Research Paper

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In-silico Study: The role of myricitrin from the leaves of Syzygium cumini in breast cancer treatment through apoptosis pathway

Murugesan Viji [1,3] | Krishnamoorthy Yasiha[2] | Subramanian Sathiya Jothi[2] | Sowntharrajan Aishwariya[1,3] | Christopher Ireen[1,3] | Sabapathy Indu[1,3] | Sekar Hinduja[1,3] | Manikkam Rajalakshmi*[1,2,3]

1. DBT-BIF Centre, Holy Cross College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli, Tamil Nadu, India.
2. PG & Research Department of Zoology, Holy Cross College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli, Tamil Nadu, India.
3. PG & Research Department of Biotechnology& Bioinformatics, Holy Cross College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli, Tamil Nadu, India.

Abstract:

Myricitrin, a naturally occurring flavonoid glycoside, exhibits a wide spectrum of pharmacological activities, including anti-bacterial, anti-viral, anti-allergic, antioxidant, anti-diabetic, anti-allodynic, anti-inflammatory, and anti-cancer effects. This study investigates the anticancer potential of myricitrin, isolated from the leaves of *Syzygium cumini*, against breast cancer-associated molecular targets using an in-silico approach. The primary objectives were to evaluate the compound's compliance with Lipinski's Rule of Five, assess its ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile, and analyze protein–ligand interactions relevant to breast cancer progression and apoptosis regulation. Physicochemical evaluation revealed that myricitrin satisfies Lipinski's Rule of Five, indicating favorable drug-likeness properties for oral bioavailability. ADMET predictions further demonstrated favorable pharmacokinetic and safety profiles. Molecular docking studies revealed that myricitrin exhibited strong binding affinities toward key apoptotic and cell-cycle regulatory proteins, including Caspase 8, NF-κB/p65, CDK4, CDK6, Bcl-2, and Bak. Notably, hydrogen bond interactions and hydrophobic contacts contributed significantly to the stability of these complexes. The interactions with both pro-apoptotic (Caspase 8, Bak) and anti-apoptotic (Bcl-2) proteins suggest a potential dual modulatory mechanism in apoptosis regulation, making myricitrin a promising candidate for targeted breast cancer therapy. The findings provide compelling *in-silico* evidence for the anticancer potential of myricitrin, supporting its role as a therapeutic lead compound. Further *in vitro* and *in vivo* studies are warranted to validate these interactions and establish its clinical applicability. This study highlights myricitrin as a powerful herbal bioactive candidate with potential for the development of novel breast cancer therapeutics.

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1. Introduction

In the global level, one of the leading factors of death is cancer. The count of recent instances of cancer has increased to 19.3 million, and according to the Global Cancer Statistics 2020, there's been 10 million cancer-related mortalities. It is envisaged that there will be 28.4 million new cases of cancer globally by the year 2040, a startling 47% upsurge from the existing level (Sung *et al.* 2021). The most effective cancer therapies inhibit tumour growth and prevent metastasis. Breast cancer is a diverse disease that is most common in women and men as well. It ranks as the second most common reason of cancer associated fatalities worldwide (Lukasiewicz *et al.* 2021). Females over 50, early menarche, nulliparity, advanced age at menopause, fewer children and less exposure to breastfeeding, obesity, and increasing alcohol intake are risk factors for breast cancer. Hormone therapy, targeted therapy, radiation therapy, operation, and chemotherapy are among the treatments used to manage and treat breast cancer (Collaborative Group on Hormonal Factors in Breast 2012). Scientists are currently searching for alternative methods of treating breast cancer as there are adverse effects of current medicines. Due to the chemo preventive and chemotherapeutic properties, plant-based substances, also referred to as phytochemicals, are being used to develop new anticancer drugs (Choudhari *et al.* 2019; Mazurakova *et al.* 2022; Wei *et al.* 2023). In cancer patients, phytochemicals and their derivatives can improve therapy effectiveness and minimize side effects. Several of these phytoconstituents are naturally occurring bioactive compounds with potent anticancer properties (Asma *et al.* 2022; Sofi and Tabassum 2023). Phytochemicals often exert their effects by modulating molecular signaling pathways associated with cancer progression (Ahmed *et al.* 2022; Situmorang *et al.* 2024). The specific mechanisms include enhancement of antioxidant defences, inactivation of carcinogens, inhibition of cell proliferation, inducing cell cycle block and apoptosis, and immune response's modulation. Myricitrin, a 3-O-rhamnoside of myricetin, is a flavonoid (family Myricaceae). It is found in the leaves, pulp and skin of *Syzygium cumini*. It is normally located in tea, fruits, berries and medicinal plants (Agraharam, Girigoswami, and Girigoswami 2022). Myricitrin displays a wide range of pharmacological activities, with antibacterial, antiviral, anti-allergic, antioxidant, antidiabetic, anti-allodynic, anti-inflammatory, and anticancer properties. Myricitrin has been stated to possess anti-cancer activities against prostate cancer PC-3 cells, ovarian cancer cells, breast cancer (MCF-7), endometrial cancer (Ishikawa) cells, HL 60 leukaemia cells, Colorectal cancer and multiple myeloma cells (Semwal *et al.* 2016). The current article aimed to examine the anticancer potential of myricitrin withdrawn from the *Syzygium cumini* leaves by targeting cell cycle regulators, apoptotic markers, reactive oxygen species (ROS), and NF-κB signaling proteins through molecular docking analyses (Abdulrahman and Hama 2023). The novelty of the present study is attributed to the strategic selection of both the phytochemical compound and apoptosis-associated molecular targets, which, to the best of our belief, have not been explored in combination in prior studies (Wani *et al.* 2023). Specifically, this work represents the first in silico evaluation of myricitrin isolated from the leaves of *Syzygium cumini* for its potential interaction with key pro-apoptotic and anti-apoptotic proteins implicated in breast cancer (Almatroodi and Rahmani 2025). By investigating the previously unexplored intersection between the bioactive compound myricitrin, derived from the leaves of *Syzygium cumini*, and the regulation of apoptosis in breast cancer, this study addresses a critical knowledge gap and establishes a novel foundation for future experimental and translational research in natural compound-based cancer therapeutics (Barh and Viswanathan 2008; Kumar *et al.* 2023).

