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IN-SILICO STUDY: MYRICETIN FROM THE STEM BARK OF *SYZYGIUM CUMINI* INHIBITS THE GROWTH OF NON-SMALL CELL LUNG CANCER CELLS THROUGH THE EGFR PATHWAY

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Keywords:

Epidermal growth factor receptor (EGFR), Small cell lung cancer (SCLC), Non-Small cell lung cancer (NSCLC), Protein data bank (PDB), Myricetin, Docking

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ABSTRACT: Around the world, cancer frequently leads to death. Lung cancer is the primary cause of cancer-related deaths globally. Through *in-silico* analysis, this study sought to assess the anticancer effectiveness of myricetin on human lung cancer cells. The study's goal is to assess how well myricetin adheres to the Lipinski rule of 5. To evaluate the ADMET properties (Absorption, Distribution, Metabolism, Excretion, Toxicity) for myricetin. To predict the target-ligand interaction. The results from these studies supported that the myricetin follows the Lipinski rule of 5 and ADMET properties. Myricetin has a better H bond interaction. The results of the *in-silico* analysis used in this work serve as encouraging evidence for the prediction of the mechanism by which myricetin acts to cause apoptosis via the EGFR pathway. The results from the molecular docking study suggested that myricetin inhibited critical tumorigenic effects through apoptosis. Thus myricetin could be further explored as a promising chemotherapeutic agent in lung cancer treatment.

INTRODUCTION: Of all malignant tumours, lung cancer has the highest rates of morbidity and mortality in the globe [1]. In 2020, lung cancer accounted for 18% of all cancer-related deaths and 11.4% of all new cancer cases. In 2025, it's anticipated that there will be a substantial increase in cases, reaching 81,219 cases among men and 30,109 cases among women. In India, there are grave concerns about lung cancer's rising prevalence and slow diagnosis [2].

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Lung adenocarcinoma, the most typical type of lung cancer, affects both smokers and nonsmokers as well as persons under 45 years old. Adenocarcinoma accounts for roughly 30% and 40%, respectively, of primary lung cancers in smokers who are men and women. These numbers among non-smokers are about 60% for males and 80% for women [3].

Smoking, using alcohol, and eating betel nuts are the three main lifestyle factors linked to an increased risk of cancer. Smoking has been linked to an increased risk of developing lung, hepatoma cellular carcinoma, oral cavity, neural progenitor cells, oesophageal, urinary bladder, and cervical cancer in a dose-response relationship [4]. It has been demonstrated that lung cancer is connected with a diminished capacity to detoxify particular types of

cancer-causing chemicals or tobacco carcinogens, even though it is uncommon for lung cancer to result from genetic abnormalities of oncogenes or tumour suppressor genes [5]. The two primary types of lung cancer are small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC), with non-small cell lung cancer accounting for 80–85% of diagnoses [6].

Every kind of cancer cell develops and disperses differently. Based on histological classifications, NSCLC is typically divided into three categories: squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma [7]. Only 3-4% of cases of other, less frequent subtypes, such as bronchioloalveolar carcinoma (BAC), occur, while BAC features are present in 10-15% of adenocarcinomas. SCLC accounts for about 15–25% of cases of lung cancer with neuroendocrine morphological features [8].

Therapy for Lung Cancer: Every cancer treatment aims to kill cancerous cells while leaving healthy ones alone. The most widely used cancer therapies include chemotherapy, radiation therapy, and surgery. These therapies can be applied independently, in combination with other therapies, or both. Surgery is frequently used as the initial line of treatment for the majority of malignancies, especially solid tumours, and entails the removal of any tissue that is malignant. To confirm a biochemical diagnosis and further ascertain the size and distribution of the tumours, ultrasound and/or CD scanners are utilised as diagnostic instruments. In radiation therapy, high-energy X-rays are utilised to reduce cancer size. It is frequently used in conjunction with surgery or an alternative kind of chemotherapy as a neo-adjuvant therapy to facilitate surgery by reducing tumours. It is regarded as a local treatment because it only affects the region surrounding the cancer [9].

Chemotherapy Drugs and Treatment: Chemotherapy, which employs drugs or chemicals to kill cancer cells, has a wide range of effects. Anticancer drugs currently come in a variety of distinct categories based on their mechanisms of action, including the following:: a) anti-metabolites that substitute for the normal RNA and DNA building blocks b) mitotic inhibitors that prevent mitosis and cell division; c) alkylating agents that damage DNA; d) antibiotics that interfere with DNA replication enzymes; e) topoisomerase inhibitors that prevent topoisomerase I or II from unwinding DNA during replication and transcription; and f) corticosteroids that are used to treat cancer and to relieve the side effects from other drugs [10].

