REVIEW PAPER

Mahanimbine as an AKT1 Modulator in Breast Cancer: Mechanisms and Therapeutic Potential

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ABSTRACT

Breast cancer is the number one cause of morbidity and mortality attributable to cancers in women worldwide. Treatment failure is often due to metastases, recurrence, and resistance to targeted therapies. Dysregulated activation of phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) signaling pathway, especially that involving AKT1, has been implicated as a critical mechanism in the progression of breast cancer by means of enhancing cell proliferation, cell survival, angiogenesis, epithelial-mesenchymal transition, and drug resistance. AKT1, therefore, has become an interesting therapeutic target. Mahanimbine, a carbazole alkaloid found in *Murraya koenigii* (curry leaf), has shown promising anticancer activity via induction of apoptosis, inhibition of proliferation, migration, invasion, and regulation of numerous oncogenic signaling pathways. This paper critically assesses the evidence on the therapeutic potentials of mahanimbine as a regulator of AKT1 signaling in breast cancer. Preliminary results show that mahanimbine inhibits AKT/mTOR signaling in pancreatic cancer along with having pro-apoptotic and anti-metastatic properties in breast cancer models. There is, however, no experimental evidence yet showing AKT1 inhibition in breast cancer which is a huge knowledge gap. Other issues such as comparison between mahanimbine and clinically approved AKT inhibitors, molecular mechanisms, experimental biomarkers, and appropriate approaches for evaluating the efficacy of mahanimbine will be considered in this review. Furthermore, various challenges such as lack of pharmacokinetic information, poor water solubility, no studies on breast cancer xenografts, and no clinical trial will also be discussed in this paper.

Keywords: Breast cancer, AKT-1, *Murraya koenigii*, Mahanimbine, apoptosis

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Introduction

Cancer development is an intricate and complex phenomenon, which is highly influenced by the tumor microenvironment. This makes the need for devising new therapies targeting specific traits and characteristics of different cancers more imperative than ever[1]. Breast cancer is still the most common type of malignant neoplasm, remaining one of the major causes of cancer-related deaths in women globally. In spite of remarkable advances in the early diagnosis and targeted treatment of breast cancer, the risk of recurrence, metastasis, and therapy resistance hinders clinical outcomes. This disease is extremely heterogeneous, featuring several molecular subtypes, namely, luminal A, luminal B, HER2-enriched, and triple-negative breast cancer (TNBC) with specific properties and treatment response [2]. Signaling pathways involved in the development of breast cancer include, for example, the phosphatidylinositol-3-kinase/protein kinase B (PI3K/AKT) pathway which is often dysregulated [3]. The AKT1 kinase as a part of PI3K/AKT signaling axis is responsible for cell proliferation, survival, metabolism, angiogenesis, and apoptosis. The overactivation of AKT1 leads to the development of uncontrolled tumor growth, metastases, epithelial-mesenchymal transition (EMT), therapy resistance, making it an attractive therapeutic target [4]. Despite the clinical activity of selective AKT inhibitors, such as capivasertib, there are issues of toxicity and drug resistance, which makes a search for alternative approaches relevant [5]. Natural bioactive substances have been proven to be efficient modulators of oncogenic signaling pathways[6]. Thus, mahanimbine – a carbazole alkaloid obtained from the plant *Murraya koenigii* (L.) Spreng. – has been shown to have antiproliferative, pro-apoptotic, anti-invasive, and anti-angiogenic activities in breast cancer cells [7]. It has also been found that mahanimbine inhibits AKT/mTOR signaling in experiments on pancreatic cancer cells, which gives reason to consider its potential in targeting AKT1-mediated pathways [8]. However, there is no sufficient data about the role of the

interaction of mahanimbine with AKT1 in breast cancer cells. This review will analyse the current state of knowledge about the biology of AKT1 in breast cancer and discuss the potential of using mahanimbine as a novel natural AKT1-targeted agent in breast cancer therapy.

