Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 4691-4701 | ISSN:2251-6727

In silico analysis of phytochemicals from Nutmeg that inhibit cancer cell adhesion pathways

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(Received: 16 February 2026 Revised: 14 March 2026 Accepted: 25 April 2026)

KEYWORDS

Myristica fragrans, Docking, Adhesion pathway, Myricetin, Anti-cancer

ABSTRACT:

Introduction: Phytochemicals from Nutmeg are reported to have anticancer activity by multiple mechanisms. However, their effect on cell adhesion pathway is still not completely explored

Objectives: To perform in silico analysis of four major phytochemicals from Nutmeg against target enzymes of cell adhesion pathway.

Methods: Ligands viz. Elemicin, Machilin A, Myristic and myricetin were docked against targets viz. FAK, Src, ILK and ROCK1. Dasatinib was used as a positive control. Their interaction was studied and ADMET results were reported.

Results: Of the studied ligands, Myricetin demonstrated the strongest and most consistent interaction with all four cancer-related kinases. Machilin A showed moderate interaction and other two compounds showed relatively weak interactions.

Conclusions: These findings indicate that polyphenolic compounds from *Myristica fragrans* may exert anticancer activity through multi-target modulation of adhesion-related kinase signaling pathways involved in tumor progression and metastasis.

1. Introduction

Cancer progression is a multifactorial process involving dysregulated cell proliferation, evasion of apoptosis, metabolic reprogramming, and enhanced migratory and invasive capabilities.[1] Among these processes, alterations in cell adhesion signaling and cytoskeletal regulation play a critical role in tumor progression and metastasis. Adhesion-associated kinases regulate the interaction between cells and the extracellular matrix and coordinate signaling pathways that control migration, invasion, and survival of cancer cells. Dysregulation of these pathways contributes significantly to malignant transformation and metastatic dissemination.[2, 3]

One of the key mediators of cell adhesion signaling is Focal Adhesion Kinase (FAK), a non-receptor tyrosine kinase that localizes to focal adhesion complexes. FAK integrates signals from integrins and growth factor receptors to regulate cytoskeletal dynamics, cell survival, and motility.[4] Overexpression or hyperactivation of FAK has been reported in multiple malignancies, including breast, colorectal, ovarian, and pancreatic cancers, and has been associated with enhanced tumor invasiveness and poor clinical prognosis.[5] Consequently, inhibition of FAK signaling has emerged as a promising therapeutic strategy for preventing tumor progression and metastasis.[6]

Closely associated with FAK signaling is Proto-oncogene tyrosine-protein kinase Src (Src), a proto-oncogenic tyrosine kinase that participates in several oncogenic signaling cascades.[7] Src regulates cellular proliferation, angiogenesis, and metastatic behavior through phosphorylation of multiple downstream substrates involved in cytoskeletal organization and adhesion turnover. Aberrant Src activation is a common feature in many cancers and contributes to tumor aggressiveness, resistance to apoptosis, and enhanced invasive capacity. Due to its central role in tumor biology, Src has become an important target in anticancer drug discovery.[8]

Another critical component of integrin-mediated signaling is Integrin-linked kinase (ILK). ILK functions as an adaptor and signaling scaffold linking integrins to

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JCHR (2026) 16(2), 4691-4701 | ISSN:2251-6727

intracellular signaling pathways that regulate cell survival, proliferation, and epithelial–mesenchymal transition (EMT).[9] Dysregulation of ILK signaling has been implicated in tumorigenesis, particularly through its involvement in the PI3K/Akt pathway and regulation of β-catenin signaling. Increased ILK expression has been associated with enhanced tumor cell survival, invasion, and resistance to chemotherapy.[10]

In addition to these kinases, cytoskeletal tension and cellular contractility are strongly influenced by Rho-associated protein kinase 1 (ROCK1), a downstream effector of the Rho GTPase signaling pathway. ROCK1 regulates actomyosin contraction, cell motility, and focal adhesion dynamics. Elevated ROCK signaling has been linked to increased tumor cell migration and metastatic potential. Inhibition of ROCK signaling has therefore been proposed as a strategy to reduce tumor invasion and metastasis.[11, 12]

Due to their central roles in regulating tumor cell adhesion, migration, and survival, FAK, Src, ILK, and ROCK1 represent important therapeutic targets in anticancer drug development. Several synthetic inhibitors targeting these kinases have been investigated; however, many of them are associated with toxicity, off-target effects, or limited clinical efficacy. Consequently, there is growing interest in identifying naturally derived compounds capable of modulating these signaling pathways with improved safety profiles.[13]