Lung cancer is treated with bleomycin, doxorubicin, etoposide (VP-16), cisplatin, and methotrexate, among other anticancer drugs. Given that these drugs have been demonstrated to increase the expression of the Fas ligand (FasL) on the surface of cells that express the Fas receptor, it is possible that Fas cross-linking is the mechanism by which these drugs cause apoptosis [11].

Natural compounds have long been known to contain anticancer agents [12]. Natural products and their derivatives make up around 63% of the process in the development of innovative medications [13]. Cancer has long been treated using traditional Chinese medicine (TCM) in China and other nations [12]. Herbal medicines frequently cost minimal money, are easily accessible, and show little harmful consequences when used in therapeutic settings [14].

Myricetin, a flavonoid is frequently discovered in tea, wines, berries, fruits, and medicinal herbs [15]. A wide variety of plant-based foods and beverages contain flavonoids, which can be broadly categorised as flavonols, flavones, anthocyanins, catechins, flavanols, and isoflavones [16]. Some of the biological actions of flavonoids that may help prevent cancer include free radical scavenging, antimutagenic and antiproliferative properties, modulation of cell signalling and cell cycle, and suppression of angiogenesis [17]. According to certain studies, myricetin has anti-inflammatory, anti-oxidative, and anti-proliferative properties [18]. Myricetin inhibits the proliferation of cells that are cancerous of the lung, breast, thyroid, liver, leukaemia and prostate, according to earlier research [19]. In this study, we have analysed the ability of myricetin from the stem bark of *Syzygium cumini* to induce apoptosis through the EGFR pathway by an *in-silico* approach.

Methodology:

Ligand Preparation: The 2D structure of ligand Myricetin was generated using ACD/ Labs

Chemsketch. Their pharmacokinetic properties like the LIPINSKI rule of 5 and ADMET properties were analysed using the SwissADME tool.

Determination of Lipinski Rule: Another crucial element of computer-based drug synthesis is the Lipinski rule. When a chemical interacts with the lipid bilayers in the body, the "rule of five" is used to estimate how much of it will be absorbed or how permeable it will be. When evaluating these features, Lipinski's "rule of five" states that a substance satisfies all five of the following conditions to meet the drug-like criteria. 500 g/mol or less is the minimum molecular weight. The octanol/water partition coefficient is less than 5 as determined by (log P 5). Less than five hydrogen bond donors are present. There are just 10 hydrogen bond acceptors, mostly N and O atoms.

Determination of the Data of ADMET: An extensive investigation of the ADMET projection is regarded to be necessary for the development and discovery of novel medicinal drugs. The ADMET qualities are the most useful for measuring the properties and *in-silico* pharmacokinetic parameters of the predicted drugs. It enables rapid and provisional assessment of ADMET properties before a complete *in-vitro* analysis of the compounds. This is advantageous because recently created substances could be harmful to health. To project ADMET data, the online web tool SwissADME has been used. The chemical properties and molecular structures are used to calculate and measure these ADMET values.

Protein Preparation: The three-dimensional structure of EGFR (PDB ID: 4ZAU_A), KRAS (PDB ID: 4OBE_A), RAF (PDB ID:3OMV_A), MEK (PDB ID:3W8Q_A), ERK (PDB ID:2ERK _A), were obtained from Protein Data Bank (PDB). The receptors were prepared by using the BIOVIA Discovery Studio Visualizer 2021 Client software.

Molecular Docking: PyRx software was used to create the *in-silico* investigations, while the BIOVIA Discovery Studio Visualizer 2021 Client software was used to visualise the outcomes.

RESULTS AND DISCUSSION:

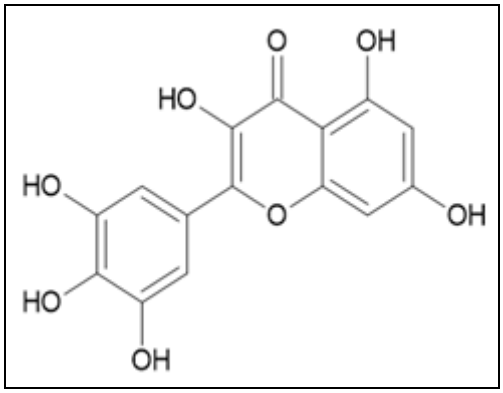


FIG. 1: 2D STRUCTURE OF MYRICETIN

TABLE 1: LIPINSKI RULE OF 5 -MYRICETIN WAS OBTAINED THROUGH SWISSADME

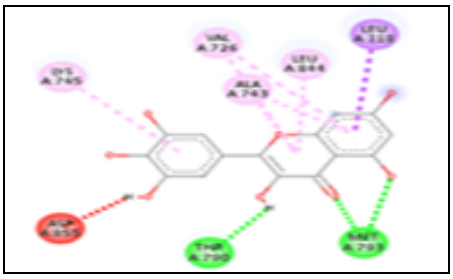
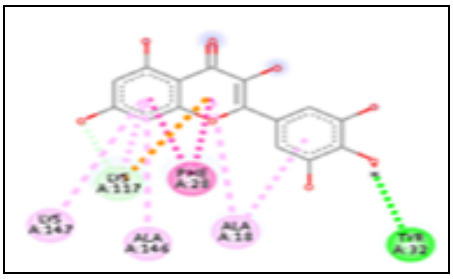
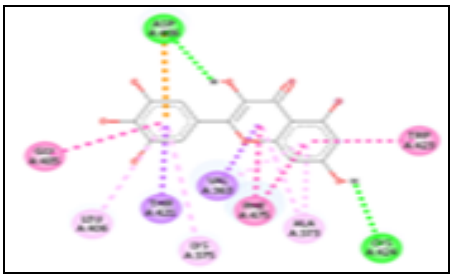
Ligand	Mol. Weight	LogP	# Rotatble bonds	# Acceptors	# Donors	Surface area
Myricetin	318.237	1.6936	1	8	6	126.902

TABLE 2: ADMET PROPERTIES OF MYRICETIN WAS OBTAINED THROUGH SWISSADME

ADMET Properties	Myricetin
Internal absorption (Human) (% Absorbed)	65.93
BBB permeability (log BB)	-1.493
CYP2D6 substrate	No
CYP2D6 inhibitor	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

TABLE 3: DEPICTING THE BINDING AFFINITY AND H BOND INTERACTION WHEN THE PROTEINS WERE DOCKED WITH LIGANDS

Target Type	Proteins	Binding affinity (kcal/mol)	H bond interaction with bond length	Other interactions with bond length
			Myricetin	
Lung cancer	EGFR	-8.1	THR A:790 (2.21Å) MET A:793(1.83Å,2.86Å)	Pi-Sigma interaction: LEU A:718 (3.91Å) Pi-Alkyl interactions: LYS A:745 (5.17Å) VAL A:726 (4.95Å,5.09Å) ALA A:743 (3.93Å,5.22Å) LEU A:844 (4.74Å) Unfavorable Donor-Donor interaction: ASP A:855 (1.71Å)
	KRAS	-8.7	TYR A:32 (2.57Å)	Pi-Alkyl interactions: LYS A:147 (5.27Å) ALA A:146 (5.07Å) ALA A:18 (4.11Å,4.94Å) Carbon Hydrogen bond interaction: LYS A:117 (2.72Å) Pi-Pi T-shaped interaction: PHE A:28 (4.88Å,5.03Å)
	RAF	-8.0	ASP A:486 (2.54Å) CYS A:424 (2.86Å)	Pi-Sigma interactions: THR A:421 (3.71Å) VAL A:363 (3.99Å) Pi-Alkyl interaction: LEU A:406 (5.27Å) LYS A:375 (5.39Å) ALA A:373 (4.04Å,4.41Å) Pi-Pi Stacked interactions: GLY A:485 (4.98Å) PHE A:475 (4.03Å,4.04Å)
	MEK	-9.5	LYS A:97 (2.77Å)	Pi-Pi Stacked interaction: TRP A:423 (5.56Å) Pi-Alkyl interactions: VAL A:82 (4.74Å,4.87Å) LEU A:74 (4.80Å) ALA A:95 (4.43Å) Pi-Sigma interaction: LEU A:197 (3.48Å) Pi-Sulfur interaction: CYS A:207 (4.01Å) MET A:143 (5.95Å)
	ERK	-7.5	ASP A:86 (2.59Å) PHE A:352 (1.86Å) ASP A:18 (2.62Å)	Pi-Alkyl interaction: PRO A:91(4.91Å,5.05Å) PRO A:354 (4.33Å) ALA A:90 (4.59Å) Unfavorable Acceptor-Acceptor interaction: GLN A:353 (2.97Å) Pi-Sigma interaction: ILE A:88 (3.89Å) Amide-Pi Stacked interaction: ARG A:89 (4.22Å ,4.25Å)