Mahanimbine: Chemistry and Pharmacology

Mahanimbine is a natural carbazole alkaloid mainly isolated from the leaves of the plant *Murraya koenigii* (L.) Spreng. (Rutaceae), which is known as the curry leaf plant[9]. The mahanimbine molecule consists of a tricyclic carbazole core structure combined with a pyran ring and isoprenyl lipophilic side chains, enabling good membrane permeability and pharmacological diversity[5]. Because of its aromatic core structure and lipophilicity, mahanimbine is expected to be able to interact with various molecular targets and become an excellent lead for anticancer drugs[10]. *Murraya koenigii* is found in India, Sri Lanka, Bangladesh, and other parts of Southeast Asia, where it has been used as an ayurvedic herb in the treatment of diabetes, inflammatory conditions, gastrointestinal problems, and infectious diseases for a long time[11]. Among over forty carbazole alkaloids discovered in this medicinal plant, mahanimbine is one of the main bioactive components responsible for different pharmacological properties [12]. Usually, mahanimbine is obtained from dried leaves using organic solvents like methanol, ethanol, chloroform, or hexane, then purified using silica gel column chromatography, preparative thin-layer chromatography, and HPLC[13]. Identification of the structural formula can be done through NMR (^{1}H and ^{13}C NMR), mass spectrometry (MS), infrared spectroscopy (IR), and ultraviolet-visible spectroscopy (UV-Vis). From the results of pharmacological research, it is shown that mahanimbine possesses many biological activities, including antioxidant, anti-inflammatory, antimicrobial, antidiabetic, anti-obesity, and anticancer properties. In particular, it is demonstrated experimentally that mahanimbine increases insulin sensitivity, prevents adipogenesis, and decreases the level of lipids in animal models with high-fat diet[14]. Moreover, it induces apoptosis and inhibits cell proliferation, angiogenesis, metastasis, and oncogenic signaling pathways (such as AKT/mTOR and STAT3) in breast cancer and other cancer types [15].

PI3K/AKT1 Signaling in Breast Cancer

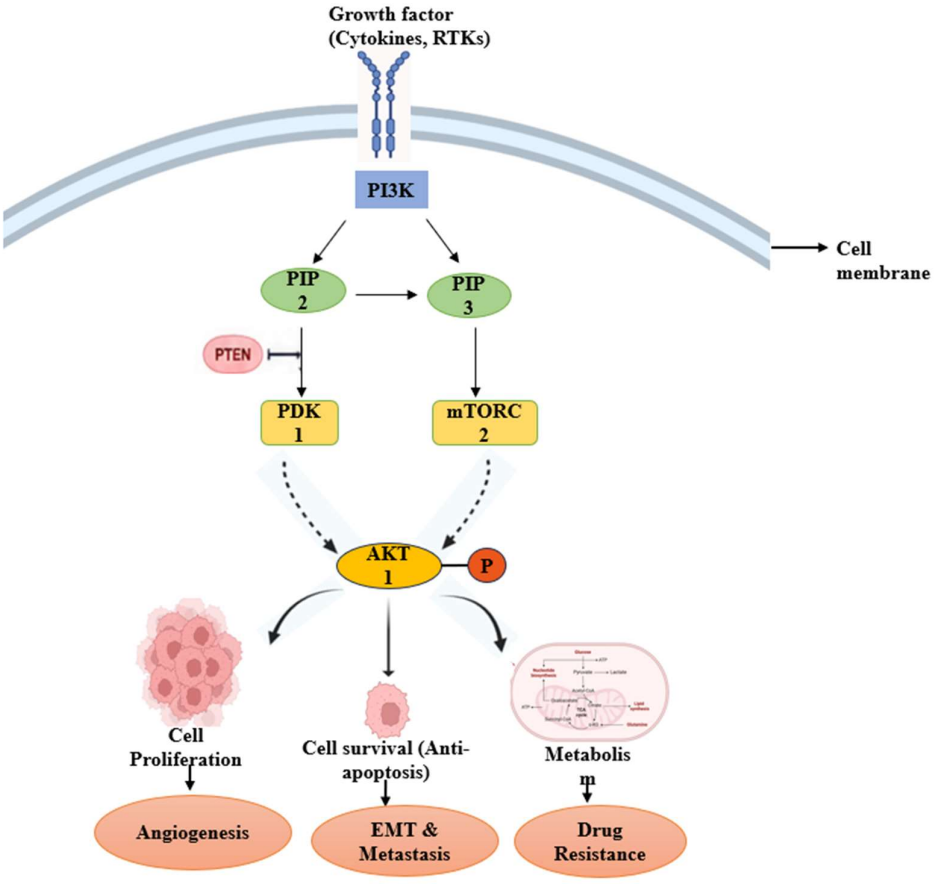

Fig 1: PI3K/AKT Pathway and Role of AKT1 in Breast Cancer

ligand: Over activation of AKT1 leads to: uncontrolled tumour growth; metastasis; EMT; therapy resistance; poor prognosis

