Scholars Academic Journal of Pharmacy
Abbreviated Key Title: Sch Acad J Pharm
ISSN 2347-9531 (Print) | ISSN 2320-4206 (Online)
Journal homepage: http://saspublishers.com

OPEN ACCESS
Pharmacy

Investigation of Flavonoids Derivatives as PLK-1 Targeted Inhibitor and their Potential Against Lung Tumorigenesis: *In-silico* Molecular Docking

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DOI: https://doi.org/10.36347/sajp.2025.v14i03.003 | **Received:** 07.02.2025 | **Accepted:** 11.03.2025 | **Published:** 15.03.2025

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Abstract | **Original Research Article**

***Background*:** Lung cancer continues to be the primary cause of cancer-related deaths among both men and women in the United States and globally. Approximately 90% of lung cancer cases are attributable to smoking and the utilization of tobacco products. Nonetheless, additional factors including radon gas, asbestos, air pollution exposure, and chronic infections may contribute to lung carcinogenesis. Recent studies have demonstrated that natural bioactive compounds called polyphenols, derived from plants, possess anticancer properties, effectively eliminating abnormal or malignant cells while preserving normal cells. Flavonoids exhibit antioxidant, antiviral, anticancer, and anti-inflammatory properties. These inexpensive pharmaceutical compounds exhibit considerable biological activities and are advantageous for various chronic conditions, including cancer. ***Purpose*:** This study aimed to assess the anti- lung tumorigenesis activity of *natural* flavonoid through *in-silico* molecular docking. ***Method*:** Polo like kinase 1[PLK 1] was chosen as the target proteins in the current investigation. The bond was found using the Auto Dock software using a grid-based docking method. Compounds' 2D structures were generated, converted to 3D, and subsequently energetically lowered up to an arms gradient of 0.01 using the Merck Molecular Force Field (MMFF). ***Result*:** Flavonoids (Fisetin, genistein & naringenin) found to be effective anti-lung cancer component and effectively binds to be target protein *PLK-1* with binding energy-7.8, -6.91, -7.17 kcal/mol for *fisetin, genistein and naringenin* respectively and showed potent inhibitory action on PKL 1. ***Conclusion*:** The results of the current investigation demonstrated that the chosen lead molecules (fisetin, genistein, and naringenin) had significant inhibitory effects on the target *PLK-1 enzyme*, consequently disrupting mitosis and genomic integrity in cancer cells. The molecular docking analysis demonstrated significant binding energy.

Keywords: *Flavonoids*, molecular docking, *PLK-1 enzyme*, fisetin, genistein, and naringenin.

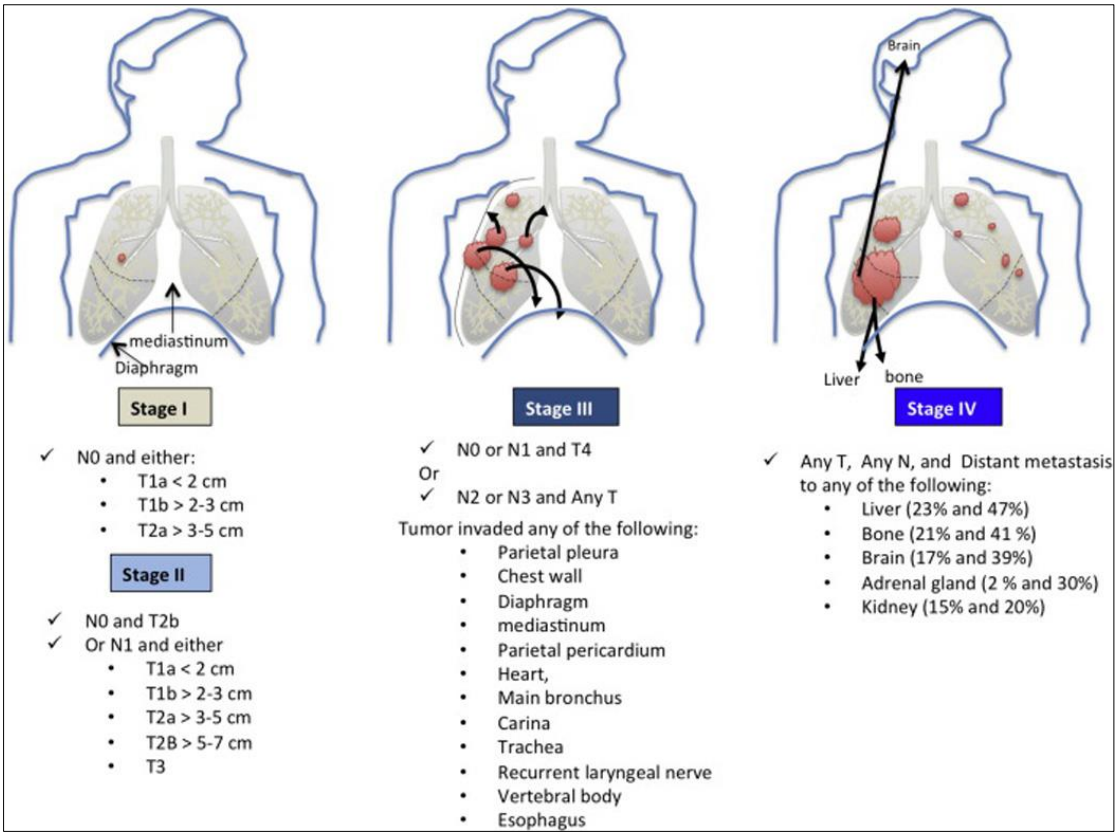
INTRODUCTION

Lung cancer continues to be among the most commonly diagnosed cancers globally. Despite recent advancements in treatment modalities, the condition can be catastrophic for patients, their families, and doctors striving to deliver optimal clinical care. Contributing factors include the unfavourable prognosis and outcomes most patients encounter post-diagnosis, the numerous comorbidities like heart failure or advanced chronic obstructive pulmonary disease (COPD) that complicate disease management, and the tendency for diagnosis to occur relatively late in the disease progression [1-5].

