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Probing Cancer Protein Inhibition: Unveiling Insights via Molecular Docking and Dynamics Simulation

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ABSTRACT: Millet is recognized as a valuable source of energy and protein, renowned for its exceptional nutritional composition enriched composed of micronutrients and phytochemicals. The metabolites from the millet were used against the major cancer receptors of humans. Proso millet, a popular minor millet variety, is known for its potential to contribute to the prevention of chronic illnesses. Limited research has been conducted on the metabolites found in proso millet for potential applications in cancer treatment. The current study focuses on the phytocompounds of Proso millet compounds that could act as cancer inhibitors through molecular docking and simulation studies using BIOVIA Discovery Studio. Eleven different cancer proteins targeting different types of cancer were studied. The findings from this study demonstrate that the metabolite Myricetin displays a robust interaction with eight cancer targets. The lower binding energies observed, particularly with the Epidermal Growth Factor Receptor, indicate a high affinity between myricetin and the target protein. The Molecule-CHARMm force field was used to direct the molecular dynamic simulation, which resulted in significant potential energy reductions, demonstrating successful optimization and system stability. This study reveals the potential of Myricetin as a potent anticancer-promoting activity against cancer.

Keywords: Anticancer, Myricetin, Molecular docking, Molecular dynamic simulation, Proso millet.

INTRODUCTION

Cancer is one of the most common illnesses in the world with a high mortality rate. Numerous factors are directly or indirectly linked to cancer. High-mortality cancer (Torre *et al.*, 2015) experiences a process of complex and multistep development. Despite significant advancements in cancer research, the disease still seriously threatens human health. Computer-aided studies can provide for complement molecular research (Friedman, 2011). Numerous cancers have a particular reliance on proteins and are only sensitive to their inhibition(Otto & Sicinski 2017). The protein's substrate-binding site is the primary driver of the predominance of enzyme inhibitors as targets for contemporary cancer therapeutics. Compared to other proteins, cancer proteins typically exhibit higher levels of connectivity and betweenness, shorter shortest-path distances, and weaker clustering coefficients (Sun & Zhao 2010). The epidermal growth factor receptor (EGFR) is a crucial member of the HER family of proteins and holds great importance in cell signaling and oncogenesis (James & Ramanathan 2018).

Millets are a significant source of energy and protein and have high nutritional value due to their high content of micronutrients and phytochemicals, which have been shown to have antioxidant, anticancer, antidiabetic, antiaging, antihypertensive, cardioprotective, and many other health benefits(Shah *et al.*, 2021). One of the major minor millets *Panicum miliaceum* L. is primarily grown for its nutritional value to people living in Asia and North America. Due to their potential health benefits in the reduction of the risk of developing chronic diseases, the phytochemical content of edible proso millet needs to be investigated further. Proso millet exceeds other major cereal grains due to its remarkable mineral content. Its high fiber and antioxidant levels offer substantial protection against cardiovascular diseases and cancer (Zhang *et al.*, 2014). Moreover, Proso Millet showcases prebiotic properties, promoting a healthy gut (Das *et al.*, 2019). Natural organic compounds found in plants called phytochemicals play a role in preventing disease and

promoting health. Because of their antibacterial and antioxidant properties, examining these phytochemicals aids in identifying bioactive substances involved in disease prevention (Mounika *et al.*, 2022). The phytoconstituents in proso millet owing to their anticancer and antioxidant properties have not been reviewed more impact when compared to other similar crops.

The present study focuses on Molecular docking and molecular dynamics to reveal the anticancer potential of the compounds that could be crucial to reporting the metabolites of Proso millet as a cancer inhibitor. These studies aim to understand the molecular interaction between bioactive compounds and various cancer peptides. The target and compound confinement to carry out the biological activity will be made clear by molecular docking. Through the use of molecular dynamics (MD) program stability of the favorable docking results was evaluated.

MATERIAL AND METHODS

A. Data Source

The protein receptors for various cancer types along with their biological activities were retrieved through literature mining and a data set was constructed. The three-dimensional structures of the target protein were obtained from the protein structure database PDB (Protein Data Bank) (https://www.rcsb.org/). Table 1 lists cancer targets along with their PDB IDs. The metabolite data of Proso millet were screened using data from earlier *Insilco* studies. A ligand library was constructed with 48 metabolites present generated in SDF (Structured Data File) format from the Pub Chem Database(https://pubchem.ncbi.nlm.nih.gov/). A detailed workflow is explained in Fig. 1.