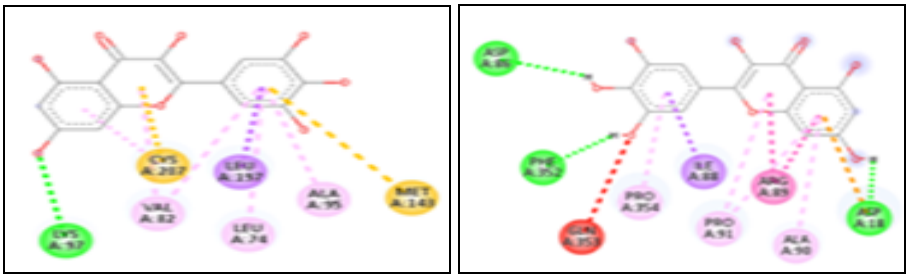


FIG. 2: MOLECULAR DOCKING ANALYSIS OF MYRICETIN AGAINST EGFR, KRAS, RAF, MEK AND ERK

Epidermal Growth Factor Receptor (EGFR) is a transmembrane tyrosine kinase receptor and a member of the ErbB family of receptors. Members of the ErbB family include EGFR (ErbB1), ERBB2 (HER2/neu), ERBB3 (HER3), and ERBB4 (HER4) [20]. The cytoplasmic domain of EGFR, which has the tyrosine kinase region and tyrosine autophosphorylation sites, the transmembrane domain, and the extracellular ligand-binding domain all contribute to its structure. According to earlier research, EGFR overexpression was found in 60% of NSCLC and was linked to a poor prognosis [21].

The EGFR mutation is commonly acknowledged as the primary oncogenic-driven mutation in certain NSCLCs because of the well-studied activating mutation in the EGFR kinase domain [22]. Exons 18–24, which are proximal to the enzyme's ATP-binding pocket, encode the EGFR kinase domain. The bulk of EGFR kinase domain mutations are found in exons 18–21. These mutations boost the EGFR's kinase activity, which in turn causes signal pathways that encourage NSCLC cell growth to become overactive. Phosphatidylinositol 3-kinase (PI3K)/Akt/mTOR, interleukin 6 (IL-6)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3), and mitogen-activated protein kinases (MAPK)/extracellular signal-regulated kinases (ERK) are the three primary downstream signalling pathways that EGFR activates [23].

The rat sarcoma virus (Ras) gene family includes the Kirsten rat sarcoma viral oncogene homolog (KRAS) gene. About 30% of lung adenocarcinomas (34% in smokers and 6% in non-smokers) have KRAS mutations. They typically occur at codons 12 or 13 in lung adenocarcinoma [24]. Ras/Raf/MEK/ERK pathway activation increases cell growth and prevents apoptosis [25] and cell senescence [26].

All multicellular organisms rely on the process known as programmed cell death (PCD) or apoptosis to control cell division, keep tissues in a state of homeostasis, and get rid of harmful or undesired cells. Defects in physiological apoptosis may have a role in several human diseases, including cancer. The discovery of apoptosis mechanisms, its effector proteins, and the genes encoding apoptosis has enabled the discovery and development of novel medications that can decrease the apoptotic threshold or increase apoptosis susceptibility in cancer cells [27].

Targeting the EGFR Pathway: In this study, natural compound myricetin was screened with the active site of EGFR, KRAS, RAF, MEK and ERK. Myricetin was previously recognised as an anticancer substance. The results show that Myricetin obeys Lipinski's rule of 5 and ADMET properties.

Myricetin interacted with LEU A:718, LYS A:745, VAL A:726, ALA A:743, LEU A:844 and ASP A:855 residues of EGFR. THR A:790 and MET A:793 residues of EGFR H-bonded with myricetin. Myricetin interacted with LYS A:147, ALA A:146, ALA A:18, LYS A:117 and PHE A:28 residues of KRAS. TYR A:32 residues of KRAS H-bonded with myricetin. Myricetin interacted with THR A:421, VAL A:363, LEU A:406, LYS A:375, ALA A:373, GLY A:485, PHE A:475 and TRP A:423 residues of RAF. ASP A:486 and CYS A:424 residues of RAF H-bonded with myricetin. Myricetin interacted with VAL A:82, LEU A:74, ALA A:95, LEU A:197, CYS A:207 and MET A:143 residues of MEK. LYS A:97 residues of MEK H-bonded with myricetin. Myricetin interacted with PRO A:91, PRO A:354, ALA A:90, GLN A:353, ILE A:88 and ARG A:89 residues of ERK. ASP A:86, PHE A:352 and ASP A:18 residues of ERK H-bonded with myricetin.