Phosphoinositide 3-kinase (PI3K)/AKT/mTOR signaling is a core regulator for cellular proliferation, growth, metabolism, and survival[3]. Typically, stimulation of this pathway occurs following the ligand-binding to RTKs such as EGF and IGF. This leads to RTK autophosphorylation and recruitment of PI3K, which in turn mediates the transformation of PIP2 into PIP3 [4]. Increased levels of PIP3 at the plasma membrane enable the recruitment and activation of AKT, specifically AKT1, through the phosphorylation by PDK1 and mTORC2[16]. Activation of AKT1 further leads to the phosphorylation of a wide array of substrates, among them the mammalian target of rapamycin (mTOR), which controls protein synthesis and growth of cells. mTOR works within two different complexes, mTORC1 and mTORC2, where mTORC1 increases protein synthesis, ribosome biogenesis, and inhibits autophagy [17]. Alteration of this pathway due to PI3K mutations, lack of PTEN (negative regulator of PIP3), and hyperactivation of AKT is commonly seen in various types of cancer[18]. Even though the three isoforms of AKT are structurally similar, AKT1 and AKT2 differ in their biological functions[19]. AKT1 mainly stimulates the proliferation and survival of cells via the inhibition of pro-apoptotic factors such as BAD and caspase-9 while AKT2 has a bigger role in regulating the metabolism of glucose and is heavily associated with cancer cell migration and metastasis[20]. Recent studies show that AKT1 can be an inhibitor of the motility of cells in some cases whereas AKT2 encourages invasion[21]. The PI3K/AKT/mTOR pathway affects many characteristics of cancer in a major way[22]. First, it increases the proliferation of cancer cells via enhanced protein synthesis and cell cycle progression, second it inhibits apoptosis through the inactivation of pro-apoptotic proteins and third it promotes metastasis through regulation of cytoskeleton and epithelial-mesenchymal transition (EMT)[3]. Due to its significant impact on oncogenesis, it is widely used as a therapeutic target with inhibitors available in clinic.

Evidence of MN Modulating AKT Pathways

Mahanimbine (MN) is an anticancer compound obtained from *Murraya koenigii* due to the capability of this natural agent to regulate multiple signaling pathways associated with carcinogenesis[23]. Despite the lack of docking studies that investigate the specific interaction of MN and AKT1, several structure-based computational approaches have recognized AKT1 as a potential drug target for other phytochemicals containing similar chemical structures[24]. Thus, computational modeling has revealed that the hydrophobic carbazole scaffold of MN possesses certain druggability properties allowing to form hydrogen bonds and hydrophobic interactions with catalytic residues, which play an essential role in kinase activation and hence can serve as a rationale for further studies focused on computational validation of binding affinity of MN with AKT1[25]. AKT pathway inhibition by MN has been experimentally studied only for pancreatic cancer cells. Pei et al. showed that MN was capable of suppressing the phosphorylation of AKT and the downstream pathway of mTOR, contributing to the suppression of cell proliferation and the induction of G0/G1 arrest and apoptosis [26]. As a result of that process, MN blocked STAT3 signaling, providing the proof that AKT/mTOR suppression is achieved due to the inhibition of AKT phosphorylation without changes in the expression level of total AKT protein [27]. For breast cancer cells, Hobani et al. have found that MN induced mitochondria-mediated apoptosis in MCF-7 cells via the ROS production, mitochondrial membrane depolarization, caspase-3/7 and -9 activation, Bax/Bcl-2 ratio regulation, as well as MMP-2 and MMP-9 inhibition, resulting in reduced migration and angiogenic potential[7]. Nonetheless, in the experiment, there were no data concerning the inhibition of AKT (p-AKT) or mTOR protein. Hence, based on the evidence obtained from the pancreatic cancer cells, MN probably inhibits AKT/mTOR signaling; however, direct evidence for the inhibition of p-AKT in breast cancer cells is still lacking[26].