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2. Materials and Methods

2.1. Ligand preparation

PubChem is a publicly accessible chemical information database maintained by the National Institutes of Health (NIH), United States. PubChem aggregates biological activity descriptions for a chemical from hundreds of bases and made accessible for all. The canonical SMILES of myricitrin were taken from PubChem. ChemSketch was employed to illustrate the 2D structure of the ligand myricitrin (Wang *et al.* 2009).

2.2. Drug-likeliness properties

The pharmacokinetic profiling of myricitrin was conducted utilizing the pkCSM tool, a computational platform designed for the prediction of drug-likeness and ADMET properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity) (Pires, Blundell, and Ascher 2015; Bitew *et al.* 2021). The tool employs graph-based structural signatures to model and predict essential pharmacokinetic parameters, including compliance with Lipinski's Rule of 5, solubility, permeability, and potential toxicity. Through pkCSM analysis, molecular descriptors such as lipophilicity, molecular weight, hydrogen bonding capacity, and rotatable bonds were evaluated, alongside predictive models for absorption rates, distribution characteristics, metabolic stability, route of excretion, and toxicity risks (Wu *et al.* 2020; Ahmad *et al.* 2023). This integrated in-silico approach enables rapid and reliable assessment of a compound's suitability as a drug candidate, supporting lead optimization in drug development (Agamah *et al.* 2020; Du *et al.* 2023; Kanan *et al.* 2021).

2.3. Protein Preparation

The 3D structure of Cell cycle proteins, Cyclin-D1 (PDB ID:2W99-A), Cyclin-D3 (PDB ID:3G33-B), Cyclin-Dependent Kinase 4 (CDK4) (PDB ID:3G33-A), Cyclin-Dependent Kinase 6 (CDK6) (PDB ID:1G3N-A), Cyclin Dependent kinase inhibitor 4c (p18 INK4c) (PDB ID:1G3N-B), Cyclin Dependent kinase inhibitor 1 (p21WAF1 /CIP1) (PDB ID:1AXC-B), Cyclin-dependent kinase inhibitor 1B (p27 KIP1) (PDB ID:1JSU-C), Apoptotic proteins, B-cell lymphoma-extra-large (Bcl-xL) (PDB ID:1G5J-A), B-cell leukemia/lymphoma 2 protein (BCL-2) (PDB ID: 1G5M-A), Caspase 3 - apoptosis-executing protease) (PDB ID:1GFW-A), Caspase 9 - apoptosis-initiating protease (PDB ID:1NW9-B), Caspase 6 - apoptosis-executing protease (PDB ID: 2WDP-A), Caspase 8 - apoptosis-initiating protease (PDB ID: 5JQE-A), BCL-2-associated X protein (Bax) (PDB ID: 2K7W-B), BCL-2 antagonist/killer (Bak) (PDB ID: 2YV6-A), ROS (Reactive Oxygen Species) proteins, Catalase (CAT) (PDB ID: 1QQW-A), Superoxide dismutase (SOD) (PDB ID: 1SPD-A), Glutathione peroxidase-2 (GPx-2) (PDB ID: 2HE3-A), Peroxiredoxin (PDB ID: 1OC3-A), NF-κB Subunit proteins, Nuclear factor NF-kappa-B p52 subunit (NF-κB/p52) (PDB ID: 1A3Q-A), Nuclear factor NF-kappa-B p65 subunit (NF-κB/p65) (PDB ID: 1NFI-A) and Nuclear factor NF-kappa-B p100 subunit (NF-κB/p100) (PDB ID: 3DO7-B) were found from Protein Data Bank (PDB) (Velankar *et al.* 2021). The receptors were equipped by eliminating water molecules, nucleic acid groups, native ligand groups and heteroatoms, accompanied by the accumulation of polar hydrogen atoms to optimise receptor-ligand interactions using BIOVIA Discovery Studio Visualizer 2021 Client software (Iqbal *et al.* 2023).

2.4. Grid box generation

Grid box generation is a critical stage in molecular dockage, as it states the spatial boundaries within which the ligand explores potential binding conformations with the target protein. The grid sizes were fixed to 25 × 25 × 25 Å, and the center coordinates were manually defined based on the position of key active site residues (Forli *et al.* 2016; Yang, Chen, and Zhang 2022). These coordinates were identified using either the co-crystallized ligand present in the protein layout or through predicted binding pocket analysis (Gao and Skolnick 2012). This ensured that the grid adequately covered the most relevant region of the protein for ligand interaction. The selection of grid parameters was done to optimize the accuracy of docking outcomes while maintaining computational efficiency (Agu *et al.* 2023; Forli *et al.* 2016).

2.5. Molecular Docking

Molecular docking was executed using PyRx version 0.8, which incorporates AutoDock Vina as its default docking engine. Ligand molecules were energy minimized using the Open Babel module integrated within PyRx to optimize their geometries prior to docking (Agyapong *et al.* 2021; Eberhardt *et al.* 2021). The docking protocol employed the default parameters of AutoDock Vina, with the exhaustiveness value set to 8 to achieve a balance between computational efficiency and conformational sampling accuracy. Docking results were examined based on holding affinity scores, expressed as Vina scores (kcal/mol), where lower values indicate more favourable interactions (Ivanova and Karelson 2022; Trott and Olson 2010). To authenticate the dependability of the docking protocol, re-docking of native co-crystallized ligand was performed. The predicted binding pose was then compared to the experimentally observed position using Root Mean Square Deviation (RMSD) analysis. An RMSD value of ≤ 2.0 Å was considered indicative of reliable and reproducible docking performance (Ramirez and Caballero 2018; Mukherjee, Balius, and Rizzo 2010).