Natural products have historically served as an important source of anticancer agents. Numerous plant-derived phytochemicals exhibit antiproliferative, anti-inflammatory, and anti-metastatic activities. Among medicinal plants, *Myristica fragrans* has attracted considerable attention due to its diverse pharmacological properties. Extracts of this plant have demonstrated antioxidant, anti-inflammatory, antimicrobial, and anticancer activities in various experimental models. The biological activity of this plant is largely attributed to its rich content of bioactive phenylpropanoids and polyphenolic compounds.[14]

Several phytochemicals isolated from Myristica fragrans, including Elemicin, Machilin A, Myricetin, and Myristicin, have been reported to possess potential anticancer properties. These compounds have shown inhibitory effects on cancer cell proliferation, induction of apoptosis, and modulation of signaling pathways associated with tumor progression. In particular, polyphenolic compounds such as Myricetin are known to interact with multiple cellular targets and have been shown to interfere with kinase signaling pathways involved in cancer development.[15]

Despite increasing evidence supporting the anticancer potential of these phytochemicals, the molecular mechanisms underlying their activity remain incompletely understood. In silico molecular docking approaches provide a valuable strategy for investigating potential interactions between bioactive compounds and protein targets involved in cancer signaling. Computational docking allows the prediction of binding affinity, interaction patterns, and possible inhibitory mechanisms, thereby facilitating the identification of promising lead compounds for further experimental validation.[16]

2. Objectives

Therefore, the present study aimed to investigate the potential anticancer activity of selected phytochemicals derived from *Myristica fragrans* through molecular docking analysis against key adhesion-related kinases involved in tumor progression, namely FAK, Src, ILK, and ROCK1. By evaluating the binding affinities and interaction profiles of these compounds with the catalytic domains of these kinases, this study seeks to provide insights into the possible molecular mechanisms through which these phytochemicals may exert anticancer effects and to identify potential lead compounds for further therapeutic development.

3. Methods

The active compounds that were reported to be present in the *Myristica fragrans* plant were carefully chosen based on their abundance and known anticancer activities. Hence only four compounds were selected, evaluated and compared by molecular docking analysis. The potential antitumor activity of phytochemicals derived from Myristica fragrans, molecular docking was performed against four key kinases involved in tumor progression and metastasis, viz. Focal Adhesion Kinase (FAK), Proto-oncogene tyrosine-protein kinase Src (Src), Integrin-linked kinase (ILK) and Rho-associated protein kinase 1 (ROCK1). Four phytochemicals were evaluated viz. Elemicin, Machilin A, Myricetin and Myristicin.

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Protein preparation

The structure (3D crystal) of adhesion targets and their pdb bumbers are shown in table 1. They were downloaded from Protein Data Bank (www.rvcsb.org/pdb) They were cleared of non-essential water molecules, heteroatoms and the complexes attached to the receptor molecule.Then hydrogen atoms were supplied to the targeted molecule receptor.

Ligand preparation

The identified crystallography structure of selected ligands were adopted from PubChem and was converted to PDB format using PyMOL software. They were cleaned of unwanted attached atoms and Gasteigar charges were added. Details of the ligands are shown in table 2.At the binding location, the grid box size was set to 35 Å.

Docking Softwares

Scientiflow tool (from scientiflow.com) was used to automate the entire process which used RDKit for ligand format conversion and standardization, Gypsum-DL for tautomer and enentiomer generation, Gnina for docking with deep learning based scoring and based on Autodock vina. Protein ligand interaction profiling was done using PLIP and generation of 2D interaction maps were done using PandaMapColor. For ADMET prediction SwissADME was used.

Table 1. Details of Proteins

Enzyme	**Pathway Role**	**PDB ID**
FAK (PTK2)	Central adhesion signaling hub	2AL6
Src	FAK partner, adhesion phosphorylation	2SRC
ILK	Integrin–actin linkage regulator	3KMW
ROCK1	Cytoskeletal tension & adhesion maturation	2ETR

Table 2. Characteristics of the Ligands

Parameter	**Elemicin**	**Machilin A**	**Myricetin**	**Myristicin**
Heavy atoms	15	24	23	14
H-bond donors (HBD)	0	0	6	0
H-bond acceptors (HBA)	3	4	7	3
Aromatic rings	1	2	3	2
Rotatable bonds	5	5	1	3
Molecular weight (g/mol)	208.25	326.39	312.19	192.21
logP	2.44	4.2	4.32	2.15