MN vs Known AKT Inhibitors

Activation of the PI3K/AKT pathway has become a potential therapeutic strategy in breast cancer treatment, resulting in the development of clinically approved selective AKT inhibitors, namely ipatasertib and capivasertib[28]. Both drugs are ATP-competitive pan-AKT inhibitors which inhibit the kinase activity of AKT1, AKT2, and AKT3 enzymes, suppressing the downstream signaling of mTOR, GSK-3β, and FOXO proteins. Capivasertib showed a clinical benefit in HR+/HER2-advanced breast cancer patients with alterations in the PI3K/AKT/PTEN pathway and recently gained regulatory approval in combination with fulvestrant[29]. Moreover, ipatasertib showed promising efficacy in patients with TNBC and activation of the PI3K pathway [30]. On the contrary, mahanimbine (MN) is a naturally-occurring carbazole alkaloid extracted from *Murraya koenigii* and exhibits multitarget pharmacological activity. Unlike the above-listed molecules, MN does not act as highly selective kinase inhibitor; it promotes apoptosis, inhibits proliferation and migration, suppresses angiogenesis, modulates AKT/mTOR and STAT3 signaling pathways in experimental pancreatic cancer models[26]. MN induces mitochondrial apoptosis and inhibits MMP-2/9-mediated invasion in breast cancer models; however, suppression of AKT1 phosphorylation has not been experimentally proven yet[7]. As a result, MN can be considered a multi-pathway regulator with reduced toxicity compared to the synthetic kinase inhibitors; nevertheless, MN's potency, pharmacodynamics, and target specificity need to be further studied [31].

Compared to the natural AKT regulators, such as curcumin, resveratrol, quercetin, berberine, epigallocatechin gallate (EGCG), and sulforaphane (which show their ability to inhibit PI3K/AKT signaling by suppressing AKT phosphorylation, PTEN activation, and upregulation of the receptor tyrosine kinases)[32], MN is rather underexplored despite promising results in preclinical studies. Another crucial point in the targeted AKT therapy is the isoform specificity of the molecule since AKT1 mainly regulates tumorigenesis and cell survival, while AKT2 stimulates EMT, cell migration, invasion, metabolism, and metastasis. Currently, clinically used AKT inhibitors have pan-AKT inhibitory activity; this feature may lead to such side effects as hyperglycemia and dermatological toxicity[5]. Whether MN specifically affects AKT1 or shows pan-AKT inhibitory activity requires further investigation.

Preclinical Models and Assays

For an extensive preclinical investigation of mahanimbine (MN) as a prospective AKT1-targeted therapeutic agent, many *in vitro* and *in vivo* studies involving clinical models of breast cancer need to be performed [33]. For example, human breast cancer cell lines MCF-7 (estrogen receptor-positive) and MDA-MB-231 (triple negative breast cancer) represent valuable tools for evaluating the effectiveness of MN. The proliferation rate can be measured using MTT, CCK-8, or clonogenic assays, while apoptosis can be quantified with Annexin V/propidium iodide staining, caspase-3/7 assay, TUNEL staining, JC-1/Rhodamine-123 staining of mitochondrial membrane potential, and Western blot analysis of apoptosis markers (Bax, Bcl-2, cleaved caspase-3, caspase-9, and PARP) [7]. As AKT1 activation primarily occurs through phosphorylation, the measurement of phosphorylated AKT (Ser473 and Thr308), total AKT, phosphorylated mTOR, p70S6K, 4E-BP1, GSK-3β, and FOXO3a represents the gold standard for studying AKT pathway inhibition by means of MN[34]. Quantitative RT-PCR and immunofluorescent analysis can provide supplementary data on the AKT gene expression and protein localization, respectively. While no data on MN-induced reduction of the phosphorylation level of AKT in breast cancer cells are available at present, MN has been found to inhibit AKT/mTOR signaling in pancreatic cancer cells [9]. Having successfully performed in vitro investigations, the therapeutic effect of MN needs to be studied in orthotopic or subcutaneous xenograft mouse model based on MCF-7 or MDA-MB-231 cells[8]. In addition to tumor volume, metastasis, survival rate, and the presence of toxicity, immunohistochemical analysis of Ki-67, cleaved caspase-3, phosphorylated AKT, phosphorylated mTOR, CD31, VEGF, and MMP-2/9 will provide additional information about the anti-proliferative, anti-apoptotic, angiogenesis-inhibiting, and invasion-inhibiting effects of MN[26][7]. Overall, all the above-listed biomarkers represent a complex tool for the evaluation of MN action as a prospective AKT1-targeted therapeutic agent for breast cancer.

