RESEARCH PAPER

In Silico Evaluation of Kaempferol Targeting PI3K/AKT Pathway in Melanoma: A Network Pharmacology and Molecular Docking Study

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Abstract

Introduction:

Melanoma is a highly aggressive form of skin cancer, often complicated by drug resistance, toxicity, and high recurrence rates. The growing interest in plant-derived compounds have been highlighted. Kaempferol, a natural flavonoid, for its broad pharmacological activities, including anticancer potential. However, its specific role in targeting Melanoma associated pathways remains insufficiently explored.

Materials and methods:

Network Pharmacology tools including SwissTargetPrediction, GeneCards, InteractiVenn, STRING, Cytoscape, and DAVID Bioinformatics were employed to identify key targets and pathways. KEGG pathway analysis was used to determine involvement in melanoma-related signalling. Molecular docking was performed to assess the binding affinity of Kaempferol with identified targets.

Results:

Network pharmacology revealed top 10 key Melanoma related target, among these **AKT1** linked to PI3K/AKT signalling pathways. Molecular docking showed strong binding affinities of Kaempferol to the target, supporting its potential as a multitargeted anticancer agent.

Conclusion:

The integrated computational approach highlights Kaempferol's promising therapeutic potential in Melanoma management. Its ability to interact with critical targets and pathways involved in Melanoma progression supports further *in vitro* and *in vivo* investigations for its development as a novel anticancer agent.

Keywords: Melanoma, Kaempferol, Network Pharmacology, Molecular Docking

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1. Introduction

Melanoma, one of the most severe and fatal forms of skin cancer, is caused by melanocytes, the pigment-producing cells found in the basal layer of the epidermis[1]. Despite making up a small portion of all skin cancer cases, melanoma is the primary cause of skin cancer-related mortality globally because of its high recurrence rate, quick spread, and resistance to traditional treatment[2]. Genetic abnormalities, molecular dysregulation, and environmental factors all contribute to the disease's development by promoting unchecked proliferation, angiogenesis, and apoptosis inhibition[3]. Due to medication resistance, systemic toxicity, and limited long-term efficacy, melanoma continues to be a significant clinical concern despite the advancements made through immunotherapy and targeted molecular treatments[4]. These difficulties highlight the urgent need for safe and effective alternative therapy approaches[5].

1.1 Plant-Derived Compounds and the Role of Flavonoids

Natural products and bioactive chemicals produced from plants have become significant sources of novel pharmacophores for the development of anticancer drugs in recent decades[6]. Phytoconstituents often show multi-target activity, little side effects, and superior biocompatibility when compared to manufactured medications, according to extensive pharmacological studies[7]. Flavonoids, Among the different groups of secondary metabolites, a class of polyphenolic chemicals present in fruits, vegetables, and medicinal herbs has garnered a lot of attention because of their extensive therapeutic potential[8].

The anti-inflammatory, chemopreventive, and antioxidant properties of flavonoids are well known. By modifying the enzymes and signaling pathways involved in oxidative stress, inflammation, and cancer, they function as natural regulators of important cellular processes[9]. Because of its well-established anticancer, anti-inflammatory, and antioxidant qualities, kaempferol, a naturally occurring flavonol, stands out as a particularly interesting chemical within this class[10].

1.2 Melanoma: Molecular Basis and Therapeutic Challenges

The molecular pathogenesis of melanoma involves mutations in several key genes that regulate cell growth and apoptosis. Alterations in *BRAF*, *NRAS*, and *PTEN* lead to continuous activation of two major oncogenic pathways: the phosphatidylinositol-3-kinase/ serine/threonine kinase 1 (PI3K/AKT) and the mitogen-activated protein kinase (MAPK) cascades. These signalling pathways promote melanoma cell survival, proliferation, and metastasis while suppressing programmed cell death[11,12].

Although BRAF inhibitors such as vemurafenib and dabrafenib, and MEK inhibitors such as trametinib and cobimetinib, initially demonstrate clinical benefits, resistance commonly arises due to adaptive activation of compensatory signalling loops[13]. Moreover, standard chemotherapy and radiotherapy often lack tumor selectivity and cause significant systemic toxicity[14]. Consequently, there is a growing need for therapeutic agents capable of simultaneously modulating multiple pathways to overcome the redundancy and adaptability inherent to melanoma cells.

