricetin target genes were most distributed in the cytoplasm and cytosol, 83.3% involving HSP90AA1, SRC, AKR1C3, MAPK14, and ESR1 genes. This confirms that the mechanism of action of active compounds tends to occur in areas of signal transduction and metabolic regulation that are crucial for cancer cell survival. The dendritic growth cone indicates that some molecular targets, such as HSP90AA1 and SRC, play a role in cytoskeleton reorganization and cancer cell migration, important aspects in the metastatic process [52]. Lastly, the secretory granule lumen, which contains HSP90AA1 and MAPK14, suggests that myricetin can also affect cellular secretion systems, including exosomes and secretoryranules that play a role in communication between cancer cells and their environment [49]. The interaction of myricetin with these proteins occurs mainly in the intracellular environment, which is rich in biological activity, making it a potential agent for targeting lung cancer through regulation of cell structure and signaling.

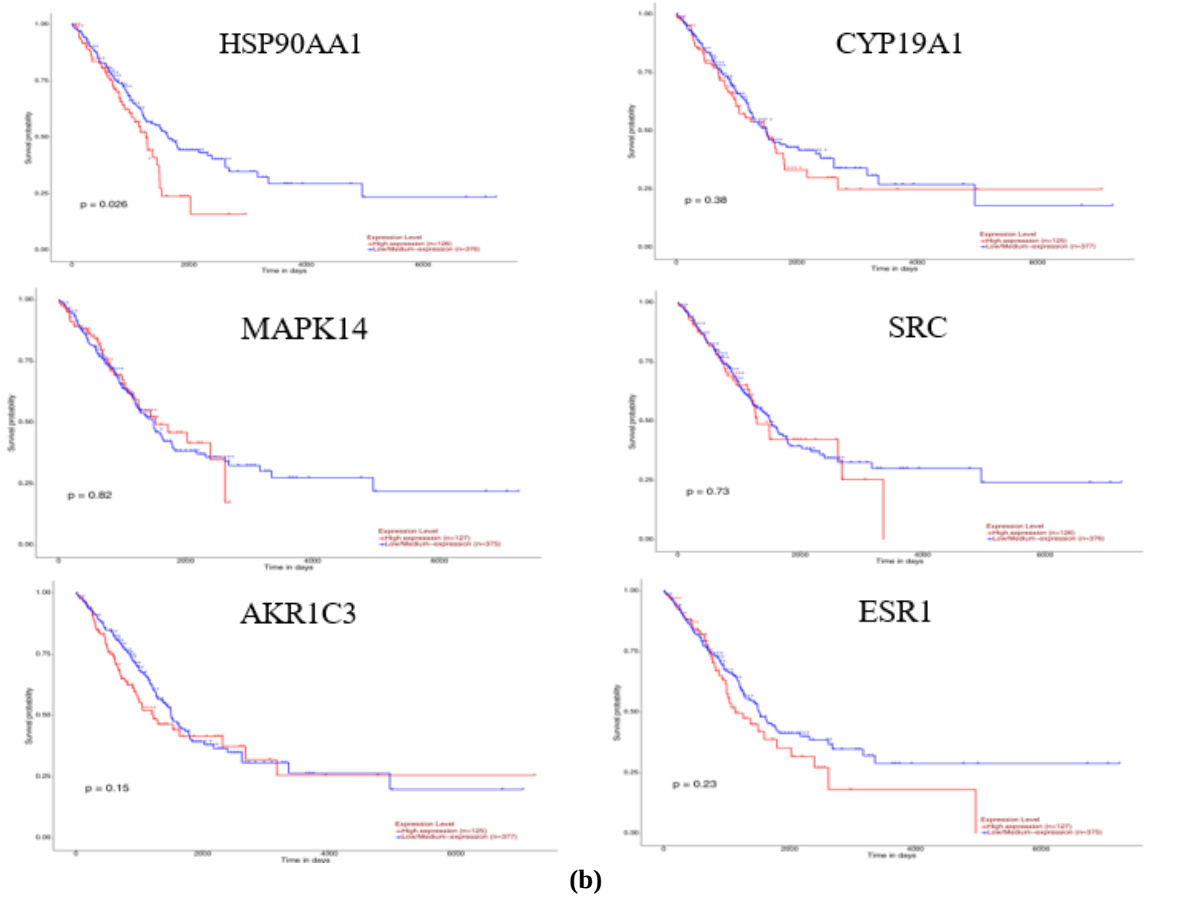
3.4. Prognostic value of potential target genes of myricetin.