2.5. Protein-Ligand visualization

The docking poses were further analyzed to identify the main molecular relations, with hydrogen bonds, hydrophobic associates, and π–π stacking, by means of the BIOVIA Discovery Studio Visualizer 2021 Client software (Iqbal *et al.* 2023). By bringing its result into the BIOVIA Discovery Studio Visualizer 2021 Client program, that showed 3D and 2D connections of the docking output through the bond length, we accomplished to find an important interface between the ligands and the receptor binding site (Bhat *et al.* 2022).

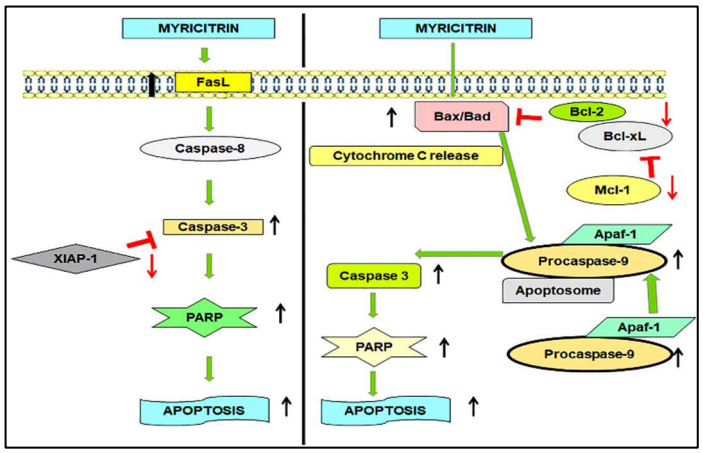

Figure 1. Myricitrin-Induced Apoptosis via Dual Activation of Extrinsic and Intrinsic Pathways

3. Results and Discussion

3.1. Dual Activation of Extrinsic and Intrinsic Pathway

The **figure 1** depicts the dual apoptotic pathways activated by myricitrin in cancer cells. In the extrinsic pathway, myricitrin upregulates Fas ligand (FasL) expression on the cell membrane, leading to Fas receptor activation and subsequent initiation of caspase-8. Activated caspase-8 directly cleaves and activates caspase-3, which then mediates poly (ADP-ribose) polymerase (PARP) cleavage, a hallmark of apoptosis (Jan and Chaudhry 2019). Additionally, myricitrin downregulates X-linked inhibitor of apoptosis protein-1 (XIAP-1), alleviating its inhibitory effect on caspase-3 and thereby amplifying apoptotic signaling. In the intrinsic (mitochondrial) pathway, myricitrin promotes the activation of pro-apoptotic proteins Bax and Bad while suppressing anti-apoptotic

proteins Bcl-2, Bcl-xL, and Mcl-1. This shift in the Bcl-2 family protein balance triggers mitochondrial outer membrane permeabilization, facilitating the release of cytochrome c into the cytosol (Chaudhary *et al.* 2016). Cytochrome c binds to apoptotic protease-activating factor-1 (Apaf-1) to form the apoptosome, which recruits and activates procaspase-9 into caspase-9. Caspase-9 subsequently activates caspase-3, further enhancing PARP cleavage and executing apoptosis. These pathways converge at caspase-3 activation, demonstrating that myricitrin induces apoptosis through coordinated modulation of both death receptor and mitochondrial signaling cascades, highlighting its potential as a therapeutic agent in cancer treatment (Han *et al.* 2022).

3.2. Structure and chemistry of Myricitrin

Myricitrin is a flavonoid glycoside compound with the molecular formula $C_{21}H_{20}O_{12}$ and a molecular weight of 464.38 g/mol. Structurally, it is the 3-O-α-L-rhamnopyranoside of myricetin, meaning myricitrin consists of the flavonol aglycone myricetin linked to an α-L-rhamnose sugar moiety at the C-3 position as shown in the **figure 2**. The compound exhibits the characteristic flavonoid backbone featuring three ring systems: two aromatic rings (A and B) connected by a heterocyclic pyran ring (C) (Hwang and Chung 2018). The aglycone portion (myricetin) contains six hydroxyl groups positioned at C-3, C-5, C-7 (on rings A and C), and C-3', C-4', C-5' (on ring B), making it a hexahydroxyflavone. The rhamnose sugar unit is attached via a glycosidic bond at the 3-position, contributing three additional hydroxyl groups. This extensive hydroxylation pattern is responsible for myricitrin's potent antioxidant properties and biological activities. Myricitrin appears as a light yellow to yellow-orange crystalline powder with a melting point of 197°C. The compound is soluble in polar solvents like DMSO (up to 93 mg/mL) and methanol, with specific optical rotation of -152° to -160° (c=0.5, MeOH). Its IUPAC name is 5,7-dihydroxy-3-[(2S,3R,4R,5R,6S)-3,4,5-trihydroxy-6-methyloxan-2-yl]oxy-2-(3,4,5-trihydroxyphenyl)chromen-4-one (Behl *et al.* 2021).

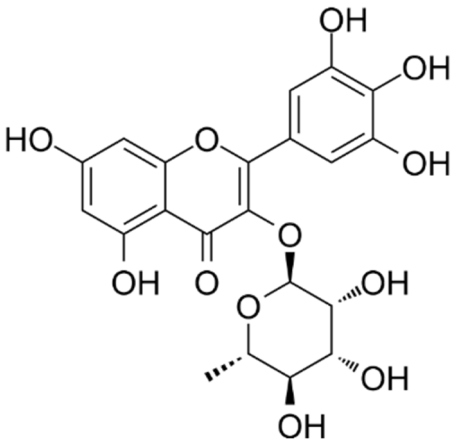

Figure 2. Chemical structure of myricitrin, known for its antioxidant, anti-inflammatory, and anticancer properties, and it exerts cytotoxic effects in cancer cells through modulation of both extrinsic and intrinsic apoptotic pathways.