B. Protein structure preparation

Protein structure preparation optimizes the structure for computational analyses by ensuring accuracy and removing unwanted components. The target receptors were prepared for the docking analysis by using BIOVIA Discovery Studio software (DS4.5, Accelrys, Inc., San Diego, CA, USA) by analyzing the protein report for the removal of the monomeric chain and non-essential water molecule, as well as the addition of hydrogen atoms and other heteroatoms. The other parameters like building loops and protonation were set to TRUE by default. The preparation steps include cleaning the protein, inserting the missing residues, refining and minimizing loops, and finally protonating the proteins using the force field CHARMm.

C. Selection and Preparation of Ligands

The BIOVIA Discovery Studio was used to prepare and optimize the ligands. The process of preparing a ligand involves steps like altering ionization and producing tautomers and isomers. To generate 3D coordinates for the phytocompound, the bad valency parameter was set to TRUE.

Table 1: Cancer targets along with their PDB IDs and description.

Target	Description	PDB ID
APC	A vital Wnt signaling regulator that causes colon polyps and an increased risk of colorectal cancer when combined with APC syndrome (Beaux *et al.*, 1999; Lawrence & William 2009)	3NMX
EGFR	EGFR is a promising therapeutic target for treating oral cancer, where it is linked to tumor growth and treatment resistance. Potential for EGFR signaling inhibition through targeted therapies (Bundela *et al*., 2014; Sigismund *et al.*, 2018)	3W2S
FGFR2	The FGFR pathway has emerged as an attractive target for gastroesophageal cancer (Gordon *et al*., 2022)	1GJO
TGF-β3	TGF-beta is a key signaling pathway involved in osteosarcoma progression and bone remodeling. TGF-beta signaling dysregulation aids in pathological bone remodeling and fosters tumor growth in osteosarcoma (Lamora *et al*., 2016)	1TGJ
c-CBL	A proto-oncoprotein that prevents apoptosis to protect cells from oxidative stress. Its high expression in a variety of cancers suggests that it plays a role in the growth and spread of cancer (Yakoub *et al*., 2014)	2Y1M
KIF11	Breast cancer's prognosis is impacted by Kinesin family member 11 (KIF11), which is connected to the disease's progression (Pei *et al.*, 2017)	3L9H
PI3K	The response of head and neck tumors to PI3K inhibitors as well as their growth and migration are both significantly influenced by the EphB3 receptor (Bhatia *et al.*, 2018)	4YKN
VEGFR2	VEGFR2, which is well known for its function in angiogenesis, also encourages tumorigenesis and metastasis in gastric cancer through pro-angiogenic-independent mechanisms (Lian *et al*., 2019)	3EFL
KRA S	The prognostic significance of KRAS and BRAF mutations in Stage II and III patients with resected colon cancer (Roth *et al*., 2010)	5O2S
AKT	Due to its crucial function in cell survival, growth, and proliferation, AKT, a key signaling molecule, emerges as a promising therapeutic target for colon cancer (Song *et al*., 2019)	3MV5
HER2	In breast cancer cells that over express Her2 and become resistant to trastuzumab, the Met receptor is a significant factor (Shattuck *et al*., 2008)	3WSQ

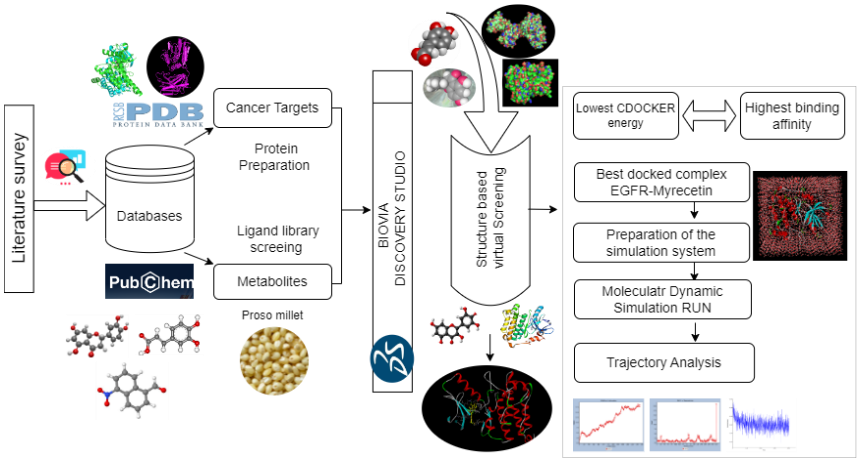


Fig. 1. The schematic representation of the workflow gives an overall view of the study.