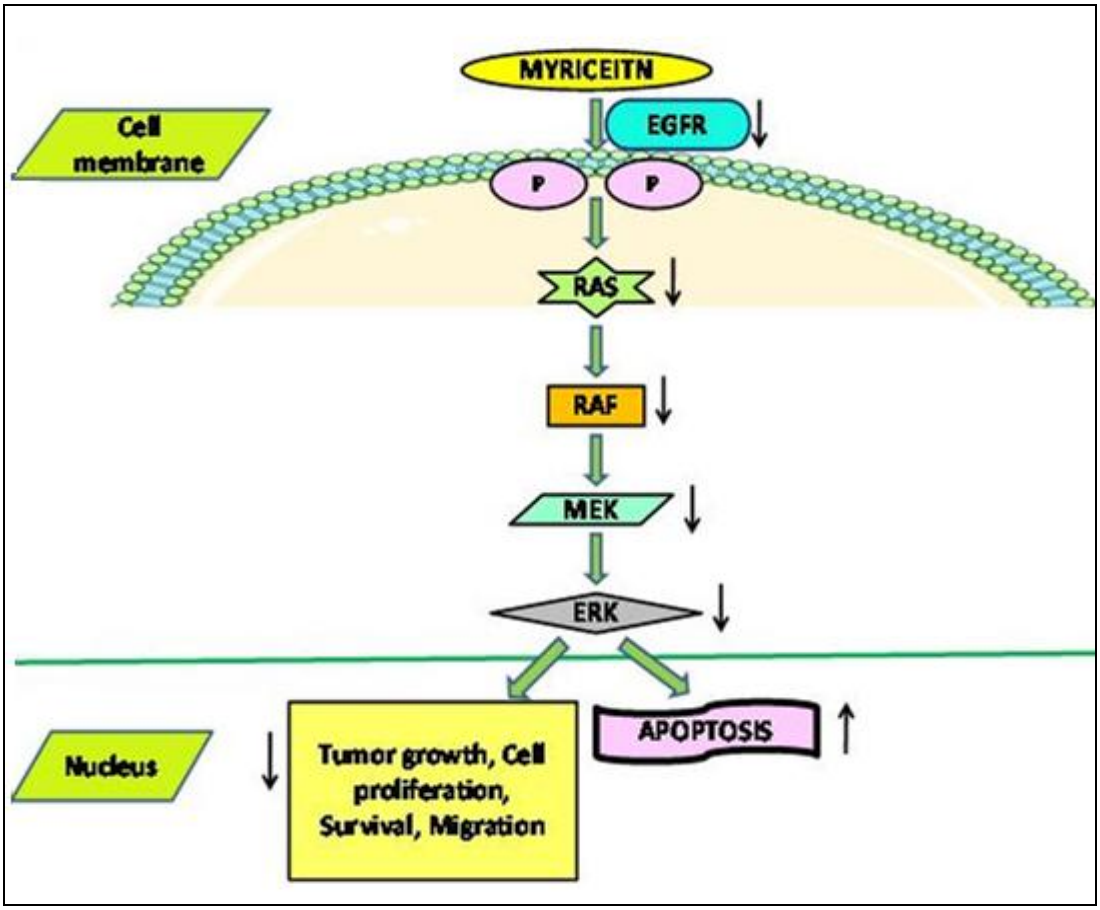


FIG. 3: SCHEMATIC REPRESENTATION OF MYRICETIN IN THE TREATMENT OF LUNG CANCER THROUGH EGFR PATHWAY

Myricetin, a naturally occurring substance, binds to the EGFR (tyrosine kinase receptor) and prevents it from being expressed. Myricetin binding causes phosphorylation, which activates RAS. Once Ras is turned on, the downstream RAF is attracted to the cell membrane and activated. After RAF is phosphorylated, MEK phosphorylates and overactivates the extracellular regulatory protein to cause ERK1/2 to become overactive. This causes an accumulation of intracellular oxygen free radicals that sets off the DNA damage response and cell senescence [28]. Finally, myricetin inhibits tumour growth, cell proliferation, survival and migration but induces the apoptosis through EGFR pathway.

CONCLUSION: In conclusion, myricetin shows better Hydrogen bond interaction with the EGFR, RAS, RAF, MEK and ERK proteins. Myricetin obeys Lipinski's rule of five and it has a better binding affinity. It can inhibit lung cancer growth by inducing programmed cell death through the EGFR pathway. This compound can be taken for further studies.

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CONFLICTS OF INTEREST: The authors have no conflicts of interest.

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