3.3. Lipinski's rule of five

Myricitrin was assessed for its drug-likeness using Lipinski's Rule of Five and its pharmacokinetic properties through ADMET analysis. A molecular weight of 464.379 Da and a logP value of 0.1943 indicate favorable drug-likeness, characterized by good aqueous solubility and low lipophilicity. The compound contains three rotatable bonds, indicating adequate molecular flexibility. However, the presence of 12 hydrogen bond acceptors, 8 hydrogen bond donors, and a high polar surface area (183.901 Å²), may limit its passive absorption across biological membranes (Table 1).

Table 1: Myricitrin-LIPINSKI rule of 5

Ligand	Myricitrin
Mol. Weight	464.379
LogP	0.1943
Rotatable bonds	3
Acceptors	12
Donors	8
Surface area	183.901

Table 2: ADMET properties of Myricitrin.

Ligand	Myricitrin
Human Oral absorbtion	43.334
BBB permeability	-1.811
CYP2D6 substrate	No
CYP2D6 inhibitor	No
Total clearance	0.303
AMES toxicity	No
Oral Rat Acute Toxicity	2.537
Oral Rat Chronic Toxicity	3.386
Hepatotoxicity	No

3.4. ADME/T Properties

ADMET predictions indicated moderate intestinal absorption (43.334%) and poor blood-brain barrier permeability (log BB: -1.811), which is favorable for non-CNS-targeted therapies. Importantly, Myricitrin does not act as a substrate or inhibitor of the CYP2D6 enzyme, signifying low risk for metabolic drug–drug interactions. Its total clearance rate (0.303 log ml/min/kg) reflects moderate elimination potential. Toxicological predictions indicate that myricitrin is non-mutagenic (negative AMES test), non-hepatotoxic, and exhibits low acute toxicity (LD_{50}: 2.537 mol/kg), along with a high threshold for chronic toxicity (LOAEL: 3.386 log mg/kg-bw/day). Overall, these findings shows that Myricitrin exhibits a favorable pharmacokinetic and safety profile, supporting its potential as a lead compound in the development of therapeutics for breast cancer (Table 2).

3.5. Molecular Docking

As a first selection process in drug discovery, molecular docking is an essential in silico method that predicts the interface and binding affinity among a ligand and its target protein. Binding affinity, commonly expressed in kcal/mol using docking software such as Auto Dock Vina, represents the power of the ligand–target interaction; more negative values indicate a sturdier and more favorable binding interaction. A binding affinity between ≤ and 6.0 kcal/mol is generally regarded as moderate, but affinities between ≤ and 8.0 kcal/mol indicate significant binding and possible biological activity. Docking analyses were performed against proteins associated with the cell cycle, apoptosis, reactive oxygen species (ROS), and NF-κB signaling pathways. Myricitrin interacted with 22 targets (Cyclin D1, Cyclin D3, CDK4, CDK6, P18 INK4c, P21 CIP1, P27 KIP1, Bcl-xL, Bcl-2, Caspase 3, Caspase 9, Bax, Caspase 6, Bak, Caspase 8, Superoxide dismutase, Catalase, Glutathione peroxidase-2, Peroxiredoxin, NF-κB/p52, NF-κB/p65, NF-κB/p100) among them myricitrin showed higher binding affinities towards Catalase, CDK4, and NF-κB/p65 (-8.6, -8.3, and -7.8). Myricitrin showed seven hydrogen bond interactions with the following proteins NF-κB/p65 (GLN A:142(2.64 Å), ASN A:139(2.47 Å), ASN A:137(2.25Å, 2.68Å), ARG A:73(1.81Å, 2.80Å), VAL A:163(2.69 Å), ARG A:174(2.39 Å), LEU A:175(2.25Å, 2.49Å) and Caspase 8 (ASP A:26(2.63Å), TRP A:242 (2.65Å), GLU A:123 (1.88Å), GLY A:312 (2.83Å), ASP A:248 (2.12Å), ARG A:328 (2.39Å), SER A:245 (2.56Å). It showed five hydrogen bond interactions with CDK4 (LEU A:166 (2.59Å), GLN A:173(2.90 Å), ALA A:21(2.22 Å,2.25 Å,5.36 Å), TYR

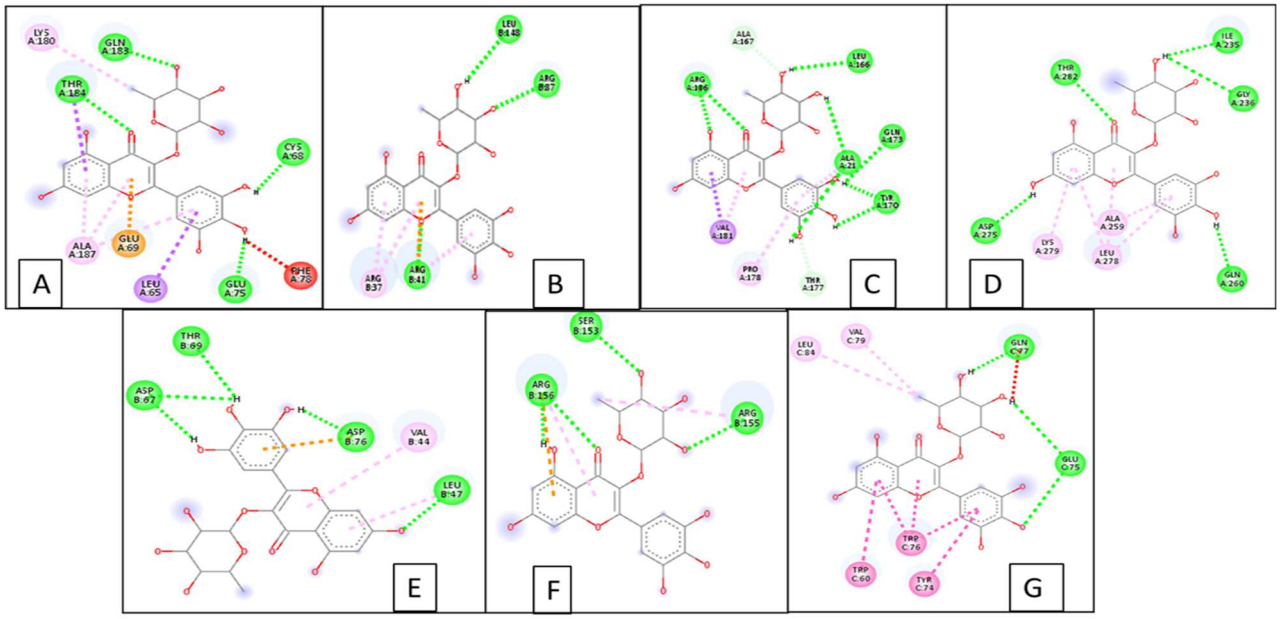

Figure 3. Molecular interaction between Myricitrin and cell cycle proteins such as Cyclin D1, Cyclin D3, CDK4, CDK6, p18 INK4c, p21 CIP1 and p27 KIP1.

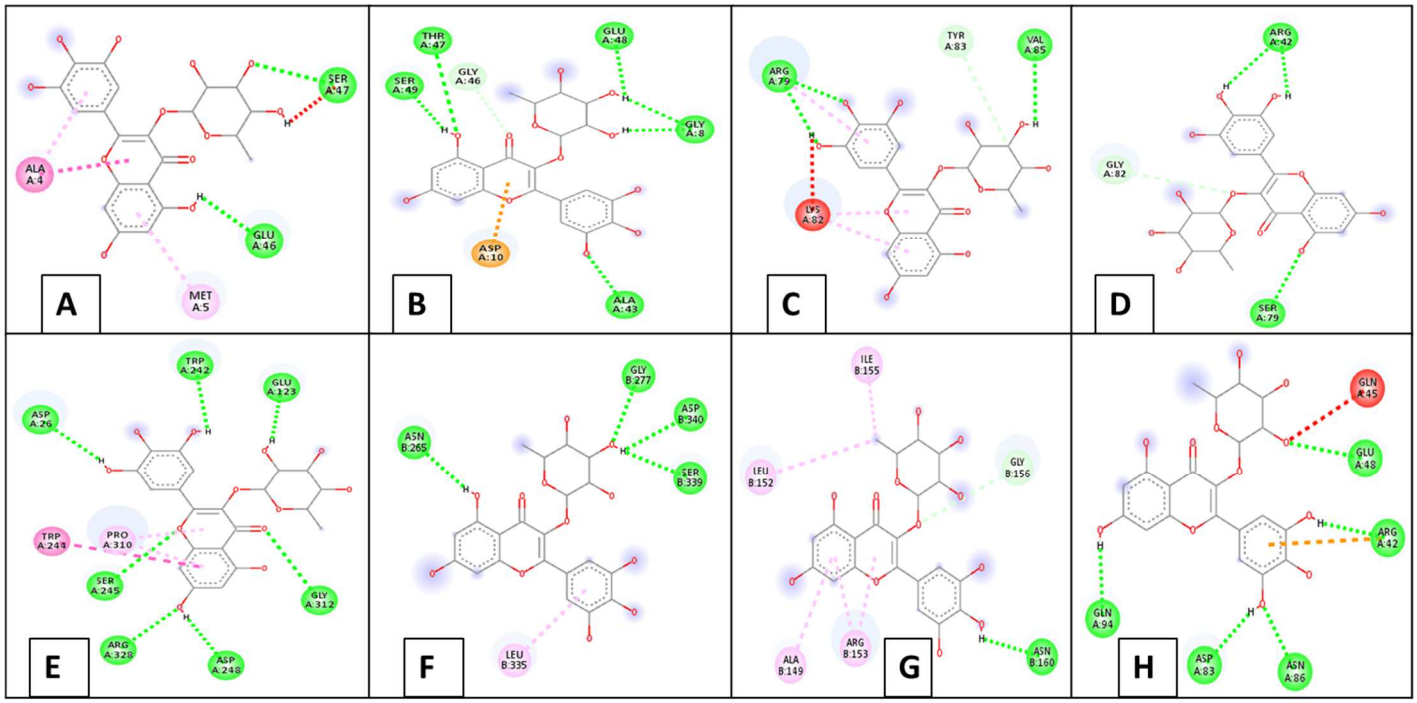

Figure 4. Molecular interactions between Myricitrin and apoptotic proteins such as Bcl-xL, BCL-2, Caspase 3, Caspase 6, Caspase 8, Caspase 9, Bax and Bak.

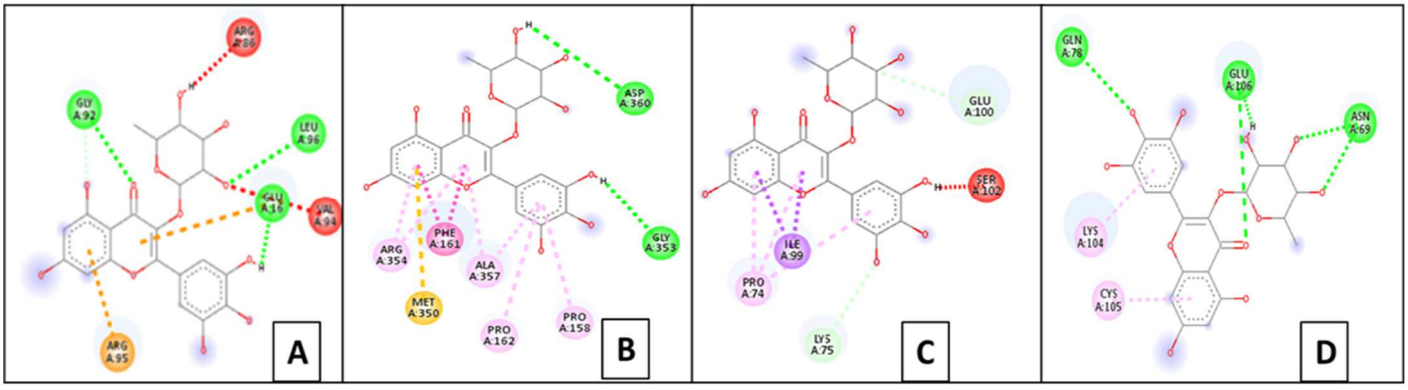

Figure 5. Molecular interaction between Myricitrin and ROS proteins such as Peroxiredoxin, Catalase, Superoxide dismutase and Glutathione peroxidase-2.