Challenges and Future Directions

However, several limitations hinder the clinical application of MN as a prospective AKT1-targeted anticancer drug. First, there is a lack of sufficient information concerning the pharmacokinetics (PK) and bioavailability of MN. Similar to most plant-derived alkaloids, MN is insoluble in water. Thus, MN's absorption, plasma half-life, tissue distribution, metabolism, and excretion have not been systemically studied yet, which implies that there is an absence of adequate data about the effective dosage, oral bioavailability, and pharmacodynamics[35]. Therefore, extensive PK and toxicity studies in an appropriate animal model should be conducted before clinical trials of MN are carried out [36]. Secondly, MN's ability to interact directly with the target protein AKT1 should be proven by further experiments. As mentioned above, MN is a naturally derived carbazole alkaloid which, probably, will affect several signaling pathways simultaneously. For instance, MN could have an effect on NF-κB, MAPK, apoptosis via the production of ROS, and mitochondrial dysfunction[37]. Such multitarget activity can provide higher efficacy but, at the same time, lead to off-target and toxicity issues that should be investigated by kinase profiling and phosphoproteomics studies [10]. It is worth mentioning mahanimbine is just studies *in vitro* on breast cancer. Future researches should pay attention to the rational development of MN's analogs with better aqueous solubility, metabolic stability, and specific AKT1-targeting through the use of the structure-based drug design and medicinal chemistry methods. Combination therapies with MN and common chemotherapeutic drugs, PARP inhibitors (e.g., olaparib), endocrine treatment, or AKT inhibitors (capivasertib) can provide enhanced therapeutic effects and overcome the problems related to developing resistance. Further improvements in molecular docking studies, pharmacokinetics and delivery via nanocarriers are anticipated to be key factors in the pre-clinical and clinical developments of mahanimbine (MN) as a targeted cancer treatment[7][38].

Aspect	Current Evidence	Limitation/Research Gap	References
Source	Mahanimbine is a major carbazole alkaloid isolated from *Murraya koenigii* (curry leaves).	Standardization of extraction and purification methods is required.	[39]
Chemical Characteristics	Lipophilic prenylated carbazole alkaloid possessing a tricyclic	Limited structure–activity relationship (SAR) studies.	[35][37]

	carbazole nucleus with pyran ring.		
Breast Cancer Activity	Inhibits proliferation, induces mitochondrial apoptosis, suppresses migration, angiogenesis, and MMP-2/MMP-9 expression in MCF-7 cells.	Validation in additional breast cancer subtypes (e.g., MDA-MB-231, HER2+) is limited.	[7]
AKT/mTOR Signaling	Experimental inhibition of AKT/mTOR and STAT3 signaling demonstrated in pancreatic cancer cells.	Direct confirmation of AKT1 inhibition in breast cancer has not yet been reported.	[26]
In Silico Evidence	AKT1 is a promising molecular target for phytochemicals; carbazole scaffold is compatible with kinase-targeted drug discovery.	No published molecular docking study specifically evaluates mahanimbine–AKT1 interaction.	[40][41]
AKT Biomarkers	Recommended biomarkers include p-AKT (Ser473), p-mTOR, p70S6K, FOXO3a, GSK-3β, Ki-67, cleaved caspase-3, and PARP.	These biomarkers have not yet been comprehensively evaluated following MN treatment in breast cancer models.	[42][43]
***In Vivo* Evidence**	Anticancer efficacy demonstrated in non-breast cancer experimental models; metabolic safety evaluated in rodents.	Breast cancer xenograft studies evaluating MN remain unavailable.	[44]
Pharmacokinetics	Preliminary animal studies suggest biological activity after oral administration.	Comprehensive ADME, bioavailability, metabolism, and toxicity studies are lacking.	[45]
Clinical Translation	No registered clinical trials evaluating MN in breast cancer.	Clinical safety, efficacy, and dose optimization remain unexplored.	[23]
Future Perspectives	Development of synthetic analogues, molecular docking-guided optimization, nanocarrier-based delivery, and combination therapy with AKT inhibitors or PARP inhibitors may improve therapeutic efficacy.	Requires rigorous pharmacological, toxicological, and clinical validation.	[46][47]