4. Results

With regard to binding affinity analysis, the docking results showed substantial variation in binding affinity among the tested compounds. Among these compounds, Myricetin exhibited the strongest binding affinity toward all four targets, with binding energies ranging from −9.83 to −10.49 kcal/mol, suggesting strong interaction with the catalytic domains of these proteins. Machilin A also exhibited significant binding affinity, especially with Src (−9.17 kcal/mol) and ROCK1 (−8.89 kcal/mol), indicating potential kinase modulatory activity. However, Elemicin and Myristicin exhibited comparatively weaker interactions with all proteins. The best docking positions are shown in Figure 2. For comparison, dasatinib was docked against the targets and it was seen that phytochemicals said were at par with dasatinib.

Ligand–Protein Interaction Analysis

Myricetin exhibited the highest number of hydrogen bonds and interaction contacts with the kinase domains. The higher number of hydrogen bond donors and acceptors present in Myricetin have contributed significantly to its strong binding affinity. Its rigid molecular structure with minimal rotatable bonds have allowed efficient stabilization within the ATP-binding

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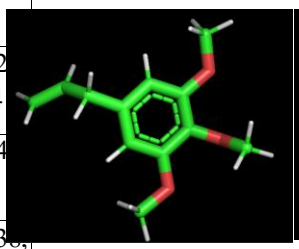
pockets of these kinases. Machilin A showed strong hydrophobic interactions with kinase residues, particularly within the Src binding pocket, where six hydrophobic interactions and a π-stacking interaction were observed. Therefore it may be suggested that Machilin A may stabilize within the hydrophobic regions of kinase catalytic pockets. Elemicin and Myristicin exhibited fewer interaction contacts and lower hydrogen bonding potential. Another possible explanation may be its relatively small molecular size and limited hydrogen bonding capacity likely contributed to weaker binding energies. Also higher structural flexibility may contribute to weaker interactions. The interactions observed were primarily hydrophobic and suggest their limited capacity to strongly modulate kinase activity.

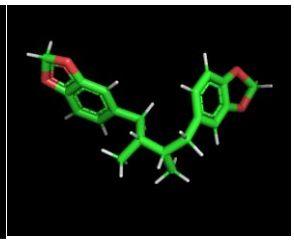
It can be seen that all the molecules used showed a maximum of 1 violation in the rule of lipinski, making them good drugs for therapy.

Table 3. Results of the molecular docking

Compounds	Enzyme	Binding Free energy Kcal/mol	Inhibition constant Ki µM	AminoAcid Residue interactions
Elemicin	FAK (PTK2)	-5.84491491	52	LEU99,GLU226, ASP124, ARG95
Machilin A	FAK (PTK2)	-7.6393795	2.51	PRO296, LYS345, GLN333, LYS289, GLU350, LEU34 THR271
Myricetin	FAK (PTK2)	-9.83408737	0.062	ARG95, CYS22 LEU99, ASP224, TYR317, ASP124, GLU128
Myristicin	FAK (PTK2)	-5.90495968	47.1	ARG97, GLU22 ARG95, ASP124
Elemicin	Src	-5.71626568	64.7	VAL281, MET34 LEU273
Machilin A	Src	-9.17219734	0.19	LYS295, THR33 PHE405, ILE336, VAL323, LEU393
Myricetin	Src	-10.4955339	0.02	THR338, ALA403, VAL281, LEU273, ASP404, MET341, LEU393, VAL323
Myristicin	Src	-6.14841938	31.4	LEU393, VAL281, ASP404, LEU273
Elemicin	ILK	-5.31857538	127	LEU199, VAL218, TRP271, ASN279, MET272, SER276
Machilin A	ILK	-8.42164993	0.67	VAL218, SER276, SER336, ASN279
Myricetin	ILK	-9.88888073	0.057	LYS220, ASN202, ASP339, ALA338, THR269, LEU207, MET272, VAL218, ASN200, SER336
Myristicin	ILK	-5.68254519	68.4	LEU207, LEU199, MET272, TRP271
Elemicin	ROCK1	-5.75066042	61.2	THR219, SER118, PHE120
Machilin A	ROCK1	-8.88844204	0.31	LYS105, THR219, PHE87, SER118, LEU107, PHE120
Myricetin	ROCK1	-9.8904171	0.057	ALA86, ILE82, ARG84, LEU106, VAL90, LYS105, PHE87
Myristicin	ROCK1	-6.11376286	33.3	ASP146, TYR39, GLN391, PHE43