1.3 Kaempferol: Structure, Sources, and Pharmacological Potential

Kaempferol-3,4′,5,7-tetrahydroxyflavone (fig-1) is a flavonol ubiquitously present in numerous edible and medicinal plants, including *Kaempferia galanga*, *Moringa oleifera*, *Camellia sinensis*, *Allium cepa*, *Brassica oleracea*, and *Ginkgo biloba*. Its polyphenolic structure, with hydroxyl substitutions at strategic positions, contributes to its strong antioxidant capacity and versatile interaction with biomolecular targets. Pharmacological investigations have established that Kaempferol possesses antioxidant, anti-inflammatory, antimicrobial, cardioprotective, neuroprotective, and anticancer activities[15,16]. In cancer biology, it exerts a wide spectrum of effects—inducing apoptosis, arresting the cell cycle, inhibiting angiogenesis, and suppressing metastatic spread. Unlike single-target synthetic drugs, Kaempferol modulates several intracellular signalling pathways simultaneously, including PI3K/AKT, MAPK, NF-κB, and JAK/STAT, thereby counteracting the multifactorial nature of tumor development[17].

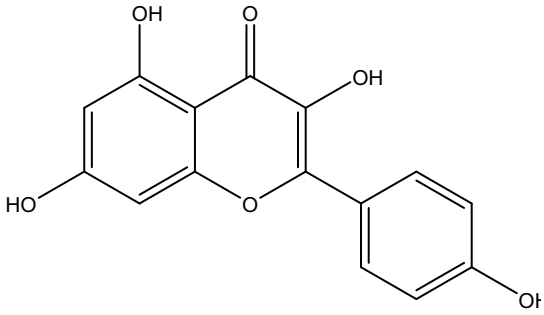


Fig 1- Structure of Kaempferol

1.4 Kaempferol and Melanoma: Mechanistic Insights

Experimental studies have demonstrated that Kaempferol inhibits melanoma cell proliferation and triggers apoptosis through multiple mechanisms. It downregulates phosphorylation of AKT and ERK, leading to the inactivation of pro-survival signals and activation of the caspase cascade responsible for apoptosis. Additionally, Kaempferol suppresses the expression of Bcl-2 and cyclin D1, resulting in mitochondrial dysfunction and arrest of the cell cycle[18].

Kaempferol also exerts anti-angiogenic effects by inhibiting vascular endothelial growth factor (VEGF) signalling, thereby reducing the vascularization necessary for tumor growth[19]. Moreover, its potent antioxidant action neutralizes reactive oxygen species (ROS), minimizing DNA damage and mutagenesis. By attenuating inflammatory mediators such as TNF-α, IL-6, and COX-2, Kaempferol further disrupts the tumor microenvironment that supports melanoma progression. Collectively, these multitarget actions make Kaempferol a strong candidate for melanoma therapy [20].

1.5 Flavonoids versus Conventional Allopathic Drugs

Conventional anticancer agents, though often effective in the short term, are frequently limited by toxicity, poor selectivity, and the emergence of drug resistance. Many allopathic drugs target a single molecular site, allowing cancer cells to develop adaptive mechanisms that bypass

inhibition. Phytoconstituents such as flavonoids, on the other hand, offer a poly-pharmacological advantage, acting on multiple signalling molecules, enzymes, and receptors concurrently. This broad spectrum of activity better reflects the complex network of interactions involved in cancer pathophysiology.

Furthermore, flavonoids like Kaempferol exhibit lower systemic toxicity and better tolerability, attributes that enhance patient safety and compliance. Their widespread occurrence in dietary plants and traditional herbal formulations also supports their long-term safety and accessibility. Thus, incorporating phytochemicals into modern oncological research bridges the disparity between modern medication discovery and conventional medicine [21-24].

1.6 Rationale and Significance of the Present Study

The global burden of melanoma continues to rise, and the limitations of current therapeutic options highlight the urgent need for novel, less toxic, and multi-targeted interventions [25]. Kaempferol, owing to its structural versatility and established pharmacological profile, emerges as a promising phytoconstituent capable of modulating key molecular pathways implicated in melanoma progression [26]. However, despite substantial evidence of its general anticancer activity, its specific molecular targets and mechanisms of action in melanoma remain poorly defined.