Conclusion

Mahanimbine appears to be a potential naturally derived carbazole alkaloid possessing considerable anti-cancer effect against breast cancer due to its capability to modulate numerous processes, among which are cell proliferation, apoptosis, migration, invasion, angiogenesis, and oxidative stress. Currently available data suggest that mahanimbine possesses considerable anti-cancer effect in preclinical experiments as it is capable to induce mitochondrial mediated apoptosis, increase reactive oxygen species production, induce cell cycle arrest, and inhibit metastasis. Experimental results also showed that mahanimbine inhibits the AKT/mTOR pathway in pancreatic cancer models, implying that AKT1 is likely to be a crucial molecular target. However, it is important to note that no direct evidence showing that mahanimbine inhibits AKT1 in breast cancer models has been published yet. Therefore, future research will need to focus on carrying out mechanistic experiments involving diverse types of breast cancer, especially MCF-7 and MDA-MB-231 cells with the use of molecular techniques like Western blotting, RT-qPCR, immunofluorescence, and phosphoproteomics in order to confirm the modulation of AKT1 and its downstream targets. Besides, it is necessary to conduct the experiments related to molecular docking, kinase binding, pharmacokinetics, toxicity and breast cancer xenograft in order to prove the target specificity, efficacy, and safety. Formulation optimization, synthesis of an analogue, and use of nanocarrier delivery system may improve mahanimbine efficacy. Finally, combination of treatments using mahanimbine along with PARP and AKT inhibitors is required to overcome drug resistance.

Statements & Declarations

Author Contributions

Ashapurna Sinha: Conceptualization, Investigation, Writing- original draft.
Farina Mujeeb: Supervision, Validation,
Ahamad Faiz Khan: Review, Editing,
Shahab Uddin: Review.
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Declaration of generative AI and AI-assisted technologies in the writing process
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Competing Interest:
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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REFERENCES