Elemicin



Machilin-A

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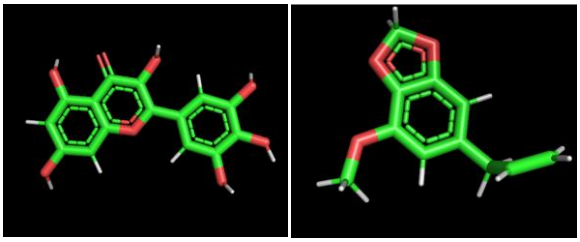
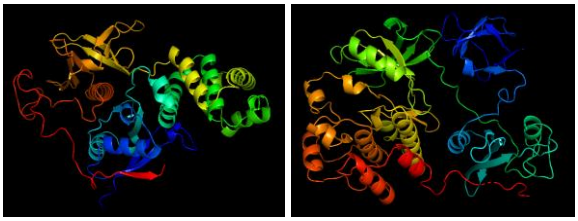
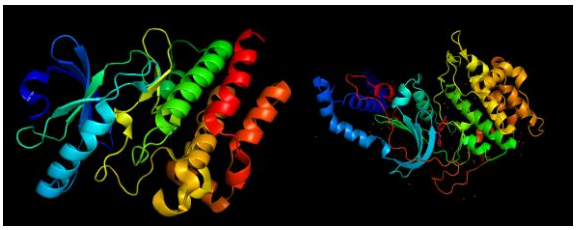


Myricetin Myristicin

Fig. 1. 3D Images of Ligands



FAK (PTK2) – 2AL6 Src - 2SRC



ILK - 3KMW ROCK1 - 2ETR

Fig. 2. 3D Images of the targets used in the study

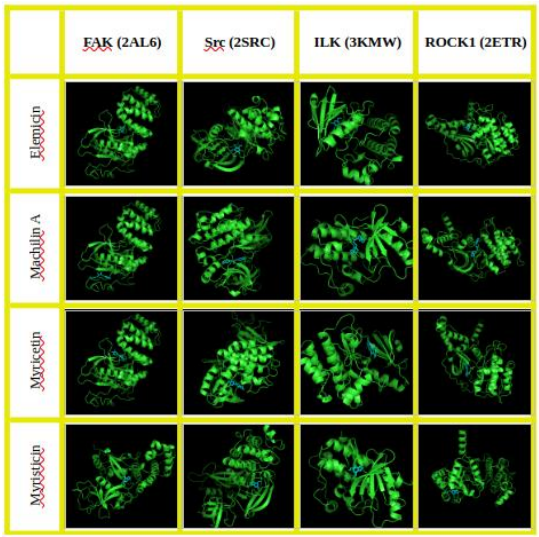


Fig. 3. Best docking positions of the ligands

Table. 4. Binding Affinity

Compound	FAK (2AL6)	Src (2SRC)	ILK (3KMW)	ROCK1 (2ETR)
Elemicin	-5.84	-5.72	-5.32	-5.75
Machilin A	-7.64	-9.17	-8.42	-8.89
Myricetin	**-9.83**	**-10.49**	**-9.88**	**-9.89**
Myristicin	-5.90	-6.15	-5.68	-6.11
Dasatinib	-7.799	-8.527	-8.704	-7.902

Table. 5. ADMET Prediction

Molecule	Canonical SMILES	MR	TPSA	iLOGP
Elemicin	C=CCc1cc(OC)c(c(c1)OC)OC	60.02	27.69	2.89
Machilin A	C[C@H]([C@@H](Cc1ccc2c(c1)OCO2)C)Cc1ccc2c(c1)OCO2	92.06	36.92	3.78
Myricetin	Oc1cc(O)c2c(c1)oc(c(c2=O)O)c1cc(O)c(c(c1)O)O	80.06	151.59	1.08
Myristicin	C=CCc1cc(OC)c2c(c1)OCO2	53.1	27.69	2.67