Flavonoids are polyphenolic chemicals exhibiting potential anti-cancer activities, characterized by minimal toxicity and high efficacy. Recent study suggests that a potential mechanism of flavonoids may involve the inhibition of receptor tyrosine kinases (RTKs). Receptor tyrosine kinases (RTKs) are critical cell surface proteins frequently dysregulated in malignancies, especially lung cancer, the primary cause of cancer-related mortality. The identified prevalent RTK abnormalities in lung cancer, along with the mechanisms by which certain flavonoids interact with these RTKs and their associated downstream signaling cascades, including MAPK, PI3K/Akt, and JAK/STAT. Subsequently, we summarized combination therapies utilizing flavonoids and receptor tyrosine kinase inhibitors (RTKIs) in lung cancer models. The research indicates that RTK inhibition may be a crucial mechanism of flavonoids. Secondly, the combination of flavonoids with RTKIs demonstrated superior inhibition of tumor growth and metastasis relative to singular therapies. The potential interaction between RTKIs and

flavonoids may significantly influence lung cancer therapy options. [6].

Flavonoids have dual action regarding ROS homeostasis—they act as antioxidants under normal conditions and are potent pro-oxidants in cancer cells triggering the apoptotic pathways and downregulating pro-inflammatory signaling pathways [7].



Stages of Lung cancer

Fisetin [8-9]

Synonym	Fisetin 5-Desoxyquercetin 2-(3,4-Dihydroxyphenyl)-3,7-dihydroxy-4H-chromen-4-one 3,3',4',7-Tetrahydroxyflavone
Molecular weight	286.24g/mol
Mol. Formula	$C_{15}H_{10}O_6$
Pharmacological Potential	antioxidant anti-inflammatory antiangiogenic anticancer activities

Genistein [10-11]

Synonym	Genistein Prunetol 4',5,7-Trihydroxyisoflavone Genisterin
Molecular weight	270.24g/mol
Mol. Formula	$C_{15}H_{10}O_5$
Pharmacological Potential	antioxidant antineoplastic agent, a tyrosine kinase inhibitor & DNA topoisomerase (ATP-hydrolysing)] inhibitor, apoptosis induction Anti-inflammatory

Naringenin [12-13]

Synonym	Naringenin (S)-Naringenin salipurpol Naringenine
Molecular weight	272.25 g/mol
Mol. Formula	$C_{15}H_{12}O_5$
Pharmacological Potential	anti-inflammatory anti-infective Antioxidant Anticancer Antimutagenic Antifibrotic Neuroprotective Antidiabetic DNA protection Hypolipidaemic Antidepressant Antihypertension Antiproliferative antispasmodic and choleretic Antiatherosclerotic expectorant effects

Experimental work

Selection of Lead molecules

Plant-derived products or their purified bioactive compounds have confirmed health-promoting effects as well as cancer-preventive effects. Flavonoids have been shown to possess a wide variety of anticancer effects: they modulate reactive oxygen species (ROS)-scavenging enzyme activities, participate in arresting the cell cycle, induce apoptosis, autophagy, and suppress cancer cell proliferation and invasiveness. Flavonoids have dual action regarding ROS homeostasis—they act as antioxidants under normal conditions and are potent pro-oxidants in cancer cells triggering the apoptotic pathways and downregulating pro-inflammatory signaling pathways [14]. Fisetin is one such naturally derived flavone that offers numerous pharmacological benefits, i.e., antioxidant, anti-inflammatory, antiangiogenic, and anticancer properties. It inhibits the rapid growth, invasiveness, and metastasis of tumors by hindering the multiplication of cancer cells, and prompts apoptosis by avoiding cell division related to actuation of caspase-9 and caspase-8 [15-16]. Fisetin plays a role in disease management through the modulation of various biological activities. Earlier studies have demonstrated fisetin's role in anti-oxidation, anti-inflammation and the attenuation of diabetic cardiomyopathy via the improvement of hyperglycemia/hyperlipidemia-mediated oxidative stress, inflammation as well as apoptosis. In addition, previous studies have described fisetin's role in different types of cancer. The therapeutic implications of fisetin in different diseases have been documented through in vitro and in vivo studies. The anti-cancer potential of fisetin has been described through the modulation of various cell signaling pathways, including inflammation, apoptosis, angiogenesis, growth factor, transcription factor and other pathways. Fisetin has been established to display anticancer properties through modulating cell signaling molecules. Moreover, fisetin and anti-cancer drugs have been used as combination therapies, and the results have shown anticancer effects with a higher efficacy and a reduction in the adverse effects of anticancer drugs [17]. Genistein has demonstrated a plethora of biomedical effects, such as anti-oxidation, anti-proliferation, and tumoricidal activities. More importantly, in vivo, in vitro, as well as in silico research into its anti-cancer properties have pointed towards a pivotal role played by genistein as an anti-tumoricidal molecule in varied types of cancer [18]. Numerous studies have deciphered naringenin's antioxidant and anticancer potential in human and animal studies. Naringenin (NGE) potentially suppresses cancer progression, thereby improving the health of cancer patients. The pleiotropic anticancer properties of naringenin include inhibition of the synthesis of growth factors and cytokines, inhibition of the cell cycle, and modification of several cellular signaling pathways. As an herbal remedy, naringenin has significant pharmacological properties, such as anti-inflammatory, antioxidant, neuroprotective, hepatoprotective, and anti-cancer activities [19].