1. A. Hasan, S. F. Rizvi, S. Parveen, N. Pathak, A. Nazir, and S. S. Mir, "Crosstalk between ROS and autophagy in tumorigenesis: understanding the multifaceted paradox," Front. Oncol., vol. 12, p. 852424, 2022.
2. X. Xiong et al., "Breast cancer: pathogenesis and treatments," Signal Transduct. Target. Ther., vol. 10, no. 1, p. 49, 2025.
3. A. Glaviano et al., "PI3K/AKT/mTOR signaling transduction pathway and targeted therapies in cancer," Mol. Cancer, vol. 22, no. 1, p. 138, 2023.
4. Y. Yuan, H. Long, Z. Zhou, Y. Fu, and B. Jiang, "PI3K–AKT-Targeting breast cancer treatments: Natural products and synthetic compounds," Biomolecules, vol. 13, no. 1, p. 93, 2023.
5. D. Hassan, C. W. Menges, J. R. Testa, and A. Bellacosa, "AKT kinases as therapeutic targets," J. Exp. Clin. Cancer Res., vol. 43, no. 1, p. 313, 2024.
6. S. Saxena, M. F. Ali Ahmad, J. Khatoon, and I. A. Ansari, "Therapeutic prospects of methanolic extracts of Datura stramonium and Datura metel against non-small cell lung carcinoma cells: in vitro evaluation of antioxidant and cytotoxic potentials.," Biochem. Cell. Arch., vol. 25, no. 2, p. 2121, 2025.
7. Y. H. Hobani, "Cytotoxicity of Mahanimbine from Curry Leaves in Human Breast Cancer Cells (MCF-7) via Mitochondrial Apoptosis and Anti-Angiogenesis," Molecules, vol. 27, no. 3, p. 971, Feb. 2022, doi: 10.3390/molecules27030971.
8. S. K. Samanta et al., "Phytochemical portfolio and anticancer activity of Murraya koenigii and its primary active component, mahanine," Pharmacol. Res., vol. 129, pp. 227–236, Mar. 2018, doi: 10.1016/j.phrs.2017.11.024.
9. E. W. C. Chan and S. K. Wong, "Constituents of carbazole alkaloids and anti-cancer properties of extracts, mahanine, isomahanine, mahanimbine, and girinimbine from Bergera koenigii," J. Appl. Pharm. Sci., 2024.
10. P. Mondal, J. Natesh, A. A. A. Salam, and S. M. Meeran, "Mahanimbine isolated from Murraya koenigii inhibits P-glycoprotein involved in lung cancer chemoresistance," Bioorg. Chem., vol. 129, p. 106170, 2022.
11. D. T. Abeysinghe, D. Alwis, K. A. H. Kumara, and U. G. Chandrika, "Nutritive importance and therapeutics uses of three different varieties (Murraya koenigii, Micromelum minutum, and Clausena indica) of curry leaves: An updated review," Evidence-Based Complement. Altern. Med., vol. 2021, no. 1, p. 5523252, 2021.
12. M. A. Tan, N. Sharma, and S. S. A. An, "Multi-Target approach of Murraya koenigii leaves in treating neurodegenerative diseases," Pharmaceuticals, vol. 15, no. 2, p. 188, 2022.
13. S. M. Jachak, A. Goyal, A. Dey, S. Kulshreshtha, and K. N. Deshmukh, "Experimental Protocols in Phytochemistry and Natural Products: An Ever-Evolving Challenge," in The Quintessence of Basic and Clinical Research and Scientific Publishing, Springer, 2023, pp. 149–168.
14. S. M. Jachak, M. S. Thakur, P. Ahirrao, and A. Goyal, "Murraya koenigii (L.) Spreng. as a natural intervention for diabesity: a review," Curr. Pharm. Des., vol. 30, no. 41, pp. 3255–3275, 2024.
15. S. K. Samanta et al., "Mahanine mediated therapeutic inhibition of estrogen receptor-α and CDK4/6 expression, decipher the chemoprevention-signaling cascade in preclinical model of breast cancer," J. Ethnopharmacol., vol. 319, p. 117235, 2024.
16. L. Truebestein et al., "Structure of autoinhibited Akt1 reveals mechanism of PIP3-mediated