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Molecule	XLOGP3	WLOGP	MLOGP	Silicos-IT Log P
Elemicin	2.53	2.44	1.97	3.06
Machilin A	5.35	4.2	3.62	5.16
Myricetin	1.18	1.69	-1.08	1.06
Myristicin	2.94	2.15	1.7	2.99
Molecule	**Consensus Log P**	**ESOL Log S**	**ESOL Solubility (mg/ml)**	**ESOL Solubility (mol/l)**
Elemicin	2.58	-2.69	0.424	0.00204
Machilin A	4.42	-5.27	0.00174	0.00000532
Myricetin	0.79	-3.01	0.314	0.000988
Myristicin	2.49	-3	0.191	0.000993
Molecule	**ESOL Class**	**Ali Log S**	**Ali Solubility (mg/ml)**	**Ali Solubility (mol/l)**
Elemicin	Soluble	-2.76	0.364	0.00175
Machilin A	Moderately soluble	-5.88	0.000432	0.00000132
Myricetin	Soluble	-3.96	0.035	0.00011
Myristicin	Soluble	-3.18	0.126	0.000655

Molecule	Ali Class	Silicos-IT LogSw	Silicos-IT Solubility (mg/ml)	Silicos-IT Solubility (mol/l)
Elemicin	Soluble	-3.64	0.0479	0.00023
Machilin A	Moderately soluble	-6.08	0.000274	0.00000839
Myricetin	Soluble	-2.66	0.698	0.00219
Myristicin	Soluble	-3.13	0.142	0.000738
Molecule	**Silicos-IT class**	**GI absorption**	**BBB permeant**	**Pgp substrate**
Elemicin	Soluble	High	Yes	No
Machilin A	Poorly soluble	High	Yes	No
Myricetin	Soluble	Low	No	No
Myristicin	Soluble	High	Yes	No
Molecule	**CYP1A2 inhibitor**	**CYP2C19 inhibitor**	**CYP2C9 inhibitor**	**CYP2D6 inhibitor**
Elemicin	Yes	No	No	No
Machilin A	No	Yes	Yes	Yes
Myricetin	Yes	No	No	No
Myristicin	Yes	No	No	No

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Molecule	CYP3A4 inhibitor	log Kp (cm/s)	Lipinski #violations	Ghose #violations
Elemicin	No	-5.77	0	0
Machilin A	Yes	-4.49	0	0
Myricetin	Yes	-7.4	1	0
Myristicin	No	-5.39	0	0
Molecule	**Veber #violations**	**Egan #violations**	**Muegge #violations**	**Bioavailability Score**
Elemicin	0	0	0	0.55
Machilin A	0	0	1	0.55
Myricetin	1	1	2	0.55
Myristicin	0	0	1	0.55
Molecule	**PAINS #alerts**	**Brenk #alerts**	**Leadlikeness #violations**	**Synthetic Accessibility**
Elemicin	0	1	1	2
Machilin A	0	0	1	3.5
Myricetin	1	1	0	3.27
Myristicin	0	1	1	2.4

5. Discussion

The current molecular docking study evaluated the interaction of phytochemicals derived from Myristica fragrans with major adhesion-related kinases that are involved in tumor progression and metastasis. The results of the present study showed that among the evaluated phytochemicals evaluated, Myricetin had the strongest binding affinity across all the protein targets used. This was followed by Machilin A, while Elemicin and Myristicin had comparatively weaker interactions.

The high binding affinity seen in Myricetin may be suggestive of this compound acting as a potential multi-target modulator of the studied adhesion signaling pathway. The binding energies ranging from −9.83 to −10.49 kcal/mol across the kinases, added with multiple hydrogen bond interactions with catalytic site residues may support this interpretation. These observations are consistent with previous studies reporting polyphenolic compounds like Myricetin having strong anticancer properties.

These findings are indicative of the interfering potential of Myricetin with Src catalytic activity, and consequent disruption of downstream oncogenic signaling cascades. Same observation is ture for ILK and ROCK1. It is suggestive of role of Myricetin in disrupting integrin-mediated signaling networks. The strong binding affinity of Myricetin toward ROCK1 may indicate inhibition of ROCK-mediated cytoskeletal remodeling and tumor cell migration. Therefore Myricetin may exert synergistic anticancer effect via disruption of interconnected signaling pathways.

With regard to Machilin A, with strong affinity towards Src and ROCK1, along with its extensive hydrophobic interactions with catalytic site residues, it may be suggested that it may stabilize within kinase binding pockets and lead to effects similar to Myricetin.

Elemicin and Myristicin had weaker binding interactions across all targets, ruling out their effect via the adhesion kinase pathway. Summarily, the results of this study show that phytochemicals from Myristica fragrans, especially Myricetin, may be a potential candidate for multi-target based cancer inhibition. and metastasis. This ability of a single compound to involve with multiple signaling proteins is an essential advantage in anticancer drugs.

These significant finding has provided insights and future directions for in vitro and clinical verification for validating the role of these phytochemicals in tumor

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treatment. Table 6 below shows the summary of literature evidence that shows the anticancer activity of Myristica Fragrans.