D. Docking Study

(i) Optimizing Binding Sites. Binding sites are specific regions within proteins where ligand molecules bind and exert their inhibitory effects on disease processes. In docking studies, protein-ligand interaction sites are among the most commonly investigated binding sites. These sites serve as focal points for understanding the molecular interactions between proteins and ligands. The active site residues for ligands were found, and they were used to define the binding site sphere for the receptor protein. The properties of the sphere were changed by expanding or contracting the binding cavity

(ii) Virtual Screening of Metabolites and cancer targets. Computer-aided drug design relies heavily on docking techniques to explore ligand-protein interactions and predict binding modes. LibDock and CDOCKER are two widely used docking protocols in Discovery Studio. For virtual screening and ligand binding analysis of cancer inhibitors, the CDOCKER modules of the Discovery Studio 4.5 software (DS4.5, Accelrys, Inc., San Diego, CA, USA) were used. The grid-based docking technique CDOCKER uses the CHARMm force field. It chooses the best docking poses based on the CHARMm energy and refines the ligand placement using molecular dynamics, simulated annealing, or minimization techniques. The metabolites present in the Proso millet were used in molecular docking for the cancer targets. The CHARMm force field was applied for energy optimization. The areas within 0.1nm of the geometric centroid of the native ligands were designated as the binding site spheres for each protein. For the docking analysis, the conformations, orientations, and annealing steps of the CDOCKER parameters were all set to their default values. The ligands were generated in a variety of conformations using the molecular dynamic protocol, and the structures were refined using the simulated annealing protocol. The CDOCKER energies were employed to estimate the binding affinity of the molecular complex for each compound.

E. Molecular Dynamic Simulation

Drug development and understanding of molecular processes are aided by the computational technique known as molecular dynamics (MD) simulation, which offers insightful information into the dynamic properties, stability, and interactions of biological systems (Filipe & Loura 2022). Using BIOVIA Discovery Studio and a solvation phase with explicit water molecules and periodic boundary conditions, MD simulations of the top-ranking docking conformation were performed. High-performance simulations of massive biomolecular systems were made possible by the CHARMm force field and NAMD, a parallel MD code, providing access to dynamic data (Kale *et al.*, 2011). The simulation time was set to 50,000ps (50 ns), and the system underwent minimization and equilibration steps, followed by heating, equilibration, and production phases lasting 40ps each. The NPT ensemble maintained constant particle, pressure, and temperature levels throughout the simulation, and GPU acceleration improved computation efficiency. With a pair list distance of 14 to account for nonbonded interactions and a precise 2fs time step, the dynamics of the system were recorded while maintaining the target temperature of 300K.

RESULTS AND DISCUSSION

A. Pharmacokinetic and Drug Likeness Screening of Phytochemicals

Using the TOPKAT algorithm, which incorporates the AMES toxicity prediction methodology, a complete pharmacokinetic screening was carried out to determine the suitability of phytocompounds from proso millet for further investigation. This method, which took into account elements like molecular weight, lipophilicity, solubility, and toxicity, provided useful insights into the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) properties of the phytochemicals. This pharmacokinetic screening ensured the selection of the most promising candidates for further analysis by identifying phytocompounds that met the desired ADMET criteria.