This study, therefore, employs a comprehensive computational method that combines molecular docking and network pharmacology to methodically explore the interactions of Kaempferol with melanoma-related targets, particularly within the PI3K/AKT and MAPK signalling pathways [27]. The study aims to identify core target proteins, elucidate the molecular basis of their interactions, and provide mechanistic insights into Kaempferol's therapeutic potential.

By unveiling the multitarget mechanisms through computational modelling, this research contributes to the growing field of computational phytopharmacology, supporting the rational design and development of flavonoid-based therapeutic agents for melanoma management. Ultimately, the findings are expected to provide a scientific foundation for further experimental validation and clinical translation of Kaempferol as a natural, safe, and effective anticancer molecule [28].

2. Materials and methods

2.1 Analysis of Network Pharmacology

2.1.1 Disease and the Selected Compound's Target Prediction

Potential molecular targets of the selected compound were predicted using the Swiss Target Prediction web server. The canonical SMILES of the compound was retrieved from the PubChem database and submitted to the Swiss Target Prediction platform, which employs both two-dimensional (2D) and three-dimensional (3D) similarity-based algorithms against a curated database of known ligand–target interactions to identify probable binding proteins [29].

To determine disease-related targets, the keyword "melanoma" was queried in the Gene Cards database with the organism restricted to *Homo sapiens* [30]. To enhance accuracy and minimize false associations, only genes with a Gene–Disease Association (GDA) score greater than 5 were considered as significant melanoma-related targets [31].

Subsequently, the Interacti Venn web tool was employed to identify overlapping targets between the compound and melanoma. The predicted targets of the compound and those associated with melanoma were imported into Set A and Set B, respectively. The intersection of both datasets represented the common target genes, which were shortlisted for downstream network analysis [32].

2.1.2 Construction of the Protein–Protein Interaction (PPI) Network

The intersecting targets obtained from the Venn diagram analysis were imported into the STRING database to construct a protein–protein interaction (PPI) network. The species was set to *Homo sapiens* to ensure human-specific protein interactions. A minimum interaction confidence score of 0.400 (medium confidence) was selected to maintain a balance between network sensitivity and specificity, while all other parameters remained at default settings. The resulting interaction network was exported in TSV format for further topological and visualization analyses [33].

2.1.3 Network Visualization

The PPI network file retrieved from STRING was visualized and analyzed using Cytoscape version 3.10.3, an open-source software platform for biological network representation. To identify the most influential targets within the network, the CytoHubba plugin was utilized. The Maximal Clique Centrality (MCC) algorithm was applied to rank the top 10 hub genes based on their connectivity and biological relevance [34]. These hub genes were considered as potential key regulators implicated in melanoma pathogenesis and were prioritized for further investigation.

2.1.4 Functional Enrichment Analysis

The top 10 hub genes identified from the Cytoscape analysis were subjected to functional annotation using the DAVID (Database for Annotation, Visualization, and Integrated Discovery) tool. The official gene symbols were uploaded as input, with *Homo sapiens* specified as the organism and "Gene List" selected as the data type. KEGG (Kyoto Encyclopedia of Genes and Genomes) pathway enrichment analysis was subsequently performed to elucidate the biological pathways and molecular mechanisms potentially

involved in melanoma [35]. The enriched pathways provided insights into the molecular interactions and signalling cascades modulated by the selected compound.

2.2 Molecular Docking Studies

2.2.1 Preparation of Ligand

The compound Kaempferol was chosen for molecular docking analysis. Its 3D structure was retrieved from the PubChem database in SDF format and converted to PDB format using Open Babel, a computational tool that enables molecular file format interconversion and structure optimization [36].

2.2.2 Preparation of Protein Structure

The 3D structures of the selected protein targets were downloaded from the RCSB Protein Data Bank (PDB). Each protein was pre-processed using BIOVIA Discovery Studio Visualizer by removing crystallographic water molecules, heteroatoms, and co-crystallized ligands. Hydrogen atoms were subsequently added to stabilize the protein structure. The refined structures were then saved in PDB format and utilized for active site determination and docking studies [37].