To further understand the prognostic potential, mRNA expression levels, and survival rates of six potential targets, network pharmacology analysis results were used to analyze them in the UALCAN database. The purpose of expression level analysis is to identify biomarkers that are highly expressed during disease progression. As illustrated in Figure 3A, analysis of patients with lung adenocarcinoma (LUAD) from the TCGA dataset revealed that tumor tissues exhibited significantly elevated expression levels of HSP90AA1, CYP19A1, MAPK14, SRC1, and AKR1C3, whereas ESR1 expression was decreased. Genes with high expression levels are generally involved in oncogenic signaling pathways, indicating that their inhibition may offer considerable therapeutic potential. Consequently, genes that were highly expressed in LUAD were further analyzed to determine their association with patient survival. As shown in Figure 3B, a Kaplan–Meier survival analysis with a follow-up period exceeding 6,000 days was performed to evaluate survival outcomes in LUAD patients. Results showed that there was a significant association between worse survival and higher expression levels of HSP90AA1 ($p<0.05$). In addition, the results showed a non-significant positive association between worse survival and higher expression of CYP19A1, MAPK14, SRC, and AKR1C3.





(a)



(b)

Figure 2. (a) Gene expression levels in normal and LUAD samples; **(b)** Relationship of gene expression level with survival of LUAD patients. High-expression genes are shown in red, and low/medium-expression genes are shown in blue. ***p<0.001.

3.5. Validation and molecular docking.

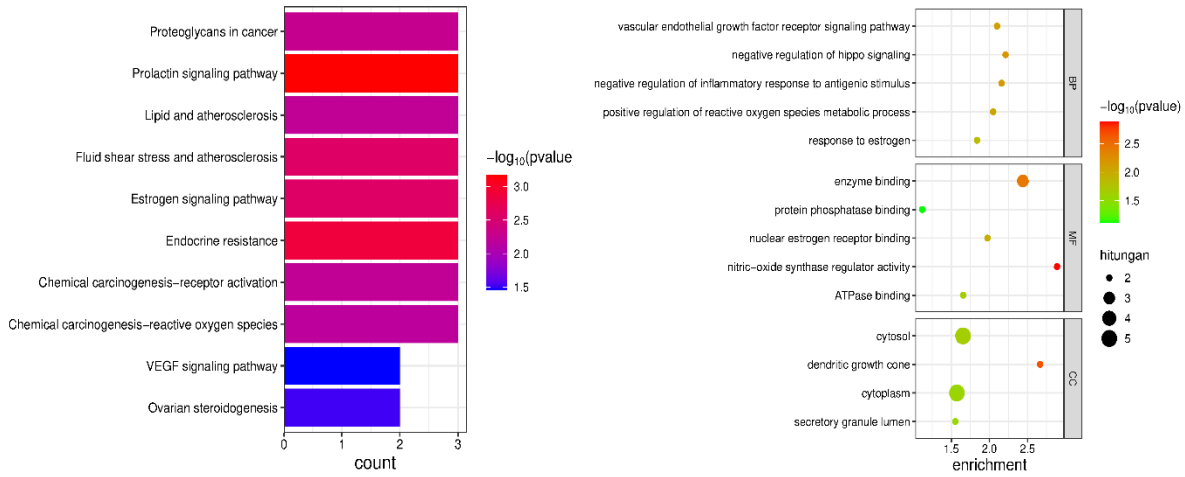
To confirm the ability of myricetin compounds to target SRC, MAPK14, AKR1C3, CYP19A1, and HSP90AA1 proteins, molecular docking simulations were performed by comparing the binding affinity of myricetin to each native ligand. Before docking, the active site of each protein is identified to ensure the ligand is placed exactly in the relevant binding pocket. As shown in Figure 3D, the RMSD values of the native ligands for all five targets were below 2 Å, indicating that the docking method employed was valid. In a previous study, Weng and Calvin [53] identified important residues on SRC proteins involved in hydrophobic bonding, including Leu273, Leu393, Gly344, and Tyr340. Then, hydrogen bonds include Met341, Lys295, Thr338, and Asp404. In silico tests on MAPK14 revealed that mebendazole forms hydrogen bonds with Met109 and hydrophobic bonds with Thr106 and Lys53. Meanwhile, the research of Marek *et al*. [54] found that the compound ASP9521 as an AKR1C3 inhibitor forms hydrogen bonds with Ser139, Tyr193, and Phe94, as well as hydrophobic bonds to Trp229 (π interaction), Ile140, and Met141 [55] targeted CYP19A1 with ziprasidone and found hydrogen bonds with Arg375, A435, and Arg115, as well as hydrophobic bonds with residues such as Phe432, Met374, Leu477, and others.