Selection of target protein

Polo-like kinase 1 (PLK1) is an essential protein in communicating cell-cycle progression and DNA damage. Overexpression of PLK1 has been validated as a marker for poor prognosis in many cancers. PLK1 knockdown decreases the survival of cancer cells. PLK1 is therefore an attractive target for anticancer treatments. Several inhibitors have been developed, and some have been clinically tested to show additive effects with conventional therapies. Upstream regulation of PLK1 involves multiple interactions of

proteins such as FoxM1, E2F and p21. Other cancer-related proteins such as pRB and p53 also indirectly influence PLK1 expression. With the high mutation rates of these genes seen in cancers, they may be associated with PLK1 deregulation. This raises the question of whether PLK1 overexpression is a cause or a consequence of oncogenesis [20]. Polo-like kinase 1 (PLK1) is overexpressed near ubiquitously across all cancer types and dysregulation of this enzyme is closely tied to increased chromosomal instability and tumor heterogeneity. PLK1 is a mitotic kinase with a critical role in maintaining chromosomal integrity through its function in processes ranging from the mitotic checkpoint, centrosome biogenesis, bipolar spindle formation, chromosome segregation, DNA replication licensing, DNA damage repair, and cytokinesis. The relation between dysregulated PLK1 and chromosomal instability (CIN) makes it an attractive target for cancer therapy [21].

Designing of Investigation

Molecular docking is one of the computational modeling methods that has a new promise in cancer cell targeting through drug designing and discovering programs. In a simple definition, molecular docking methods are used to determine the metabolic interaction between two molecules and find the best orientation of a ligand to its molecular target with minimal free energy in the formation of a stable complex. As a comprehensive approach, this computational drug design method can be thought more cost-effective and time-saving compare to other conventional methods in cancer treatment. In addition, increasing productivity and quality in pharmaceutical research can be another advantage of this molecular modeling method. Therefore, in recent years, it can be concluded that molecular docking can be considered as one of the novel strategies at the forefront of the cancer battle via targeting cancer stem cell metabolic processes [22].

Molecular docking studies

Ligand Preparation:

2D Structure of fisetin, genistein and naringenin was drawn using ChemSketch [23], the two-dimensional structure of the prepared ligand was converted into their 3-D structures optimized with 3D geometry. The optimized structure was saved in PDB format for AutoDock compatibility. The basic structures of the prepared ligand were given below:

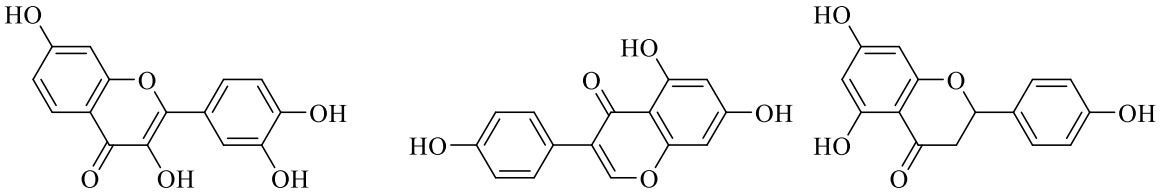


Figure 1: 2D structure of fisetin, genistein and naringenin

Preparation of the grid file

The regions of interest used by Autodock were defined by considering grid area by making a grid box around the active sites. Grid box plays a central role in process of docking as it is made to cover all the amino acids present in active sites necessary for binding other than those present in receptor. Grid box has 3 thumbwheel widgets which let us change the number of points in the x, y and z dimensions. The spacing and grid points for the considered receptor in the current study are given in table 1 [24-27].

Table 1. Grid parameters used in current docking analysis of PLK1 receptor

S. No.	Receptor	x-axis	y-axis	z-axis	Spacing	x center	y center	z center
1	PLK1	46	40	40	0.431	-48.28	11.987	16.907

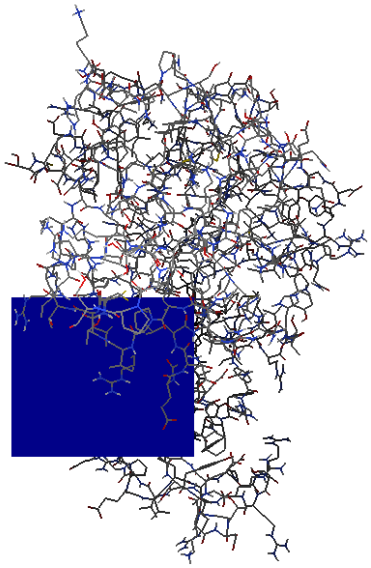


Figure 2: Grid box covering all active sites in PLK1 receptor

Preparation of the docking file

All the calculations were carried out by using Autodock 4.2 as docking tool. The visualization and other programs necessary for docking studies were performed out by means of Pymol, Chimera, DS visualizer, MMP Plus [28].

Docking Study

Crystal structure

The crystal structure of the protein consisting of PLK1 receptor is downloaded from the Protein Data Bank portal. All the primary information regarding all the receptor's structure was registered in the Protein data bank [29-30]. The complex ligand was separated by using Chimera software for all the target receptors.

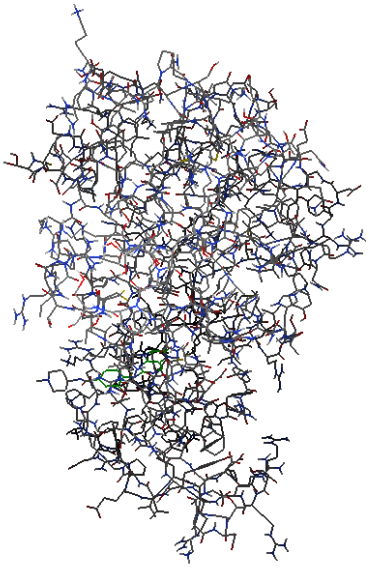


Figure 3: Crystal structure of PLK1 receptor (PDB ID-2rku)

Processing of Protein

All the downloaded receptor proteins are having only one chains, i.e. chain A, which has been selected for experimental purpose and complex ligand was removed from it. The bound ligand was separated from the macromolecular complex by using software Chimera [31-32].

Molecular Docking Simulation Studies

Docking of ligand fisetin, genistein and naringenin against PLK1 receptor was performed by

Autodock. All the bonds of each ligand were kept flexible, while no residues in receptor were made flexible [33].