2.2.3 Molecular Docking

Molecular docking simulations were carried out using AutoDock Tools 1.5.7 to investigate the binding affinity between Kaempferol and the selected target protein AKT1 (PDB ID: 8UW9). The docking parameters were optimized to identify the binding poses with the lowest binding energy, representing the most stable ligand–protein complexes. Post-docking analyses were conducted in BIOVIA Discovery Studio Visualizer, where hydrogen bonding, hydrophobic interactions, and other key amino acid residues involved in the interaction were examined. These findings provided insights into the molecular basis of Kaempferol affinity and potential inhibitory activity against the AKT1 protein [37].

3. Results

3.1 Target prediction of the compound selected and disease

Potential drug targets of **Kaempferol** were identified using the **SwissTargetPrediction** database, where its canonical SMILES retrieved from **PubChem** generated **100 target genes**. To explore disease-associated genes, data from the **GeneCards** database were screened, and only those with a **GDA score above 5** were selected, yielding **1227 melanoma-related genes**. The **InteractiVenn** web tool was employed to identify overlapping targets between Kaempferol and melanoma, revealing shared genes potentially involved in its anticancer action (Fig-2).

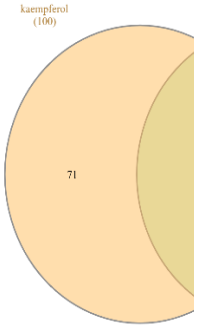


Fig 2- common targets by InteractiVenn

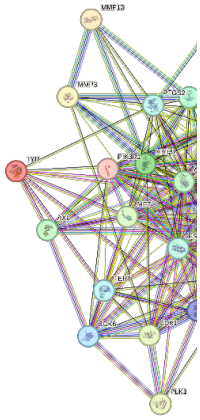


Fig 3- PPI interaction by STRING

3.2 Network pharmacology analysis

The **common targets** were analyzed using the **STRING** database to construct a **protein–protein interaction (PPI) network** with *Homo sapiens* as the species and a **confidence score of 0.4**, ensuring balanced sensitivity and specificity (Fig-3). The resulting data were imported into **Cytoscape** for network visualization (Fig-4). Using the **CytoHubba** plugin and the **MCC algorithm**, the **top 10 hub genes—AKT1, ESR1, EGFR, MMP9, PARP1, SRC, MET, MMP2, IGF1R, and PTGS2**—were identified as key nodes within the network (Fig-5). These hub genes were further analyzed using the **DAVID** database for **functional annotation and KEGG pathway enrichment**, highlighting their involvement in melanoma-associated signalling pathways.

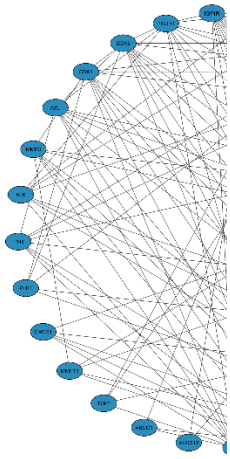


Fig 4- Network visualisation by Cytoscape

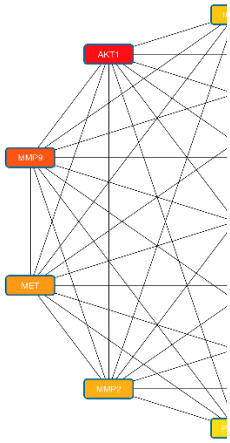


Fig 5- Top 10 targets

3.3 Molecular docking

For molecular docking, **AKT1 (PDB ID: 8UW9)** was selected as the principal target. The docking grid was set to **40 × 40 × 40** points with an

exhaustiveness value of 8. Both ligand and receptor were prepared in **PDBQT format**. Kaempferol demonstrated a strong binding affinity of **–9.2 kcal/mol** with AKT1. Visualization through **BIOVIA Discovery Studio** confirmed key amino acid interactions responsible for the stable ligand–receptor complex.