B. Molecular Docking

Phytochemicals were docked using the CDOCKER algorithm in Discovery Studio against various cancer targets. Based on an RMSD tolerance of 0 for exact pose grouping, docking results were grouped. The top binding pose was chosen based on each compound's highest negative CDOCKER interaction energy score after docked complexes were further examined for their

CDOCKER and CDOCKER interaction energies. Comparative values of the binding free energies for the cancer targets and the three best-docked compounds are listed in Table 2. The strong potential for myricetin to inhibit cancer was demonstrated by its highly promising interactions with thirteen cancer targets. Table 3 provides a comprehensive overview of the diverse interactions between myricetin and multiple targets. In contrast to other targets, myricetin showed lower CDOCKER and CDOCKER interaction energies (-44.9127 kcal/mol and -46.2099 kcal/mol, respectively) with the EGFR receptor (PDB ID: 3w2s). Significant non-bonded interactions, such as hydrophilic, hydrophobic, and pi-pi interactions, could be examined using the BIOVIA Discovery Studio's Receptor-Ligand interaction module. The complex interactions of myricetin with cancer proteins were visually represented, demonstrating the formation of significant non-bonded interactions, including hydrophilic, hydrophobic, and pi-pi interactions. The EGFR-Myricetin complex was visualized in Fig. 2, which showed the presence of four hydrogen bonds, two alkyl bonds, and two sulfur bonds. These results highlight the potential of myricetin as a candidate drug for the treatment of cancer.

C. Molecular Dynamic Simulation

The CHARMm force field analysis successfully characterized the stable molecule, supported by the Momany-Rone parameter. The molecule belongs to the ORTHO class with coordinates X=46.759, Y=68.446, and Z=105.020. The system comprises 4850 water molecules, 21 cations, and the molecule. The Molecule-CHARMm force field effectively guided the molecule through various stages of the dynamic cascade, achieving successful system conformation optimization, as evident from extensive potential energy decreases during Minimization1 and Minimization2 stages, indicating efficient guidance towards more efficient states. The molecular dynamics simulation provided valuable insights into the energetic behavior and stability of the studied system. Molecular dynamics simulation provides valuable insights into the system's energetic behavior and stability. Table 4 presents energy values obtained through Discovery Studio's molecular dynamic simulation. The gradual rise in temperature during the heating stage leads to increased system stability, with dynamic motion indicated by temperature and kinetic energy. Interactions between molecules are balanced by electrostatic and Van der Waals forces. The Production stage maintains stable kinetic and potential energy, affirming successful movement through the dynamic cascade. Overall, these findings enhance understanding of the system's energetic characteristics, paving the way for comprehensive analysis and interpretation of the simulation results.

D. Trajectory Analysis

The EGFR-Myricetin complex was subjected to a thorough trajectory analysis after a molecular dynamics (MD) simulation to investigate its dynamic behavior, stability, interactions, and conformational changes. To evaluate structural changes and atom fluctuations, important parameters including Root Mean Square Deviation (RMSD) and Root Mean Square Fluctuation (RMSF) were used. Fig 3 displays the trajectory analysis of the simulated complex EGFR-Myricetin. The RMSD analysis (Fig. 3a) showed early conformational alterations that eventually led to a stable state after about 35 ns, indicating a reliable protein-ligand interaction. In the RMSF analysis, different regions showed varying fluctuations, with some being more flexible and others being more rigid structurally, particularly residues 740 to 850 (Fig. 3b). The Radius of Gyration (Rg) analysis showed a stable peak at about 20.0 to 20.5 angstroms, indicating that the complex was consistently compact and kept in its conformation throughout the simulation (Fig. 3c). A stable conformational arrangement or binding mode between the protein and Myricetin was also indicated by the potential energy plot (Fig. 3d), which showed a gradual decrease and suggested that the complex was transitioning to more energetically advantageous states.

Millets are widely used in larger quantities as they contain more nutritional value than other major crops. It constitutes high proportion of macro and micronutrients that can be useful for the diabetic patients and can prevent from various severe diseases (Raparthi *et al.* 2022; Sathish Kumar *et al.*, 2022). Myricetin's therapeutic potential for treating human diseases has yet to be thoroughly investigated (Park *et al.*, 2016). Myricetin, a natural flavonoid abundantly found in various plant sources and commonly included in our diet (Starke & Herrmann 1976), shares structural similarities with renowned phenolic compounds such as quercetin, morin, kaempferol, and fisetin. Highly prized for its nutraceutical and antioxidant attributes, myricetin exhibits diverse pharmacological effects, including anti-inflammatory, analgesic, antitumor, hepatoprotective, and antidiabetic properties, supported by scientific evidence (Lin *et al.*, 2012). Myricetin shows cytotoxicity against diverse cancer cell lines, including hepatic, skin, pancreatic, and colon cancers, while inhibiting key cancer-related enzymes. It also displays potent anti-proliferative activity against human acute leukemia HL-60 cells (Chang *et al.*, 2007) and effectively inhibits mutagenesis induced by multiple mutagens, making it a highly potent mutagenesis inhibitor (Ong & Khoo 1997). The results of this study demonstrate the promising potential of myricetin as a therapeutic agent for cancer treatment. The compound exhibits strong interactions with multiple cancer targets, indicating its ability to inhibit cancer growth. The lower binding energies observed, particularly with the EGFR receptor, suggest a high affinity between myricetin and the target protein. The visualization of non-bonded interactions highlights the complex nature of myricetin's binding to cancer proteins. The stability and precise interaction between myricetin and the EGFR receptor, as evidenced by the formation of specific bonds, further support its potential as a therapeutic candidate. These results support the EGFR-Myricetin complex's stability and potential therapeutic value as a promising cancer protein inhibitor.