activation," Proc. Natl. Acad. Sci., vol. 118, no. 33, p. e2101496118, 2021.
17. H. Zhang, X. Xiao, Z. Pan, and S. Dokudovskaya, "mTOR signaling networks: mechanistic insights and translational frontiers in disease therapeutics," Signal Transduct. Target. Ther., vol. 10, no. 1, p. 428, 2025.
18. Q. Li, Z. Li, T. Luo, and H. Shi, "Targeting the PI3K/AKT/mTOR and RAF/MEK/ERK pathways for cancer therapy," Mol. Biomed., vol. 3, no. 1, p. 47, 2022.
19. Z. Ahmad and P. R. Somanath, "AKT isoforms in the immune response in cancer," PI3K AKT Isoforms Immun. Mech. Ther. Oppor., pp. 349–366, 2022.
20. V. Bhatia, V. Vikram, A. Chandel, and A. Rattan, "Interplay between PI3k/AKT signaling and caspase pathway in Alzheimer disease: mechanism and therapeutic implications," Inflammopharmacology, vol. 33, no. 4, pp. 1785–1802, 2025.
21. S. Basu, B. Veeraraghavan, and A. Anbarasu, "Anti-bacterial compounds from Indian curry-leaf tree Murraya koenigii have potential to inhibit carbapenem-resistant Streptococcus pneumoniae," Clin. Epidemiol. Glob. Heal., vol. 28, p. 101511, 2024.
22. M. Fatma, S. Parveen, and S. S. Mir, "Unraveling the kinase code: Role of protein kinase in lung cancer pathogenesis and therapeutic strategies," Biochim. Biophys. Acta (BBA)-Reviews Cancer, vol. 1880, no. 3, p. 189309, 2025.
23. A. Aniqa, S. Kaur, and S. Sadwal, "A Review of the Anti-Cancer Potential of Murraya koenigii (Curry Tree) and Its Active Constituents," Nutr. Cancer, vol. 74, no. 1, pp. 12–26, Jan. 2022, doi: 10.1080/01635581.2021.1882509.
24. G. Jeyaraj, B. Yang, K. Sathishkumar, S. Chokkakula, B. O. Almutairi, and W. Xie, "Pharmacogenomic and in silico identification of isoform-selective AKT inhibitors from Pithecellobium dulce for precision cancer therapy," Front. Pharmacol., vol. 16, p. 1744408, 2026.
25. J. Michael, "Structure–Activity Relationship Studies of Heterocyclic Scaffolds for Targeted Anticancer Drug Development," 2026.
26. C. Pei, Q. He, S. Liang, and X. Gong, "Mahanimbine exerts anticancer effects on human pancreatic cancer cells by triggering cell cycle arrest, apoptosis, and modulation of AKT/mammalian target of rapamycin (mTOR) and signal transducer and activator of transcription 3 (STAT3) signalling pathways," Med. Sci. Monit. Int. Med. J. Exp. Clin. Res., vol. 24, p. 6975, 2018.
27. M. Figueiredo da Silva et al., "Anticancer drug discovery from natural compounds targeting PI3K/AKT/mTOR signaling pathway," Curr. Med. Chem., vol. 32, no. 24, pp. 4859–4887, 2025.
28. F. Martorana et al., "AKT inhibitors: new weapons in the fight against breast cancer?," Front. Pharmacol., vol. 12, p. 662232, 2021.
29. C. Gong et al., "Precision diagnosis and treatment of PI3K/AKT/PTEN signaling pathway in HR-positive advanced breast cancer: perspectives from Chinese experts," Transl. Breast Cancer Res., vol. 6, p. 36, 2025.
30. N. C. Turner et al., "Capivasertib in hormone receptor–positive advanced breast cancer," N. Engl. J. Med., vol. 388, no. 22, pp. 2058–2070, 2023.
31. K. Olofinsan, H. Abrahamse, and B. P. George, "Therapeutic role of alkaloids and alkaloid derivatives in cancer management," Molecules, vol. 28, no. 14, p. 5578, 2023.
32. A. K. Sah et al., "Targeting Cancer Stem Cells with Phytochemicals: Molecular Mechanisms and Therapeutic Potential," Biomedicines, vol. 14, no. 1, p. 215, 2026.
33. P. M. K. Nair et al., "Exploring the anticancer potential of traditional herbs from Tamil Nadu: a narrative review of ethnomedicinal insights and scientific evidence," Front. Immunol., vol. 16, p. 1680062, 2025.
34. P.-J. Tsai, Y.-H. Lai, R. K. Manne, Y.-S. Tsai, D. Sarbassov, and H.-K. Lin, "Akt: a key transducer in cancer," J. Biomed. Sci., vol. 29, no. 1, p. 76, 2022.
35. S. I. A. Abdel-dayem et al., "Therapeutic Potentials of Girinimbine, A Carbazole Alkaloid: A Review," Rev. Bras. Farmacogn., vol. 36, no. 1, p. 30, 2026.
36. A. Meressa et al., "Multi-targeted molecular docking, pharmacokinetic analysis, and drug-likeness evaluation of alkaloids for anti-diabetic drug development," BRICS Heal. J., vol. 2, no. 1, pp. 53–68, 2025.
37. M. A. Tan, N. Sharma, and S. S. A. An, "Phyto-carbazole alkaloids from the Rutaceae family as potential protective agents against neurodegenerative diseases," Antioxidants, vol. 11, no. 3, p. 493, 2022.
38. A. M. Elbagory, R. M. Marima, and Z. Dlamini, "Role and merits of green based nanocarriers in

cancer treatment," Cancers (Basel)., vol. 13, no. 22, p. 5686, 2021.
39. R. Jan, A. J. Shah, T. U. Wani, S. Farooq, S. M. Jachak, and M. H. Masoodi, "Curry Leaf: An insight into its Pharmacological Activities, Medicinal Profile, and Phytochemistry," Sci. Spices Culin. Herbs-Latest Lab. Pre-clinical, Clin. Stud., vol. 4, pp. 145–168, 2021.
40. Z. Mirza and S. Karim, "Structure-based profiling of potential phytomolecules with AKT1 a key cancer drug target," Molecules, vol. 28, no. 6, p. 2597, 2023.
41. P. S. Waghmare, A. R. Chabukswar, K. G. