Evaluating the efficacy of myricetin from the stem bark *of Syzygium cumini* as a regulator in signal transduction mechanism in breast cancer by *in silico* approach

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Abstract
According to reports, cancer is the leading cause of mortality in the world and breast cancer tops the charts in second place after lung cancer. In both industrialised and developing nations, breast cancer continues to be the most prevalent cancer in women. Out of 9 women, 1 woman is at risk of breast cancer. This study investigates the anticancer efficacy of myricetin, derived from the stem bark of Syzygium cumini, on breast cancer targets through in silico analyses. The objectives of the present study were to predict compliance with Lipinski's Rule of Five, to evaluate its ADMET profile and to analyse protein–ligand interactions relevant to breast cancer progression and apoptosis regulation. The results from the in silico analyses indicated that myricetin complies with Lipinski's Rule of Five and exhibits favourable ADMET properties. Myricetin exhibited a higher binding affinity towards Catalase, CDK4 and Bcl-2, with binding energies of −9.4, −8.8 and −7.9 kcal/mol, respectively.

Myricetin showed more hydrogen bond interactions with CDK4, Caspase 9 and Bak. This study provides evidence that myricetin induces apoptosis through both extrinsic and intrinsic pathways. Myricetin exerts its anti-tumorigenic effects by inducing apoptosis. Therefore, with more research, the substance may be exploited as a powerful herbal medicinal molecule to cure breast cancer.

Keywords: Myricetin, Docking, Breast cancer, Healthcare, Drug design, Public Health, *Syzygium cumini.*

Introduction

Breast cancer is most prevalent in both women and men and it is a heterogeneous illness. It is the second most common reason for cancer-related deaths globally[1]. The BRCA-1 and BRCA-2 genes' mutations are reported to be the cause of 5–10% of breast cancer cases[2].

Risk factors for breast cancer include females who are over the age of 50, early menarche, nulliparity, older age at menopause, having fewer children and less exposure to breastfeeding, obesity and increased alcohol consumption[3]. Based on the presence or absence of three receptors, breast cancer is classified into three subtypes: progesterone receptors (PR), estrogen receptors (ER) and human epidermal growth factor receptor-2 (HER-2). At least one of the receptors is present in more than 80% of breast tumors[4].

To manage and treat breast cancer, therapies include targeted therapy, hormonal therapy, radiation therapy, surgery and chemotherapy[5]. Due to the adverse effects of existing treatments, scientists are currently looking for alternative approaches to treat breast cancer. Plant-based compounds, also known as phytochemicals, are being explored for the development of new anticancer drugs due to their chemopreventive and chemotherapeutic properties[6].

Eugenia jambolana, also referred to as *Syzygium cumini*, is a plant belonging to the Myrtaceae family. Jamun, black plum, Indian blackberry and jambolao are some of its other names. Native to South Asia, the jamun fruit is mostly found in India, Myanmar, Afghanistan and Pakistan[7]. *Syzygium cumini* has therapeutic benefits in all of its components, but particularly in its fruits, seeds, leaves, flowers and bark[8]. *Syzygium cumini* exhibits various pharmacological activities including anti-diabetic, antioxidant, anti-inflammatory, chemoprotective, hypoglycemic, astringent, gastroprotective, antidiarrheal, analgesic, antimalarial and anticancer properties[9].

A wide variety of plant-based foods and beverages contain flavonoids, which can be broadly categorized as flavonols, flavones, anthocyanins, catechins, flavanols and isoflavones. Myricetin (3,3',4',5,5',7-hexahydroxyflavone, $C_{15}H_{10}O_8$) is a flavonol which is present in the fruits, leaves, flowers and bark of *Syzygium cumini*[10]. Myricetin exhibited anticancer properties *in vitro* against pancreatic[11], liver[12], prostate[13], thyroid[14] and breast[15]. Therefore, the present study aimed to document the target-ligand interaction of myricetin from the stem bark of *Syzygium cumini* with cell cycle, apoptotic, ROS and NF-κB proteins through an *in-silico* technique.

Material and Methods

Ligand preparation: The canonical SMILES of myricetin were taken from PubChem. ACD/ChemSketch was employed to illustrate the 2D structure of myricetin[16,17].

Drug-likeliness properties: The pharmacokinetic properties, including Lipinski's Rule of 5 and ADMET characteristics, were analysed using the pkCSM tool[18].

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 (Caspase 3) (PDB ID:1GFW_A), Caspase 9-apoptosis-initiating protease (Caspase 9) (PDB ID:1NW9_B), Caspase 6-apoptosis-executing protease (Caspase 6) (PDB ID: 2WDP_A), Caspase 8-apoptosis-initiating protease (Caspase 8) (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), 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 obtained from Protein Data Bank (PDB).

The receptors were prepared by removing water molecules, nucleic acid groups, native ligands and heteroatoms, followed by the addition of polar hydrogen atoms to optimize receptor–ligand interactions using BIOVIA Discovery Studio Visualizer 2021 Client software[19].

Grid box generation: Grid box generation is a crucial step in molecular docking, as it defines the spatial boundaries within which the ligand explores potential binding conformations on the target protein. In this study, the grid box was carefully configured to encompass the entire active site of the target protein. The grid dimensions were set to 25 × 25 × 25 Å and the centre coordinates were manually adjusted according to the positions of key active site residues. These coordinates were identified using either the co-crystallized ligand present in the protein structure or through predicted binding pocket analysis. 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 optimise the accuracy of docking outcomes while maintaining computational efficiency.

Molecular docking: Molecular docking simulations were performed 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. 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 sampling thoroughness. Docking results were analysed based on binding affinity scores, expressed as Vina scores (kcal/mol), where lower values indicate more favourable interactions.

To validate the accuracy of the docking protocol, the native co-crystallized ligand was re-docked into the active site of the target protein. 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[20-23].

Visualization of target-ligand interaction: The docking poses were further analyzed to identify key molecular interactions including hydrogen bonds, hydrophobic contacts and π–π stacking, using the BIOVIA Discovery Studio Visualizer 2021 Client software. By bringing the result into the BIOVIA Discovery Studio Visualizer 2021 Client program, which showed the 3D and 2D interactions of the docking output with the bond length, we were able to find an important interaction between the ligands and the receptor binding site[19].

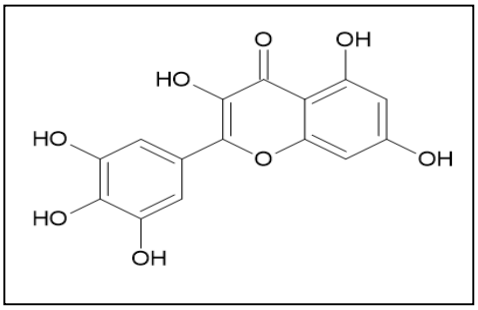

Fig. 1: 2D Structure of Myricetin

The molecular weight of myricetin is 318.237Da, LogP is 1.6936, hydrogen bond acceptors are 8 and hydrogen bond donors are 6. It has 1 rotatable bond, with a surface area of 126.902Å². The results show that myricetin obeys Lipinski's rule of 5 (Table 1).

Table 1
LIPINSKI rule of 5-Myricetin.

Ligand	Mol. Weight	LogP	# Rotatable bonds	# Acceptors	# Donors	Surface area
Myricetin	318.237	1.6936	1	8	6	126.902

Table 2
ADMET properties of Myricetin.

ADMET Properties	Myricetin
Internal absorption (Human) (% Absorbed)	65.93
BBB permeability (log BB)	-1.493
CYP2D6 substrate	No
CYP2D6 inhibitior	No
Total clearance (log ml/min/kg)	0.422
AMES toxicity	No
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.497
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg-bw/day)	2.718
Hepatotoxicity	No

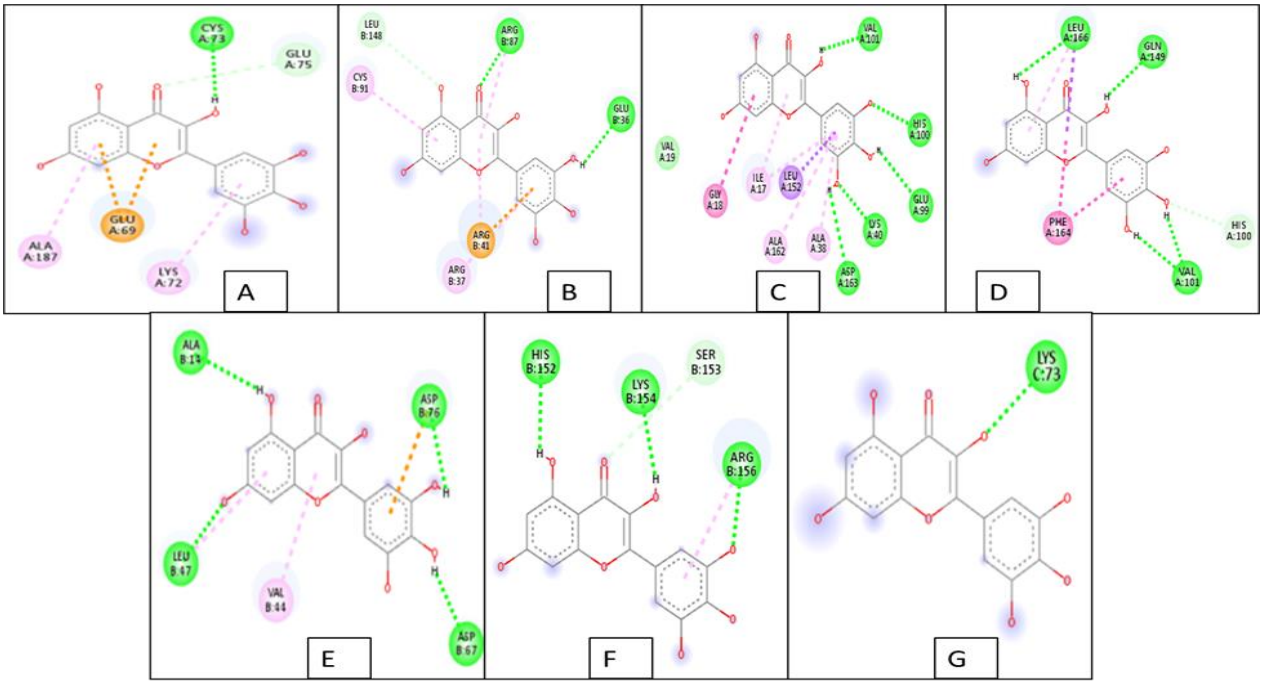

Fig. 2: Molecular interaction between Myricetin and cell cycle proteins such as Cyclin D1, Cyclin D3, CDK4, CDK6, p18 INK4c, p21 CIP1, p27 KIP1

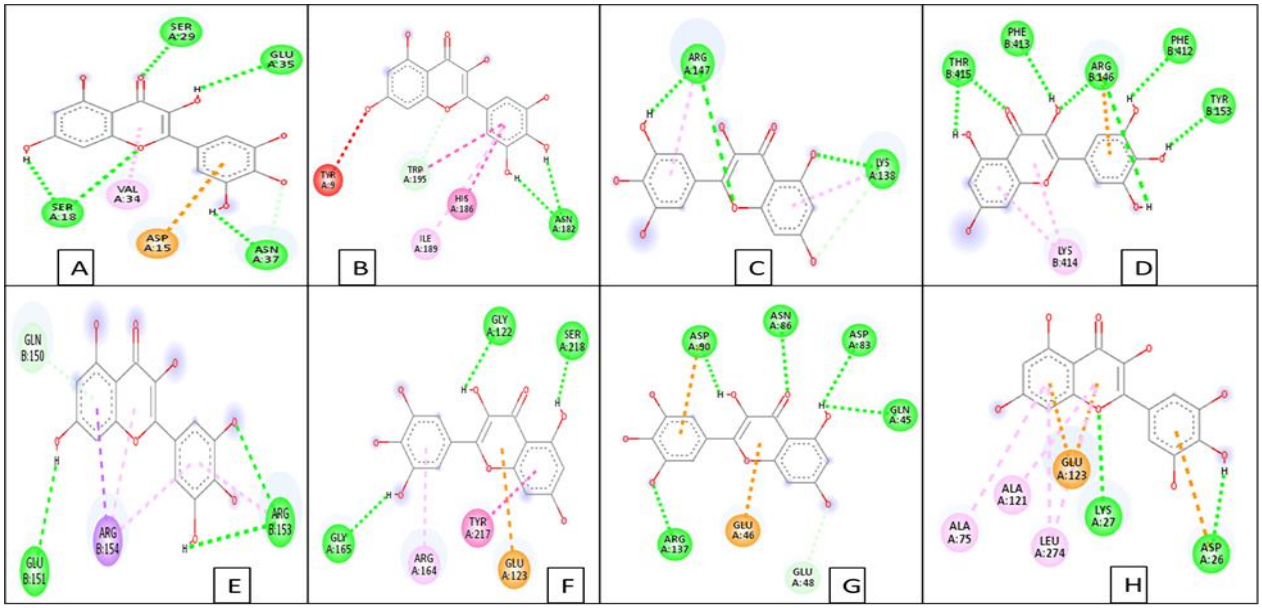

Fig. 3: Molecular interaction between Myricetin and apoptotic proteins such as Bcl-xL, BCL-2, Caspase 3, Caspase 9, Bax, Caspase 6, Bak and Caspase 8.

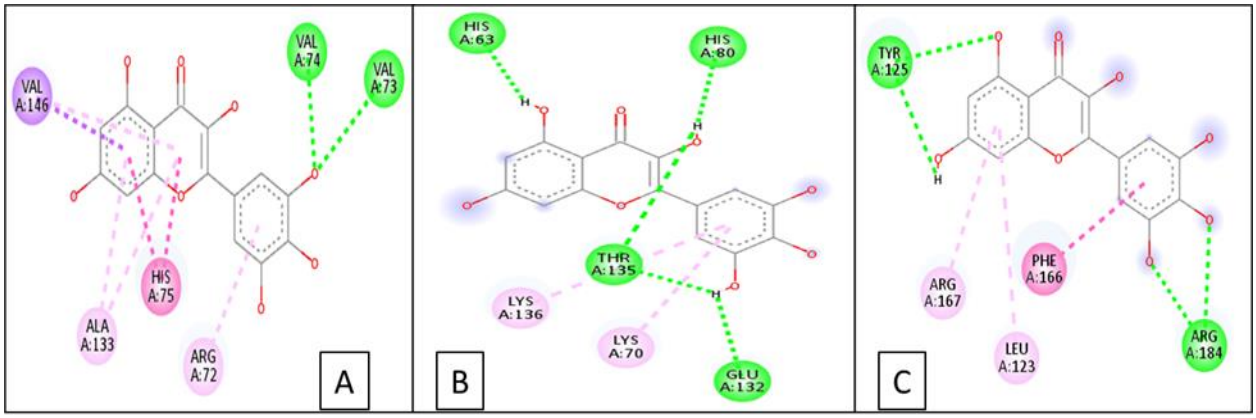

Fig. 4: Molecular interaction between Myricetin and ROS proteins such as Catalase, Superoxide dismutase and Glutathione peroxidase.

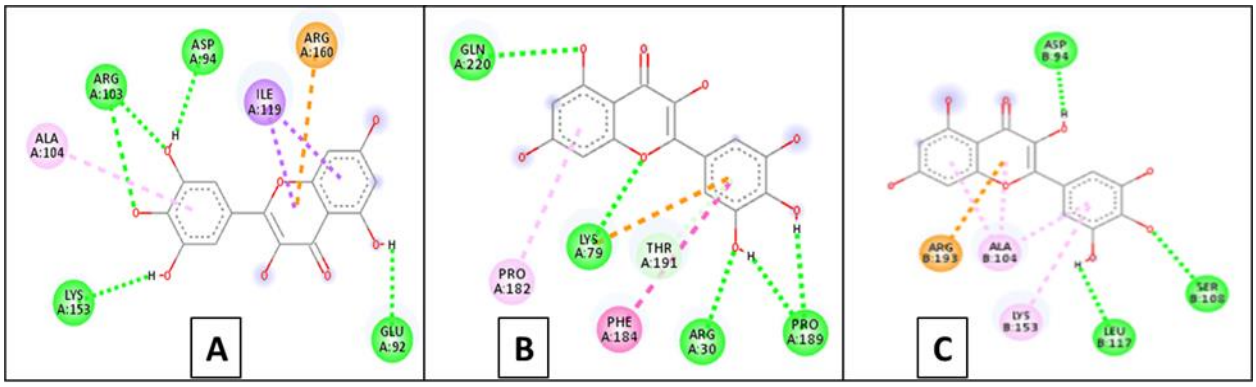

Fig. 5: Molecular interaction between Myricetin and NF-κB proteins such as NF-κB/p52, NF-κB/p65 and NF-κB/p100

Table 3
Binding affinity and H-bond interaction of myricetin with cell cycle proteins.

Target type	Proteins	Binding affinity (kcal/mol)	H-bond interactions
			Myricetin
Cell cycle proteins	Cyclin D1	-7	CYS A:73
	Cyclin D3	-6.6	ARG B:87, GLU B:36
	CDK4	-8.8	VAL A:101, HIS A:100, GLU A:99, LYS A:40, ASP A:163
	CDK6	-7.4	LEU A:166, GLN A:149, VAL A:101
	P18 INK4c	-6.3	ALA B:14, ASP B:76, LEU B:47, ASP B:67
	P21 CIP1	-5	ARG B:156, LYS: B 154, HIS B:152
	P27 KIP1	-5.6	LYS C:73

Table 4
Binding affinity and H-bond interaction of myricetin with apoptotic proteins

Target type	Proteins	Binding affinity (kcal/mol)	H-bond interactions
		Myricetin	
Apoptotic proteins	Bcl-xL	-7	SER A:29, GLU A:35, SER A:18, ASN A:37
	Bcl-2	-7.9	ASN A:182
	Caspase 3	-6.2	ARG A:147, LYS A:138
	Caspase 9	-7.2	THR B:415, PHE B:413, ARG B:146, PHE B: 412, TRY B:153
	Bax	-5.1	GLU B:151, ARG B:153
	Caspase 6	-6.6	GLY A:122, GLY A:165, SER A:218
	Bak	-7.8	ASP A:90, ASN A:86, ASP A:83, GLN A:45, ARG A:137
	Caspase 8	-7.5	LYS A:27, ASP A:26

Table 5
Binding affinity and H-bond interaction of myricetin with ROS proteins.

Target type	Proteins	Binding affinity (kcal/mol)	H-bond interactions
		Myricetin	
ROS proteins	Superoxide dismutase	-7.1	HIS A:63, HIS A:80, THR A:135, GLU A:132
	Catalase	-9.4	VAL A:74, VAL A:73
	Glutathione peroxidase	-6.3	TYR A:125, ARG A:184

Myricetin exhibits 65.93% intestinal absorption. Myricetin is neither a substrate nor an inhibitior of CYP2D6. Myricetin has -1.493 (log BB) BBB permeability, 0.422 (log ml/min/kg) total clearance, 2.497 (LD50) (mol/kg) Oral Rat Acute Toxicity and 2.718 (log mg/kg-bw/day) Oral Rat Chronic Toxicity. Myricetin exhibits neither hepatotoxicity nor AMES toxicity (Table 2).

Molecular interaction analyses were performed for the cell cycle, apoptotic, ROS (Reactive Oxygen Species) proteins and NF-KB proteins. Myricetin was docked with 21 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, NF-κB/p52, NF-κB/p65, NF-κB/p100). Among these targets, myricetin exhibited higher binding affinity towards catalase, CDK4 and Bcl-2, with binding energies of -9.4, -8.8 and -7.9 kcal/mol respectively. Myricetin showed five hydrogen bond interactions with the protein CDK4 (VAL A:101, HIS A:100, GLU A:99, LYS A:40, ASP A:163), Caspase 9 (THR B:415, PHE B:413, ARG B:146, PHE B:412, TRY B:153) and Bak (ASP A:90,

ASN A:86, ASP A:83, GLN A:45, ARG A:137) (Fig. 2, 3, 4 and 5) (Table 3, 4, 5 and 6).

Apoptosis is crucial for maintaining the growth and balance of multicellular organisms by removing malfunctioning or undesirable cells[24]. One of the hallmarks of carcinogenesis is inefficient apoptosis[25,26]. For cancer therapy, the induction of apoptosis is very important[27]. There are two primary signalling routes for apoptosis: the intrinsic (mitochondria-mediated) pathway and the extrinsic (death receptor) pathway[28]. FasL and TRAIL function as the death receptor or extrinsic pathway mediators. Myricetin binds to the FasL to activate the death receptor and other signalling molecules like FADDR **(**Fas-associated death domain receptor**)** and caspase-8. A member of the IAP (inhibitor of apoptosis) family, X-linked inhibitor of apoptosis protein (XIAP) binds and inhibits caspase-3, caspase-7 and caspase-9 with specificity. The conserved IAP family of proteins inhibits the enzymatic activity of caspases. When Caspase-8, an initiator caspase in the extrinsic route, is activated, it causes Caspase-3 to cleave several substrates including poly (ADP-ribose) polymerase (PARP), which trigger apoptosis[29].

Bcl-2 family proteins which comprise of pro-apoptotic proteins (Bak, Bad) and anti-apoptotic proteins (Bcl-2, Bcl-xL and Mcl-1), regulate the intrinsic (mitochondria-mediated) pathway. The anti-apoptotic proteins Bcl-2, Bcl-xL and Mcl-1 are inhibited by myricetin while the pro-apoptotic proteins Bak and Bad are activated.

Table 6
Binding affinity and H-bond interaction of myricetin with NF-κB proteins

Target type	Proteins	Binding affinity (kcal/mol)	H-bond interactions
		Myricetin	
NF-κB Subunit protein	NF-κB/p52	-7	ARG A:103. ASP A:94, LYS A:153, GLU A:92
	NF-κB/p65	-7	GLN A:220, LYS A:79, ARG A:30, PRO A:189
	NF-κB/p100	-7.2	ASP B:94, SER B:108, LEU B:117

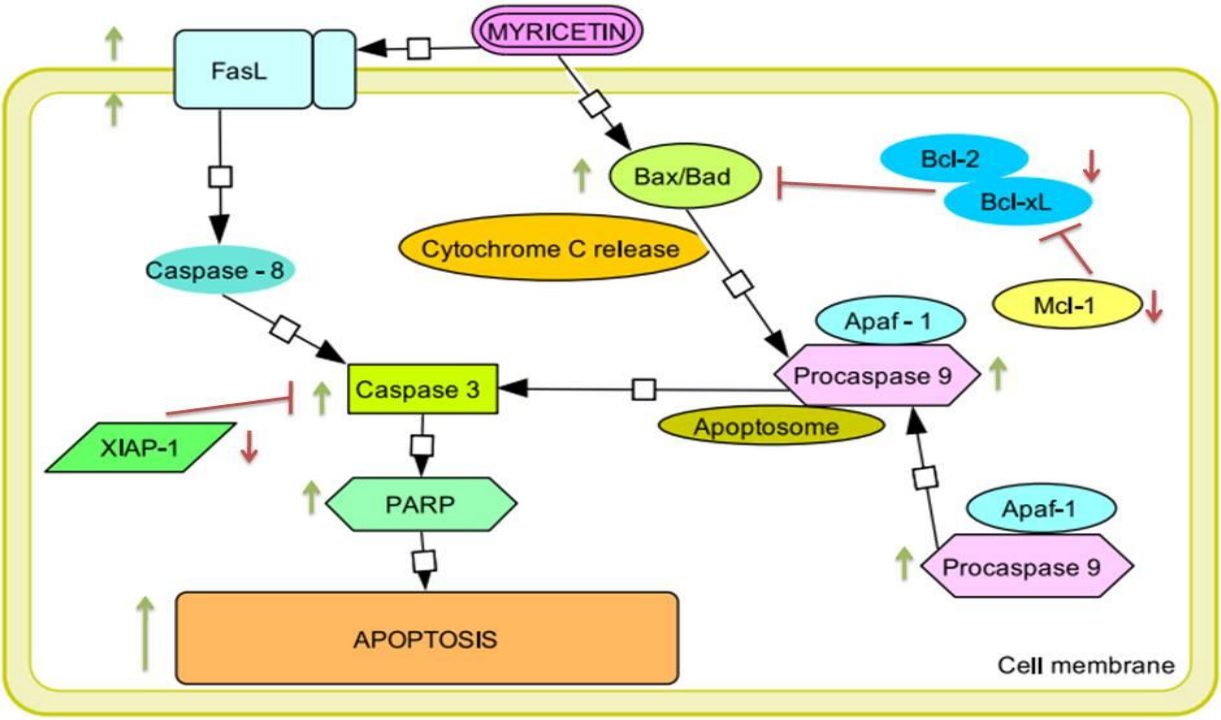

Fig. 6: Apoptosis-inducing effects of myricetin in breast cancer therapy.

This leads to the activation of caspase-9 through the formation of the apoptosome complex, which involves cytoplasmic cytochrome c and Apaf-1 and subsequent cleaves the protein caspase-3 into its active form[30,31]. A crucial member of the caspase family is caspase-3, a collection of cysteine proteases that facilitates the fragmentation of PARP to cause apoptosis. Apoptotic signals from the intrinsic and extrinsic pathways can activate apoptosis[32] (Fig. 6).

Conclusion

This study suggests that myricetin adheres to Lipinski's rule of 5 and exhibits favourable ADMET properties. Myricetin exhibited a higher binding affinity towards Catalase, CDK4 and Bcl-2, with binding energies of −9.4, −8.8 and −7.9 kcal/mol respectively. Myricetin showed more hydrogen bond interactions with CDK4, Caspase 9 and Bak. Myricetin induces apoptosis by both extrinsic and intrinsic pathways. Therefore, myricetin could be further investigated as a potential chemotherapeutic drug for the treatment of breast cancer.

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