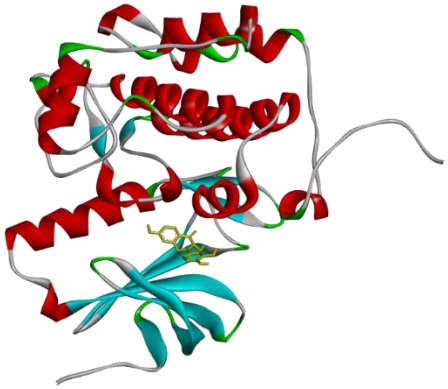


Figure 4: Binding mode of fisetin within the active site of PLK1 receptor

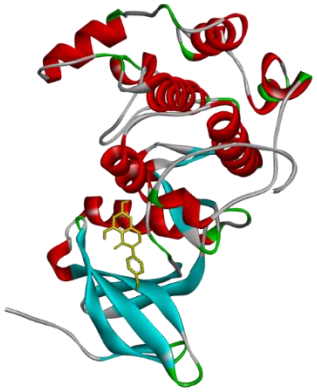


Figure 5: Binding mode of genistein within the active site of PLK1 receptor

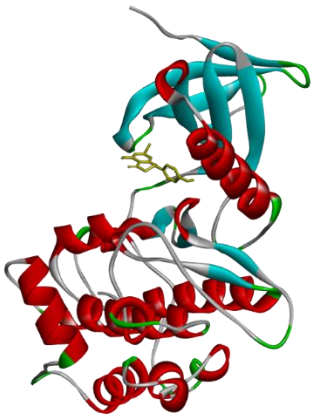


Figure 6: Binding mode of naringenin within the active site of PLK1 receptor

Toxicity & ADME-T Studies

The ligand molecules viz. fisetin, genistein and naringenin was studied by online program OSIRIS, for prediction of presence of any toxic group as well as presence of any toxic group and ADME- T properties [34].

RESULT AND DISCUSSION

Lung cancer continues to be the primary cause of cancer-related deaths among both men and women in the U.S. and globally. Approximately 90% of lung cancer cases are attributable to smoking and the utilization of tobacco products. Nonetheless, additional elements such as radon gas, asbestos, air pollution exposure, and persistent infections may play a role in lung carcinogenesis. Natural bioactive chemicals, particularly flavonoids, have demonstrated a significant impact in lung cancer prevention, with particular emphasis on the dosages employed in this research to elucidate the molecular effects and mechanisms at physiological concentrations. Phytochemicals are naturally occurring, plant-based compounds utilized in the treatment of numerous ailments, including cancer. In vitro and in vivo investigations have shown their impact on tumor proliferation, growth, and metastasis. Fisetin is a 3,3′,4′,7-tetrahydroxyflavone that provides several pharmacological advantages, including antioxidant, anti-inflammatory, antiangiogenic, and anticancer properties. Genistein is a crucial chemical constituent in the maintenance, prevention, and treatment of disorders related to metabolic syndrome and cancer. Genistein's molecular pathways influencing carcinogenesis encompass its modulation of inflammation, cell proliferation, and epigenetic alterations. The cyclooxygenase-2 (COX-2) pathway is a viable target for genistein-mediated chemoprevention. Genistein induces down-regulation of cyclin B1 (CCNB1) and targets proteins associated with G2/M checkpoints, including cell division cycle protein 2 (Cdc2) and cyclin-dependent kinase 1 (Cdk1), in many malignancies, including breast and prostate cancer. Genistein can modulate CCNB1, Cdc2, and other molecules associated with cell cycle arrest, hence inhibiting tumor cell growth [35]. Naringenin, a bioactive molecule found in several fruits, with anti-inflammatory and anticancer properties. Moreover, naringenin reduces the migration of various human cancer cell types. The impact of naringenin on lung cancer remains ambiguous. This study examined the processes by which naringenin affects the migration of A549 lung cancer cells [36]. The result of molecular docking was tabulated in table 1, showing binding energy -7.8, -6.91, -7.17 kcal/mol for *fisetin, genistein and naringenin* respectively. The binding mode showed in fig.4-6 whereas 2D &3D binding interaction was shown in fig.7-12. The IC50 showing 0.080,0.080 & 0.086 for *fisetin, genistein and naringenin* respectively. All selected lead molecules showed good interaction with selected ligand but highest binding interaction displayed by naringenin with PLK-1 enzyme having drug-likeness score 0.51almost similar to fisetin & genistein. The binding interaction of lead molecules are as follows:

Lead molecule	Vanderwaal's	CH bounding	Pi-Sigma	π -π	π-Alkyl	π-anion
Fisetin	Gly193, His105, Asp194, Leu132, Ala80, Arg134	Glu131, Cys133, Cys82	Leu130	Phen183	Leu59, Arg136, Val114	----
Genistein	Cys134, Phen183, Ser 137, ASN181, Arg 57, Gly180	Glu69, Leu59, Arg 136, Gly180	-------	-------	Arg134, Leu132	Glu140
Naringenin	Leu130, Val114, Arg134, Arg57	Glu131, Cys133, Arg136, Glu69	Leu59	Phen183	Leu132, Ala80	------

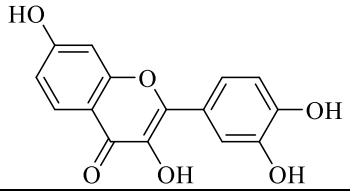
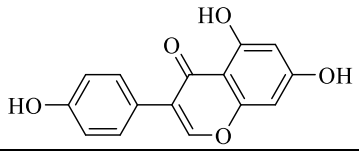
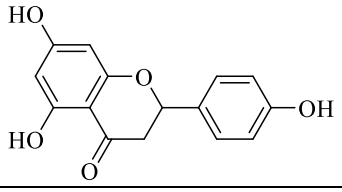
The pharmacokinetic profiling of the *fisetin, genistein and naringenin* ligand has revealed that it is having good pharmacokinetic profile associated without the presence of major toxic effects like reproductive effects, irritant effect, and tumorogenic properties, but shows the presence of some mutagenicity. The pharmacokinetic and toxicity profiling results of lead molecule was shown in fig.13-15 & table. 3-5.