Table 6. Experimental evidence supporting anticancer activity of *Myristica fragrans* phytochemicals

Author (Year)	Phytochemical / Extract	Cancer Cell Line / Model	Reported Anticancer Effect	Pathway / Mechanism
Chirathaworn et al. (2007)[17]	Methanolic extract	Jurkat leukemia T cells	Induced apoptosis; reduced proliferation	Downregulation of **SIRT1** mRNA
Akinboro et al. (2012)[18]	Methanol leaf extract	Ames test, mouse bone marrow, Allium cepa	Antimutagenic and antioxidant effects	Protection against DNA damage and mutagenicity
Paul et al. (2013)[19]	Maceligan	Not cell-specific (review)	Reported anticancer, anti-inflammatory effects	Multi-pathway modulation including oxidative stress and signaling pathways
Suthisamphat et al. (2020)[20]	Ethanolic mace extract	Kato III gastric cancer cells	Cytotoxicity and growth inhibition	Anti-inflammatory and antioxidant mediated mechanisms
Ginting et al. (2020)[21]	Lignan from root extract	MCF-7 breast cancer cells	Moderate cytotoxic activity	Likely ROS-mediated oxidative stress (not fully elucidated)
Li et al. (2021)[22]	Dehydrodiisoeugenol	Colorectal cancer cells, CDX & PDX models	Cell cycle arrest, autophagy, tumor growth inhibition	**ER stress → PERK/eIF2α and IRE1α/XBP1 → Autophagy**
Zhu et al. (2025)[23]	β-Sitosterol	T24 & 5637 bladder cancer cells	Apoptosis, reduced proliferation and migration	**BCL-2/BAX/Caspase-3** and **PI3K/AKT** pathways
Che et al. (2024)[24]	Maceligan	Colorectal cancer & macrophage co-culture	Reduced metastasis and M2 polarization	**ROS → PI3K/AKT → NF-κB** suppression
Piras et al. (2012)[25]	Nutmeg essential oil, myristicin	Caco-2 colon cancer cells	Inhibited cell growth	Likely oxidative stress and membrane disruption
Qian et al. (2025)[26]	Sabinene	HepG2 hepatocarcinoma & rat model	Apoptosis, tumor suppression	**AKT/mTOR** and **Bcl-2/Bax** pathways

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Author (Year)	Phytochemical / Extract	Cancer Cell Line / Model	Reported Anticancer Effect	Pathway / Mechanism
Mickus et al. (2021)[27]	Nutmeg essential oil constituents	Novikoff hepatoma cells	Reduced proliferation and colony formation	Inhibition of **Connexin-43 gap junction signaling**
Seneme et al. (2022)[28]	Myristicin	NCI/ADR-RES ovarian MDR cells	Enhanced chemotherapy efficacy	Inhibition of **P-glycoprotein (MDR reversal)**

From the above table, the most frequently reported mechanisms were Apoptosis induction, oxidative stress modulation, PI3K/AKT pathway inhibition, ER stress–induced autophagy and Multidrug resistance reversal. Essentially these are downstream of FAK-Src signalling pathways. This study has analyzed the phytochemicals of *Myristica fragrans* for kinase related inhibitory effect, which is a novel and more relevant pathway for anti cancer activity.

In conclusion, the findings of the present study highlight Myricetin as a promising multi-target inhibitor of adhesion-related kinases involved in cancer metastasis. By targeting key components of the FAK–Src–ILK–ROCK signaling axis, this compound may interfere with critical processes such as tumor cell migration, invasion, and survival. These results provide a mechanistic basis for further investigation of *Myristica fragrans* phytochemicals as potential anticancer agents.

Future studies may have to focus on using molecular dynamics simulations to assess the stability of ligand–protein complexes over time. In vitro kinase inhibition assays and animal studies need to be performed for clinical translation of these findings. Drugs may be developed from derivatives of Myricetin and Machilin A for use in cancer therapy.

Conclusion

The molecular docking study results suggest that

• Myricetin demonstrates the strongest and most consistent interaction with all four cancer-related kinases.

• Machilin A shows moderate to strong binding, particularly toward Src and ROCK1.

• Elemicin and Myristicin display relatively weak interactions.

These findings indicate that polyphenolic compounds from *Myristica fragrans* may exert anticancer activity through multi-target modulation of adhesion-related kinase signaling pathways involved in tumor progression and metastasis.

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