Table 2: Docking results of the compound Myricetin with cancer targets.

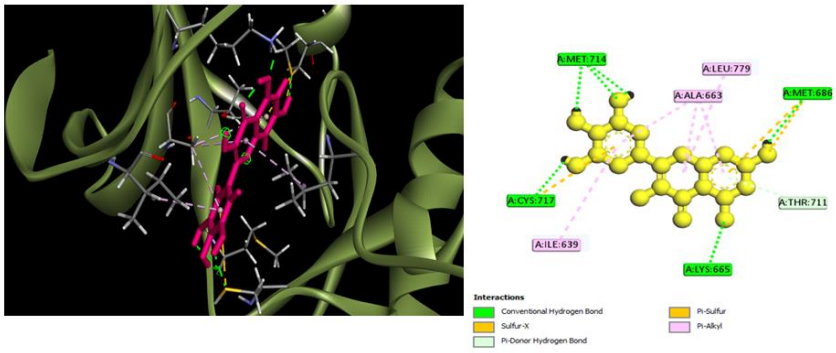
Target	Ligand	CDOCKER energy(kcal/mol)	CDOCKER interaction energy(kcal/mol)	Number of H-bonds
3NMX	3,4-Dihydroxycinnamic acid	-19.1867	-19.697	2
	4-Hydroxycinnamic acid	-17.2725	-19.3963	1
	p-Coumaryl Aldehyde	-14.1563	-17.9141	1
3W2S	Myricetin	-44.9127	-46.2099	3
	Hexadecanoic acid	-44.4802	-43.7117	1
	Eriodictyol	-38.3223	-42.9009	3
1GJO	Myricetin	-33.9295	-30.7849	5
	Hexadecanoic acid	-27.8331	-29.3011	4
	3-O-Caffeoylquinic acid	-27.6148	-38.8056	7
1TGJ	Myricetin	-25.629	-31.4588	2
	3-O-Caffeoylquinic acid	-21.6973	-32.9265	2
	Cryptochlorogenic acid	-20.7826	-28.9044	2
2Y1M	Hexadecanoic acid	-39.8377	-39.5884	1
	3,4-Dihydroxycinnamic acid	-30.5268	-31.8193	2
	Apigenin	-28.3836	-34.2956	3
3L9H	Hexadecanoic acid	-40.6252	-41.3256	4
	Myricetin	-32.3132	-34.4515	3
	Cryptochlorogenic acid	-30.3392	-38.6221	3
4YKN	3,4-Dihydroxycinnamic acid	-16.832	-23.0593	3
	p-Coumaraldehyde	-15.4874	-25.5706	3
	Hesperetin acid	-14.2677	-22.6339	1
3EFL	Hexadecanoic acid	-50.283	-48.4566	1
	Neochlorogenic acid	-41.0247	-51.063	3
	Apigenin	-33.7981	-37.476	1
5O2S	Hexadecanoic acid	-33.8476	-31.8365	1
	Myricetin	-26.328	-30.4233	5
	Hesperetin	-22.3923	-30.1371	5
3MV5	Myricetin	-26.6863	-30.6617	5
	Kaempferol	-19.9936	-24.7711	3
	Apigenin	-19.3259	-25.2361	2
3WSQ	Hexadecanoic acid	-33.8872	-31.4958	2
	Myricetin	-31.1261	-33.1558	2
	Eriodictyonone	-27.5076	-34.1653	2

Table 3: Multi-target interaction of the compound Myricetin.