Fig 6- 8UW9, 3D interaction protein ligand complex (Kaempferol)

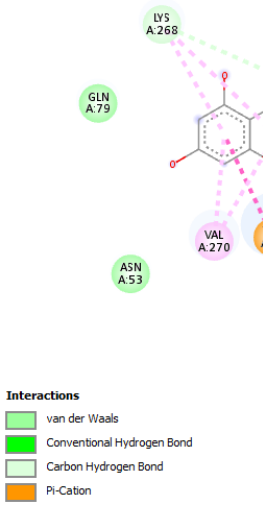


Fig 7- 8UW9, 2D interaction protein ligand complex (Kaempferol)

4. Discussion

The present study employed an integrated network pharmacology and molecular docking approach to explore the potential of Kaempferol, a naturally occurring flavonoid, in targeting the PI3K/AKT signalling pathway associated with melanoma progression. Network-based target prediction identified 100 potential protein targets for Kaempferol, while 1227 melanoma-related genes were retrieved from GeneCards. The intersection analysis revealed a subset of overlapping genes, highlighting Kaempferol's possible multitarget interactions in melanoma. This overlap reinforces the poly-pharmacological nature of Kaempferol, suggesting it may modulate multiple signalling cascades rather than a single target, which is advantageous for managing complex diseases like cancer.

The protein–protein interaction (PPI) network, constructed using the STRING database and visualized through Cytoscape, provided valuable insights into the molecular interactions between Kaempferol and melanoma-associated targets. The hub genes identified—AKT1, ESR1, EGFR, MMP9, PARP1, SRC, MET, MMP2, IGF1R, and PTGS2—represent key regulatory nodes involved in cell survival, proliferation, migration, angiogenesis, and apoptosis. Among these, AKT1 is central components of the PI3K/AKT signalling axis, a pathway frequently dysregulated in melanoma. Aberrant activation of AKT1 promotes uncontrolled cell growth, resistance to apoptosis, and enhanced metastatic potential melanoma aggressiveness [38]. The identification of these targets underscores Kaempferol's potential to interfere with crucial oncogenic signalling hubs.

Functional enrichment and KEGG pathway analyses further supported the association of the identified hub genes with key cancer-related pathways, including PI3K/AKT, MAPK, and apoptosis signalling [39]. These findings indicate that Kaempferol may exert therapeutic effects through the modulation of interconnected networks rather than isolated targets, aligning with the systems-based approach to modern drug discovery.

To validate these network-based predictions, molecular docking was performed between Kaempferol and AKT1 (PDB ID: 8UW9), representing a critical node within the pathway. The docking results revealed a binding affinity of –9.2 kcal/mol, suggesting a strong and energetically favorable interaction. 3D (Fig-6) and 2D (Fig-7) visualization of docking poses using BIOVIA Discovery Studio indicated the formation of hydrogen bonds and hydrophobic interactions between Kaempferol and key amino acid residues in the AKT1 active site. Such interactions likely contribute to the stabilization of the ligand–receptor complex and inhibition of kinase activity, thereby attenuating downstream signalling. This aligns with previous reports where Kaempferol exhibited inhibitory effects on kinases and oncogenic proteins implicated in melanoma and other cancers.

Collectively, the integration of network pharmacology and molecular docking demonstrates that Kaempferol may act as a multi-target modulator of melanoma-associated pathways, particularly through the inhibition of AKT1. The strong binding affinity and involvement of these targets in critical signalling cascades suggest that Kaempferol could hinder melanoma progression by suppressing cell survival and proliferation mechanisms.

5. Conclusion

This *in silico* study provides mechanistic insight into the potential anti-melanoma activity of Kaempferol through modulation of the PI3K/AKT pathway and related oncogenic networks. Network pharmacology revealed that Kaempferol interacts with multiple melanoma-related targets, highlighting its multitarget therapeutic potential. The PPI and KEGG analyses emphasized AKT1 as pivotal nodes linking Kaempferol's activity to melanoma pathophysiology. Molecular docking results confirmed the compound's strong affinity for AKT1, supporting its role as a possible inhibitor of the pathway's key effector.

These findings suggest that Kaempferol may serve as a promising lead molecule for the development of natural, multitargeted therapeutics

against melanoma. However, while the computational outcomes provide a strong theoretical foundation, further *in vitro* and in vivo studies are essential to validate these predictions and confirm biological efficacy. Future investigations should focus on experimental verification of binding interactions, pathway inhibition assays, and assessment of Kaempferol's pharmacokinetic and safety profiles. Overall, this research strengthens the understanding of Kaempferol's molecular mechanisms and its potential role as a novel phytochemical-based therapeutic candidate for melanoma management.

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