Table 3. Molecular docking between myricetin and target proteins.

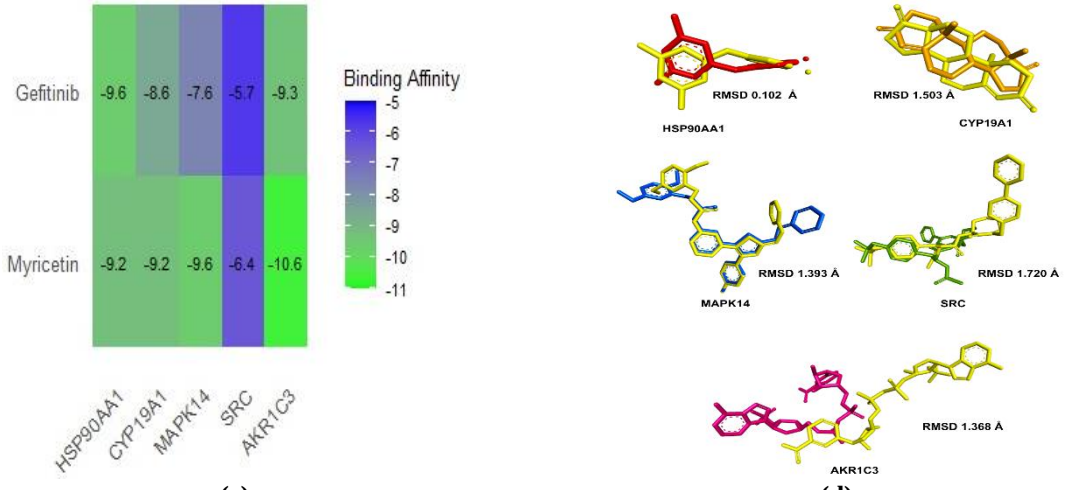
Proteins (PDB ID)	**Ligands**	**Binding affinity (kcal/mol)**	**Interactions**			
			Hydrogen bonds	**Distance (Å)**	**Hydrophobic bonds**	**Distance (Å)**
HSP90AA1 (PDB ID 3O0I)	Myricetin	-9.2	Lys58	2.34	Leu107	3.83
					Phe138	4.42
	Gefitinib	-9.6	Tyr139	2.42	Leu107	3.65
			Gly35	3.79	Phe138 Trp162	3.77 5.57
	8-[(2,4-dimethylphenyl)sulfanyl]-3-pent-4-yn-1-yl-3H-purin-6-amine*	-8.5	Asp93	2.65	Leu107	3.78
					Phe138	3.99
					Leu103	5.44
					Val150	3.99
					Tyr139	4.90
					Tyr162	3.67
CYP19A1 (PDB ID 3S79)	Myricetin	-9.2	Arg115	2.44	Ile133	3.78
			Ala438	2.07		
	Gefitinib	-8.6	Arg115	2.45	Ile133	3.95
			Ala438	2.21	Cys437	3.59
			Gly436	3.48	Ala306	4.14
			Glu302	3.72	Phe148	4.55
					Val370	4.97
					Val373	5.31
	4-Androstene-3-17-dione*	-10.7	Met374	1.90	Val370	5.23
			Arg115	2.59	Trp224	4.96
			Ala306	3.30		
MAPK14 (PDB ID 6HWT)	Myricetin	-9.6	Ala34	2.00	Val38	3.43
			Tyr35	1.94	Phe169	4.87
			Gly36	2.15		
			Ala172	2.37		
	Gefitinib	-7.6	Arg23	2.07	Arg5	4.77
					Pro350	5.47
	3-(2,5-dimethoxyphenyl)-~{N}-[4-[4-(4-fluorophenyl)-2-(2-phenylhydrazinyl)-1,3-thiazol-5-yl]pyridin-2-yl]propanamide*	-10.9	Lys53	2.89	Val38	3.55
			Met109	3.19	Thr106	3.96
			Ala172	1.78		
			Gly110	3.44		
SRC (PDB ID 1O42)	Myricetin	-6.4	Arg14	2.02	-	-
			Arg34	2.43		
			Glu37	2.97		
			Thr38	2.89		