CONCLUSION

Recently, interest in flavonoids has surged due to their potent antioxidant and anti-carcinogenic properties, which may confer potential benefits in cancer treatment. Flavonoids are secondary metabolites mostly produced by plants. As of now, over 6000 distinct flavonoids have been found, dispersed across a diverse array of plants. The fundamental structure of flavonoids consists of a 15-carbon framework, featuring two benzene rings linked by a 3-carbon chain. Consequently,

they are represented as C6-C3-C6 compounds. Certain flavonoid subclasses indicate a reduced risk of certain cancer types, including catechin and flavonols for prostate cancer, epicatechin for breast cancer, proanthocyanidins for lung cancer, flavones for colorectal cancer, and total flavonoids for gastric cancer. Consequently, due to the diverse origins of these flavonoids, the risk of cancer may be mitigated by incorporating them into a nutritious diet mostly composed of vegetables, fruits, whole grain cereals, legumes, seeds, nuts, chocolate, coffee, fruit juices, and tea. Further research is necessary to examine and validate the concept that a nutritious diet may reduce the prevalence of certain cancer forms. Human polo-like kinase 1 (PLK1) is crucial during mitosis and for the preservation of chromosomal integrity. PLK1 is overexpressed in human tumors and possesses prognostic significance in cancer, suggesting its role in carcinogenesis and its potential as a therapeutic target. The application of several PLK1 inhibitors has enhanced our understanding of mitotic regulation and enabled us to evaluate their efficacy in inhibiting tumor growth *in-vivo*. The results of the current investigation demonstrated that the chosen lead molecules (fisetin, genistein, and naringenin) had significant inhibitory effects on the target *PLK-1 enzyme*, consequently disrupting mitosis and genomic integrity in cancer cells. The molecular docking analysis demonstrated significant binding energy. The drug resemblance and IC50 of all compounds are relatively comparable. Therefore, a dietary supplement of certain flavonoids may be utilized for the prophylaxis and prevention of lung cancer.

Table 2: Results of docking of ligands like fisetin, genistein and naringenin against PLK1 receptor

S. No	Compound	Structure	B.E.	Ki	IC50
1	Fisetin		-7.8	13.16	0.80
2	Genistein		-6.91	11.66	0.80
3	Naringenin		-7.17	12.19	0.086

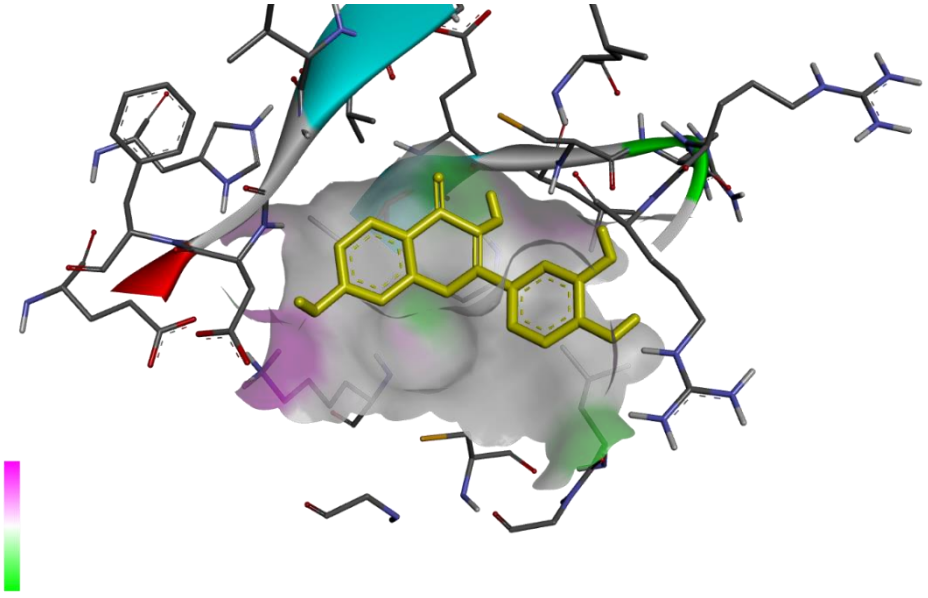


Figure 7: Three-dimensional binding mode of fisetin within the active site of PLK1 receptor

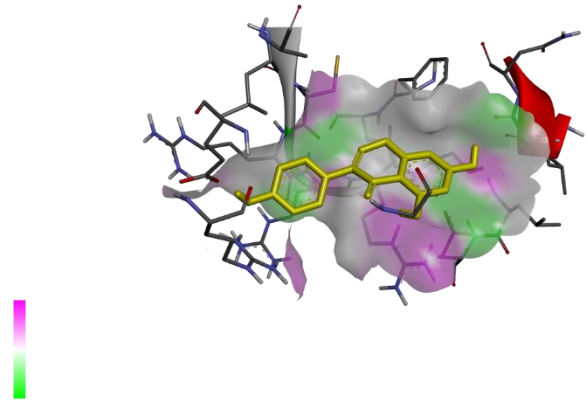


Figure 8: Three-dimensional binding mode of genistein within the active site of PLK1 receptor

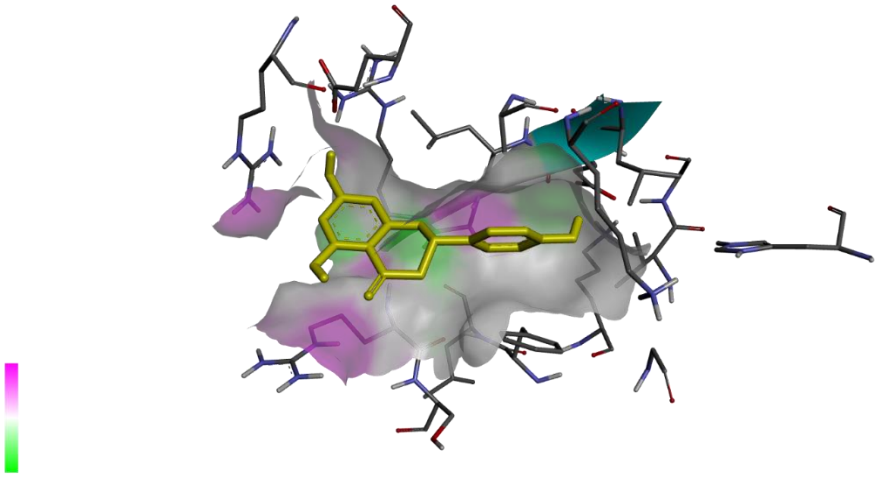


Figure 9: Three-dimensional binding mode of naringenin within the active site of PLK1 receptor