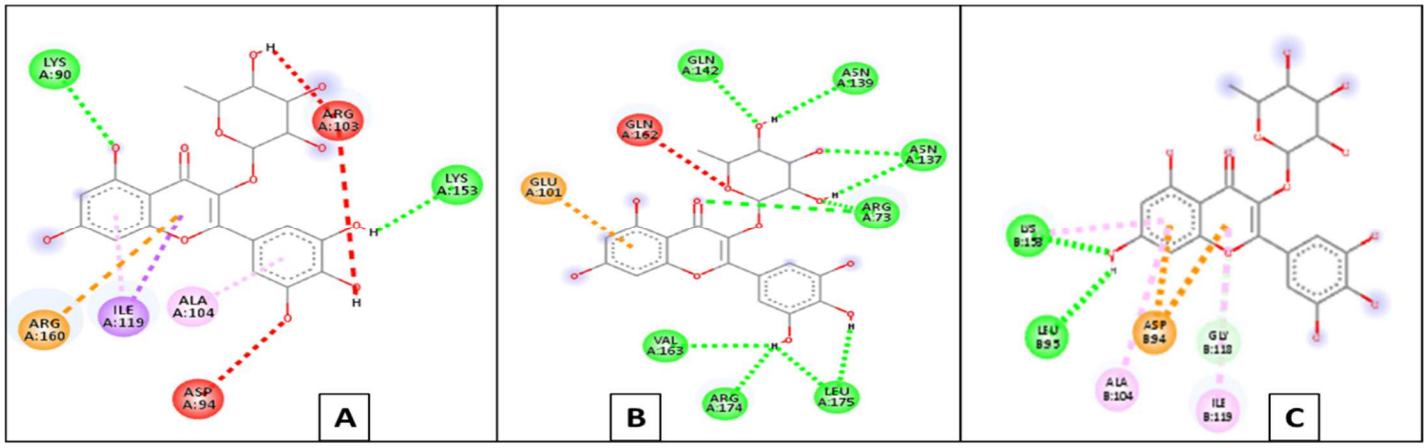

Figure 6. Molecular interaction between Myricitrin and NF-κB proteins such as NF-κB/p52, NF-κB/p65 and NF-κB/p100.

Table 3. Binding affinity and H-bond interactions of myricitrin.

Target types	Targets	Binding affinity (kcal/mol)	H bond - Myricitrin interaction with bond length
Cell cycle proteins	Cyclin D1	-7.6	GLN A:183(2.46 Å), THR A:184(2.02 Å, 3.82 Å), CYC A:68(2.98 Å), GLU A:75 (2.04Å)
	Cyclin D3	-7.7	LEU B:148 (2.93Å), ARG B:87 (2.41Å), ARG B:41 (2.21 Å,4.31 Å,4.44Å)
	CDK4	-8.3	LEU A:166 (2.59Å), GLN A:173(2.90 Å), ALA A:21(2.22 Å,2.25 Å,5.36 Å) TYR A:170(2.04Å, 2.55Å), ARG A:186(1.96Å, 2.53Å)
	CDK6	-7.8	ILE A:235 (2.29 Å), GLY A:236(2.19 Å), THR A:282 (2.10 Å), ASP A:275 (2.25Å), GLN A:260 (2.54 Å)
	P18 INK4c	-7.3	THR B:69 (2.65 Å), ASP B:67 (2.18 Å, 2.68 Å), ASP B:76 (2.89 Å, 3.51 Å), LEU B:47 (2.16 Å, 5.24 Å)
	P21 CIP1	-5.6	ARG B:156(2.24 Å, 2.26 Å, 2.49 Å, 4.21 Å, 4.50 Å, 4.73 Å), SER B:153(2.40 Å), ARG B:155(2.53 Å, 4.09 Å)
	P27 KIP1	-6.2	GLN C:77(2.03 Å, 2.39 Å), GLU C:75 (2.41 Å, 2.86 Å)
Apoptotic proteins	Bcl-xL	-7.6	SER A:47(1.59Å, 2.22Å), GLU A:46 (2.18Å)
	Bcl-2	-7.6	THR A:47(2.89Å), SER A:49(2.27Å), GLUA:48(2.03Å), GLYA:8(2.16Å, 2.17Å), ALA A:43(2.30Å)
	Caspase 3	-6.3	ARG A:79 (2.49Å, 2.61Å, 5.22Å), VAL A:85(2.81Å)
	Caspase 9	-7.3	ASN B:265 (2.33Å), GLY B:277 (2.23Å), ASP B:340 (2.33Å), SER B:339 (2.29Å)
	Bax	-5.6	ASN B:160 (2.11Å)
	Caspase 6	-6.6	ARG A:42(2.04Å,2.54Å), SER A:79 (2.39Å)
	Bak	-7.7	GLU A:48 (2.39Å), ARG A:42 (2.41Å ,4.44Å), ASN A:86 (2.01Å), ASP A:83 (2.21Å), GLN A:94 (1.97Å)
	Caspase 8	-7.7	ASP A:26(2.63Å), TRP A:242 (2.65Å), GLU A:123 (1.88Å), GLY A:312 (2.83Å), ASP A:248 (2.12Å) A, RG A:328 (2.39Å), SER A:245 (2.56Å)
ROS proteins	Superoxide dismutase	-6.8	-
	Catalase	-8.6	ASP A:360 (2.90Å), GLY A:277 (2.61Å)
	Glutathione peroxidase-2	-6.7	GLN A:78(2.92Å), GLU A:106 (2.55Å, 2.89Å), ASN A:69 (2.40Å, 2.86Å)
	Peroxiredoxin	-7.0	GLY A:92 (2.01Å, 3.51Å), LEU A:96 (2.99Å), GLU A:16 (1.96Å, 4.02Å)
NF-κB Subunit proteins	NF-κB/p52	-7.7	LYS A:90 (2.41 Å), LYS A:153 (2.23 Å)
	NF-κB/p65	-7.8	GLN A:142(2.64 Å), ASN A:139(2.47 Å), ASN A:137(2.25Å, 2.68Å), ARG A:73(1.81Å, 2.80Å), VAL A:163(2.69 Å), ARG A:174(2.39 Å), LEU A:175(2.25Å, 2.49Å)
	NF-κB/p100	-7.6	LYS B:153(2.24 Å, 5.04 Å), LEU B:95(2.51Å ,2.51 Å)