Proteins (PDB ID)	Ligands	Binding affinity (kcal/mol)	Interactions			
			Hydrogen bonds	Distance (Å)	Hydrophobic bonds	Distance (Å)
			Lys62	2.97		
	Gefitinib	-5.7	Gln78	2.51	Phe79	4.89
			Lys91	2.61		
			Thr77	3.29		
	N-Acetyl-N-[1-(1,1'-Biphenyl-4-Ylmethyl)-2-Oxoazepan-3-Yl]-O-Phosphonotyrosinamide*	-6.9	Arg34	1.58	Lys59	4.26
			Arg14	1.89	Cys44	5.18
			Glu37	1.82	Lys62	4.41
			Thr38	2.38	Leu22	5.43
					Val58	5.29
AKR1C3 (PDB ID 1RY8)	Myricetin	-10.6	Tyr55	2.93	Tyr24	4.36
			Asp224	2.04		
			Gly22	3.77		
	Gefitinib	-9.3	Tyr55	2.42	Tyr216	5.53
			Gln222	2.71	Phe306	4.98
			Ser221	3.44	Tyr24	4.33
			Trp227	3.18	Tyr55	4.71
					His117	5.23
	Nadph Dihydro-Nicotinamide-Adenine-Dinucleotide Phosphate*	-10.8	Trp227	3.48	Tyr24	5.13
			Gln222	1.82	Pro26	5.49
			Ser217	2.30		
			Tyr216	2.55		

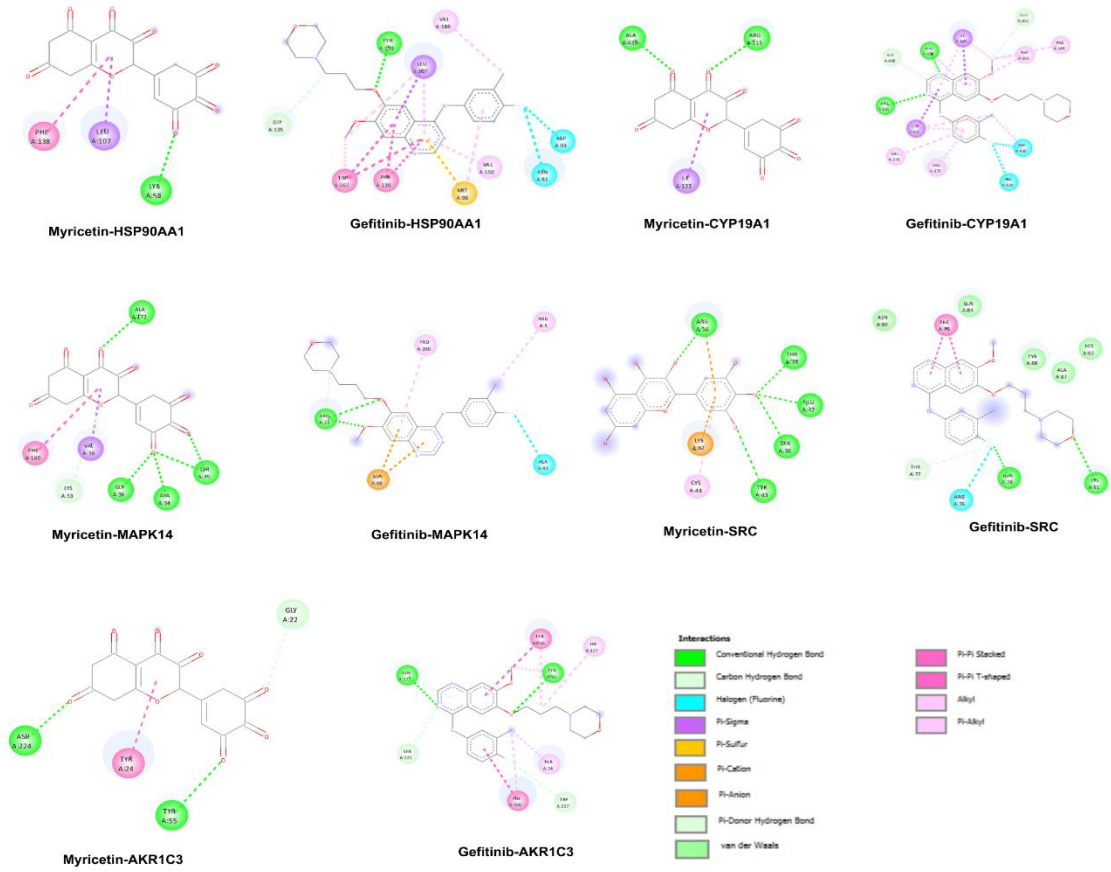
*Note: native ligand



(a) (b)



(c) (d)



(e)

Figure 3. (a) KEGG pathway analysis of target gene by top 10; **(b)** Gene ontology results of potential target of myricetin on lung cancer, including biological processes, cellular components, and molecular functions, color represents difference -log10; **(c)** Heatmap docking results; **(d)** Superimpose of native ligand before and after re-docking all native ligand in initial position shown as yellow; **(e)** Molecular interaction in 2D of myricetin and Gefitinib.