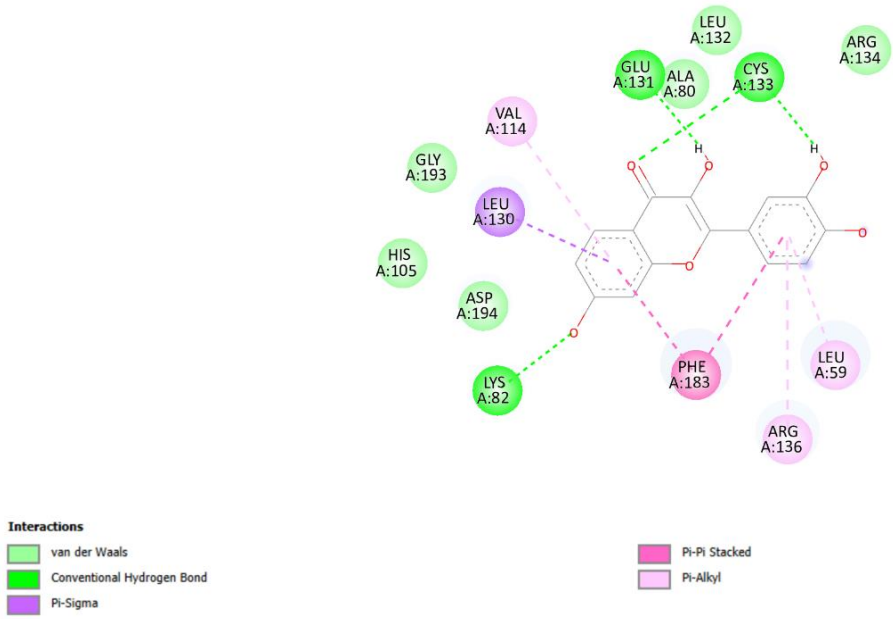


Figure 10: Two-dimensional binding mode of fisetin within the active site of PLK1 receptor

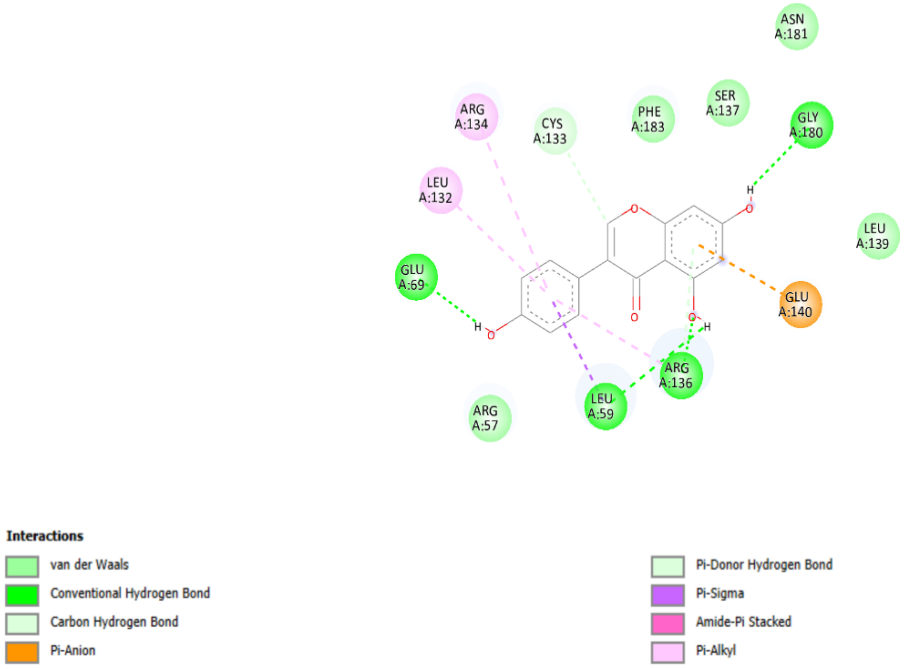


Figure 11: Two-dimensional binding mode of genistein within the active site of PLK1 receptor

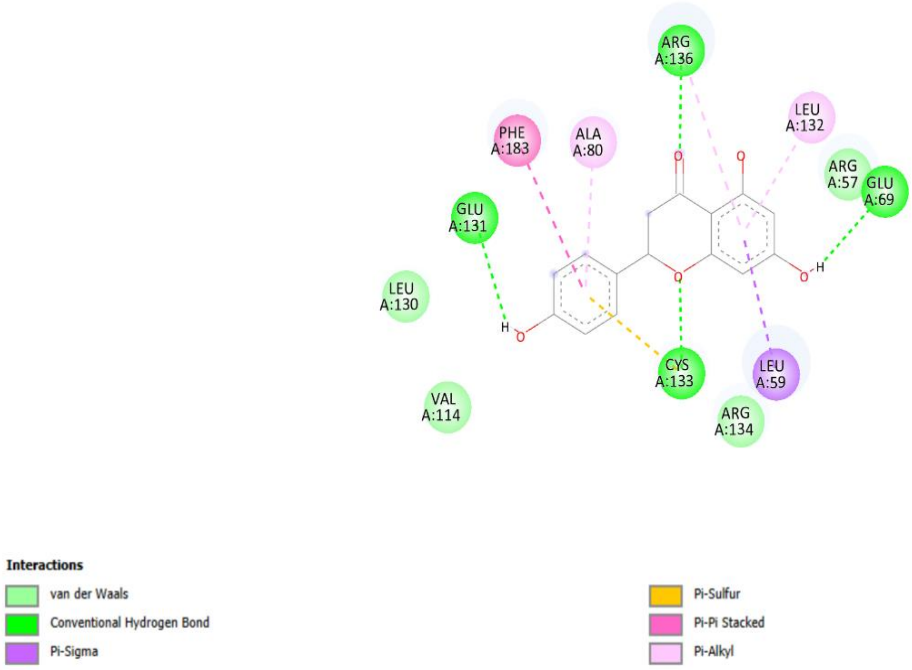


Figure 12: Two-dimensional binding mode of naringenin within the active site of PLK1 receptor