A:170(2.04Å, 2.55Å), ARG A:186(1.96Å, 2.53Å), CDK6 (ILE A:235 (2.29 Å), GLY A:236(2.19 Å), THR A:282 (2.10 Å), ASP A:275 (2.25Å), GLN A:260 (2.54 Å), Bcl-2 (THR A:47(2.89Å), SER A:49(2.27Å) GLUA:48(2.03Å), GLYA:8(2.16Å, 2.17Å), ALA A:43(2.30Å) and BAK(GLU A:48 (2.39Å), ARG A:42 (2.41Å ,4.44Å), ASN A:86 (2.01Å), ASP A:83 (2.21Å), GLN A:94 (1.97Å). Superoxide dismutase does not have any hydrogen bond interactions (**Fig. 3, 4, 5, 6 and Table 3**).

A network of molecular targets, including important modulators of the cell cycle, apoptotic pathways, redox balance, and transcriptional control, is engrossed in the regulation of cancer cell proliferation and death. The G1 to S stage transition depends on cyclin D1 and cyclin D3 and their catalytic partners CDK4 and CDK6 as well, which phosphorylate the retinoblastoma (Rb) protein to advance the cell cycle. Overexpression of these proteins contributes to uncontrolled cell proliferation in various malignancies (Feitelson *et al.* 2015). CDK inhibitors such as p18INK4c, p21CIP1 and p27KIP1 function as tumour suppressors by negatively regulating CDK activity, inducing cell cycle arrest, and inhibiting cellular proliferation. Reactive oxygen species (ROS) have two functions in cancer: they promote carcinogenesis at moderate levels while causing apoptosis at high levels. Glutathione peroxidase (GPx), peroxiredoxin, catalase, and superoxide dismutase (SOD) are antioxidant enzymes that neutralise ROS to maintain cellular redox homeostasis; their dysregulation can make cells more vulnerable to oxidative damage and apoptosis (Franklin *et al.* 1998; Abukhdeir and Park 2008).
Furthermore, the NF-κB signaling pathway, which includes subunits like NF-κB/p65 (canonical pathway) and NF-κB/p52 and NF-κB/p100 (non-canonical pathway), is a vital regulator of inflammation and cell survival. While its suppression makes tumour cells more sensitive to apoptotic triggers, persistent initiation of NF-κB in cancer cells stimulates the transcription of genes that prevent apoptosis and increase proliferation. Collectively, these targets represent crucial nodes in cancer progression and are frequently exploited in the development of targeted anticancer therapies (Sun 2011; Deka and Li 2023).

3.6. Other Interactions with Myricitrin

Myricitrin exhibits strong binding affinity with key cell cycle regulatory proteins through various non-covalent interactions. With Cyclin D1, the compound forms multiple stabilizing contacts including pi-sigma interactions with LEU A:65 (3.85-3.87 Å), alkyl interactions with LYS A:180 and ALA A:187, and a pi-anion interaction with GLU A:69 (3.63 Å). The CDK4 interaction is characterized by pi-sigma interactions with VAL A:181 (3.69-4.30 Å) and carbon-hydrogen bonds with ALA A:167 and THR A:177, indicating stable binding within the active site. CDK6 demonstrates extensive pi-alkyl interactions with ALA A:259, LEU A:278, and LYS A:279, suggesting effective inhibition potential. The interaction with P27 KIP1 is particularly notable, featuring multiple pi-pi stacked interactions with TRP C:76 and TRP C:60, along with alkyl interactions with LEU C:84 and VAL C:79. These aromatic stacking interactions typically provide strong binding stability and are crucial for protein-ligand complex formation. Myricitrin's interaction profile with apoptotic proteins reveals its dual modulatory capacity. With anti-apoptotic proteins Bcl-2 and Bcl-xL, the compound forms pi-anion interactions (ASP A:10, 4.39 Å) and amide-pi-stacked interactions (ALA A:4, 3.82-4.82 Å), respectively, potentially disrupting their anti-apoptotic functions.
Conversely, interactions with pro-apoptotic proteins like Bax involve multiple alkyl and carbon-hydrogen bonds with GLY B:156, ILE B:155, LEU B:152, and ARG B:153, suggesting enhancement of pro-apoptotic signaling. Caspase 8 exhibits pi-pi T-shaped interactions with TRP A:244 (5.50 Å) and pi-alkyl interactions with PRO A:310, indicating potential activation of the extrinsic apoptotic pathway. The interactions with Caspase 3, Caspase 6, and Caspase 9 primarily involve carbon-hydrogen bonds and pi-alkyl interactions, suggesting facilitation of the apoptotic execution phase. The binding profile with reactive oxygen species (ROS)-related proteins demonstrates myricitrin's antioxidant mechanism. Superoxide dismutase interactions include pi-sigma interactions with ILE A:99 (3.73-3.87 Å) and extensive pi-alkyl interactions with PRO A:74, enhancing enzymatic antioxidant activity. Catalase exhibits diverse interactions including pi-sulfur bonds with MET A:350, pi-pi stacked interactions with PHE A:161, and multiple pi-alkyl interactions, indicating strong binding affinity and potential enzyme activation. Glutathione peroxidase-2 and Peroxiredoxin interactions primarily involve pi-alkyl and pi-cation interactions, respectively, suggesting enhancement of cellular antioxidant defense mechanisms.