Based on Table 3, the molecular docking results in this study show that myricetin has the potential to be a potent inhibitor of all five targets. In Figure 3E of the SRC protein, myricetin forms hydrogen bonds with residues Arg14, Arg34, Glu37, Thr38, and Lys62. The native ligand also forms hydrogen bonds, with a slightly different pattern, namely Arg14, Arg34, Glu37, and Thr38. The similarity in residues Arg14, Arg34, Glu37, and Thr38 suggests that myricetin mimics the native ligand's important interactions, even forming an additional bond with Lys62, potentially increasing affinity. Based on [56], strong hydrogen bonds are in the range of 2.2-2.5 Å, while weak ones are above 3.0 Å. In this case, only one bond is very strong (Arg14 with a distance of 2.018 Å); the rest are classified as weak to moderate. In Figure 3E for the CYP19A1 protein, myricetin forms two hydrogen bonds with Arg115 and Ala438, both of which are in the strong bond category. Compared to the native ligand that binds to Met374, Arg115, and Ala306, myricetin's interaction is more stable at Ala438 and relatively equivalent at Arg115. This suggests that myricetin can form alternative bonds that are competitive with the native ligand, with interactions that are also reported in previous studies [55].

In Figure 3E of the AKR1C3 protein, myricetin forms hydrogen bonds with Asp224, Tyr55, and Gly22 residues. Only the bond with Asp224 can be categorized as a strong bond, while the other two are weak and likely to contribute less significantly. Compared to the native ligand that interacts with Gln222, Ser217, Tyr216, and Trp227 to form several strong to moderate bonds, the interaction profile of myricetin towards AKR1C3 is stronger overall.

Furthermore, based on bond affinity, myricetin has the strongest energy with AKR1C3 at -10.6 kcal/mol and MAPK14 at -9.6 kcal/mol. Then, molecular docking was also performed with the comparison drug, Gefitinib, a first-line lung cancer treatment in the protein kinase inhibitor class. Gefitinib molecular docking was performed with each target protein. The results showed that the binding affinity of the myricetin compound to the target proteins SRC, MAPK14, AKR1C3, CYP19A1, and HSP90AA1 was weaker than that of the myricetin compound, suggesting that it has great potential as a lung cancer drug. Gefitinib, when compared to myricetin, has bonds related to its binding to AKR1C3, and MAPK14 binding affinity values are -9.3 kcal/mol and -7.6 kcal/mol, respectively. These values illustrate that myricetin's potential as a lung anticancer has a stronger and more stable bond than Gefitinib. The results of this study can be further developed experimentally in the laboratory to evaluate myricetin's interaction with lung cancer cells. Gene expression analysis using Western blot or qPCR can also be conducted to assess the underlying mechanism of myricetin as a potential anticancer agent for lung cancer therapy.

4. Conclusions

Based on network pharmacology, gene expression, survival rate, and molecular docking analyses, this study reveals the potential mechanisms of myricetin as an anticancer therapeutic agent in lung cancer, involving HSP90AA1, CYP19A1, MAPK14, SRC, and AKR1C3. Myricetin is predicted to inhibit the activation of the MAPK14, SRC, and AKR1C3 pathways, thereby potentially suppressing processes such as proliferation, angiogenesis, inflammation, oxidative stress, and hormonal signaling that contribute to lung cancer progression. The findings of this study provide a theoretical basis for further pharmacological research on the mechanisms of myricetin as a potential therapeutic agent for lung cancer. Further research through in vitro experimental validation of gene expression-related effects is required.

Author Contributions

Conceptualization, D.W.C.N.; methodology, D.W.C.N., N.F.R., and B.M.; software, D.W.C.N., L.A., N.F.R., B.M., and C.B.; validation, D.W.C.N., R.T.H., and S.P.S.; formal analysis, D.W.C.N.; data curation, D.W.C.N., R.T.H., and R.F.; writing—original draft preparation, D.W.C.N., N.F.R., B.M., S.P.S., and M.J.; writing—review and editing, D.W.C.N., M.J., and R.F.; supervision, R.F. All authors have read and agreed to the published version of the manuscript.

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Informed Consent Statement

Not applicable.

Data Availability Statement

No new data were created or analyzed in this study. Data sharing is not applicable.

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Conflicts of Interest

The authors declare no conflict of interest.

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