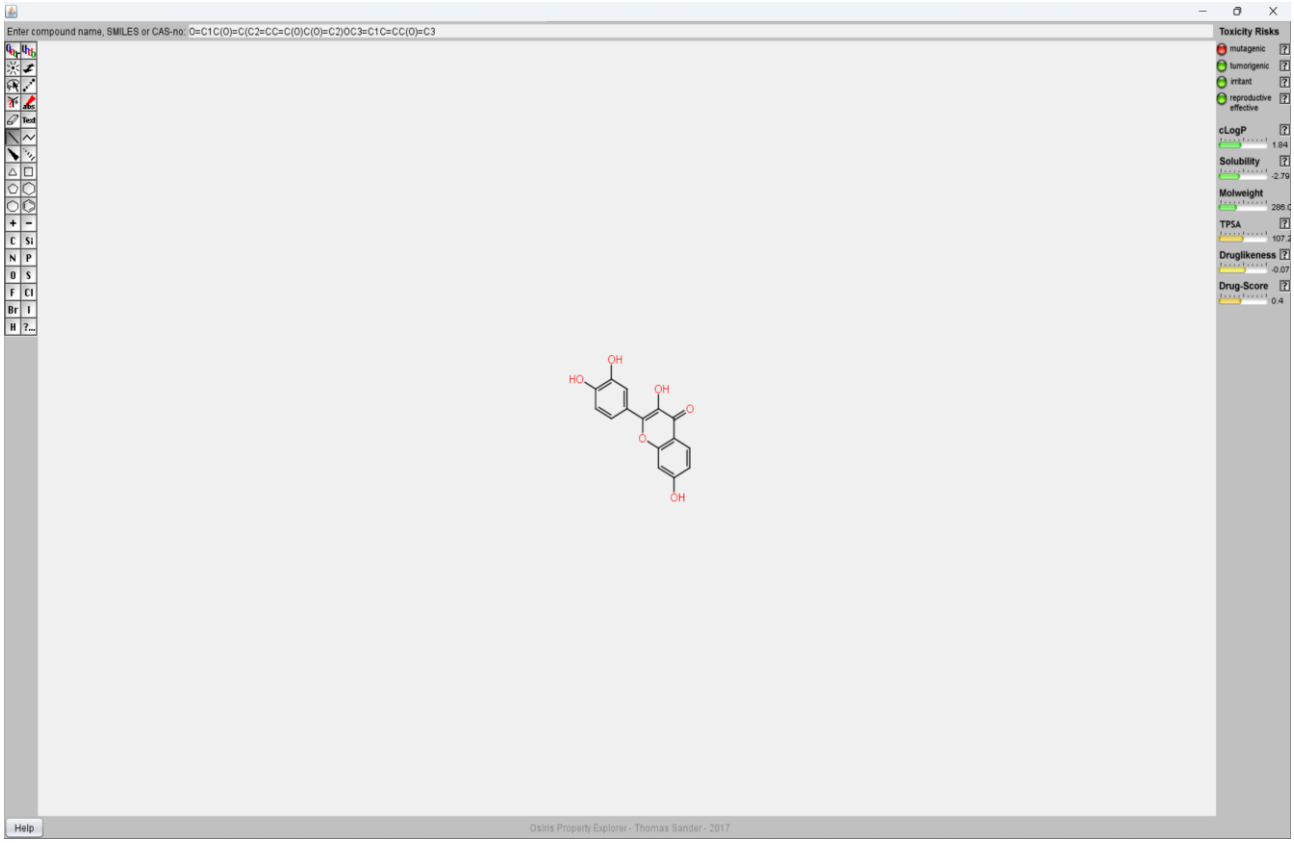


Figure 13: Pharmacokinetic and toxicity profiling of fisetin

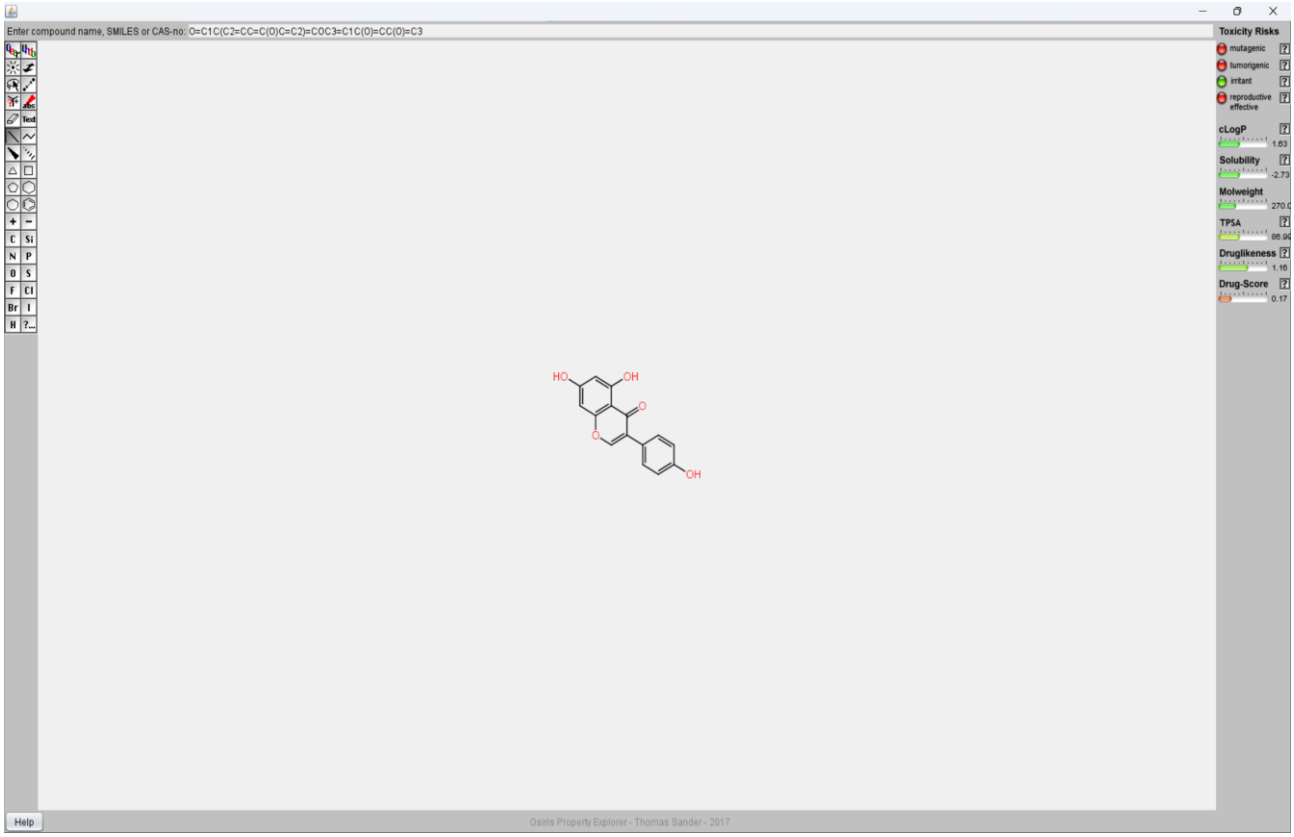


Figure 14: Pharmacokinetic and toxicity profiling of genistein

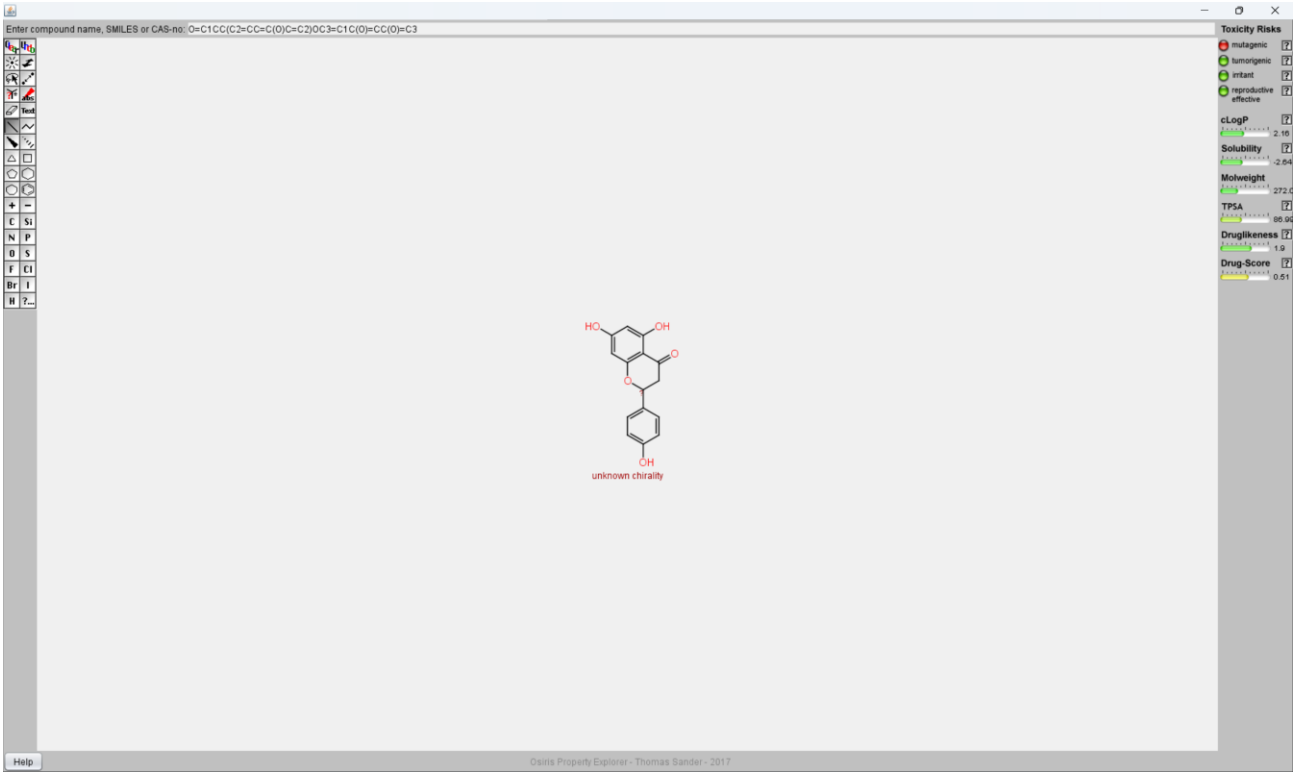


Figure 15: Pharmacokinetic and toxicity profiling of naringenin

Table 3: Pharmacokinetic Profiling of lead molecules

Compound	ADMET			
	Mutagenic	Tumorigenic	Irritant	Reproductive effectivity
Fisetin	NO	NO	Yes	NO
Genistein	NO	NO	NO	No
Naringenin	NO	NO	NO	No

Table 4: Lipinski Properties of lead molecules

Compound	*cLog P*	Solubility	Mol. wt.	TPSA	Drug likeness	Drug score
Fisetin	1.04	-2.70	286	107.2	0.03	0.4
Genistein	1.53	-2.73	270	102.1	1.16	0.17
Naringenin	2.16	-2.64	272	98.2	1	0.51

Table 5: Drug likeness of lead molecules

Compound	Lipinski rule of five	H bond donar (<5)	H bond acceptor (<10)
Fisetin	Yes	4	6
Genistein	Yes	3	5
Naringenin	Yes	3	5

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