Myricitrin's interaction with NF-κB subunits reveals its anti-inflammatory potential. NF-κB/p52 demonstrates pi-cation interactions with ARG A:160 (4.42 Å), pi-sigma interactions with ILE A:119, and multiple alkyl interactions, suggesting inhibition of inflammatory signaling. NF-κB/p65 interactions include pi-cation bonds with GLU A:101 (4.20 Å), indicating potential suppression of inflammatory gene transcription. NF-κB/p100 exhibits carbon-hydrogen bonds, pi-anion interactions with ASP B:94, and pi-alkyl interactions, further supporting anti-inflammatory activity. The predominant interaction types observed include pi-alkyl interactions (providing hydrophobic stability), carbon-hydrogen bonds (contributing to binding specificity), pi-sigma interactions (enhancing binding strength), and pi-pi stacked interactions (offering aromatic stabilization). The bond lengths generally range from 2.0-5.8 Å, with most interactions falling within optimal binding distances (3.0-5.0 Å), indicating stable and energetically favorable protein-ligand complexes. These comprehensive binding interactions demonstrate myricitrin's multi-target therapeutic potential, simultaneously modulating cell cycle progression, apoptosis, oxidative stress, and inflammation pathways, supporting its candidacy as a promising anticancer agent.

Overall, the results from the *in-silico* studies suggest that the compound exhibits a higher binding affinity and more favorable hydrogen bond interactions. Apoptosis, an exceedingly controlled form of programmed cell death, plays a serious role in upholding tissue growth and homeostasis. Additionally, it serves as a defensive mechanism to eradicate cells that are damaged, potentially malignant, or infected by viruses. Apoptotic signaling occurs via two distinct molecular mechanisms (Elmore 2007). Both pro-apoptotic and anti-apoptotic members of the Bcl-2 family regulate the permeabilization of the mitochondrial outer membrane. The death receptor-mediated (extrinsic) path is stimulated by the interaction of myricitrin with Bax/Bad (Zhou et al. 2024). The ligand myricitrin inhibits anti-apoptotic proteins such as Bcl-2, Bcl-xL, and Mcl-1, while simultaneously activating pro-apoptotic proteins including Bax, Bad, Caspase-9, Caspase-3, and PARP, ultimately leading to the induction of apoptosis. Collectively, these targets represent critical nodes in cancer development and are commonly exploited in the design of targeted anticancer therapies (Figure 1).

4. Conclusion

The present *in-silico* investigation provides compelling evidence for the therapeutic potential of myricitrin as an anticancer agent targeting breast cancer. The comprehensive molecular docking analysis revealed that myricitrin establishes favorable hydrogen bond interactions with critical apoptotic regulators including Caspase-8, NF-κB/p65, CDK4, CDK6, Bcl-2, and Bak, indicating its capacity to modulate key cellular pathways involved in cancer progression and cell death mechanisms. The pharmacokinetic profiling demonstrates that myricitrin satisfies Lipinski's Rule of Five parameters, confirming its drug-likeness potential for oral bioavailability. Furthermore, the favorable ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) characteristics

support its suitability as a therapeutic candidate with minimal toxicity concerns and optimal pharmacokinetic properties. Notably, myricitrin exhibited exceptionally strong binding affinities toward pivotal molecular targets, with catalase, CDK4, and NF-κB/p65 showing impressive docking scores of –8.6, –8.3, and –7.8 kcal/mol, respectively. These robust binding interactions suggest significant inhibitory potential against oxidative stress enzymes, cell cycle regulatory proteins, and inflammatory transcription factors, all critical components in cancer pathogenesis. The dual modulatory capacity of myricitrin toward both pro-apoptotic and anti-apoptotic proteins underscores its potential to restore apoptotic balance in malignant cells, a fundamental mechanism for effective cancer therapy. The compound's ability to simultaneously target multiple pathways including apoptosis regulation, cell cycle control, antioxidant defense, and inflammatory signaling positions it as a multi-target therapeutic agent with enhanced efficacy potential. These findings collectively establish myricitrin as a highly promising phytochemical candidate warranting extensive further investigation through rigorous in vitro cell culture studies and in vivo animal models to validate its anticancer efficacy against breast cancer and elucidate its precise mechanisms of action in biological systems.

5. Disclosure Statements

5.1. Author Contribution

M.V: Writing-Original Draft Preparation; **K.Y.** and **S.SJ**: Conceptualization; **S.A:** Methodology; **C.I:** Software; **S.I:** Validation; **S.H:** Writing-Review and Editing; **M.R:** Supervision.

5.2. Declaration of Generative AI

No generative AI or AI-assisted technologies were used in the writing or editing of this manuscript.

5.3. Ethics approval (for clinical/animal studies)

Ethical review and approval were waived for this study by the Institutional Review Board of [Holy Cross College (Autonomous), Affiliated to Bharathidasan University, Tiruchirappalli, Tamil Nadu, India], as the research involved publicly available data.

5.4. Informed Consent Statement

Not applicable.

5.5. Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

5.6. Acknowledgment

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5.8. Conflicts of Interest

The authors declare that they have no known financial, personal, academic, or other relationships that could inappropriately influence, or be perceived to influence, the work reported in this manuscript. All authors confirm that there are no competing interests to declare.

5.9. Corresponding Author Contact Information

The corresponding author **Dr. Manikkam Rajalakshmi** can be contacted via email rajalakshmi[at]hcctrichy.ac.in

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