PDB ID	CDOCKER energy	CDOCKER interaction energy	Number of H-bonds	H-bonds interacting Aminoacids
3W2S	-44.9127	-46.2099	4	LYS:665, MET:686, MET:714, CYS:717
1GJO	-33.9295	-30.7849	5	ASN:662, GLY:663, ARG:664, ARG:649, ARG:678
1TGJ	-25.629	-31.4588	2	LYS:97, GLU:99
3L9H	-32.3132	-34.4515	3	GLU:116, GLU:118, ARG:221
3EFL	-33.7981	-37.476	1	ASP:1046
5O2S	-26.328	-30.4233	5	ARG:73, GLU:91, HIS:94, ARG:102, GLU:137
3MV5	-26.6863	-30.6617	5	ARG:144, GLU:149, GLU:169, LYS:214, TYR:215
3WSQ	-31.1261	-33.1558	2	ARG:465, CYS:4

Table 4: The energy values for the complex EGFR-Myricetin.

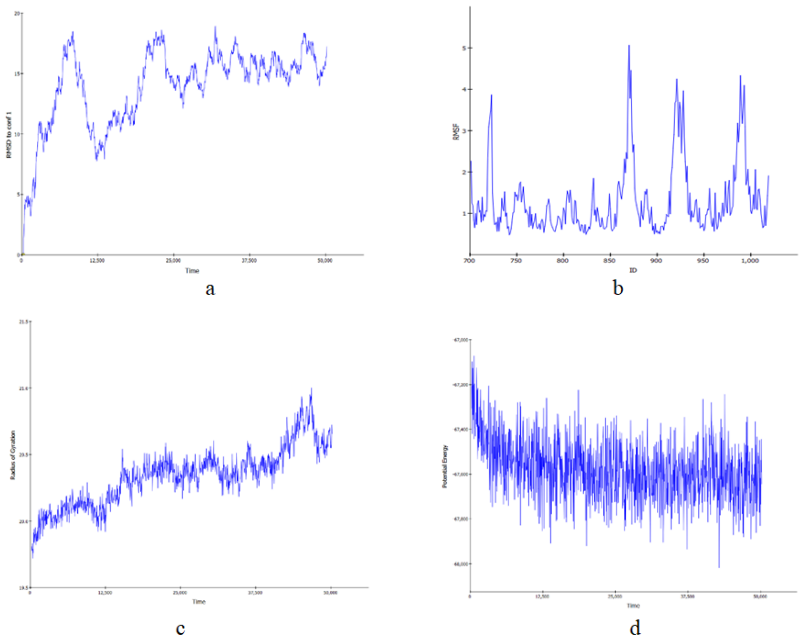
Energy Component	Value (kcal/mol)
Kinetic Energy	12577.3459
Potential Energy	-67644.1202
Total Energy	-55066.7743
Electrostatic Energy	-73496.0422
Van der Waals Energy	1307.667



(a) (b)

(a) The interaction of the docked receptor and ligand in three dimensional using Discovery Studio, (b) The 2-D image of the docked EGFR- Myricetin complex with its interacting amino acids

Fig. 2. The docked EGFR-Myricetin complex and its interaction.



a b

c d

(a) The RMSD plot of the complex showing stability over 50ns, (b) The RMSF plot shows less fluctuation for residues ranging between 740-850, (c) The Radius of Gyration plot, (d) The potential energy plot for EGFR-Myricetin complex.

Fig 3. Trajectory analysis of the simulated complex EGFR-Myricetin.

CONCLUSIONS

The phytocompounds in proso millet have the potential to treat and prevent cancer, as well as provide nutritional benefits. Bioactive substances like myricetin, an EGFR protein inhibitor, are discovered through molecular docking studies and show promise for future therapeutic uses. However, more investigation and experimental studies are required to fully confirm myricetin's efficacy and examine its clinical relevance in the treatment of cancer. These initiatives will open the door to utilizing Myricetin's potential as a strong candidate in the search for potent cancer treatments.

FUTURE SCOPE

This study aims to determine the efficacy and safety of myricetin for an array of medical applications while also examining its potential as a therapeutic agent for the treatment of cancer. Myricetin's therapeutic value and potential development as a flexible drug candidate must be confirmed by in-vivo studies.

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Conflict of Interest. None.

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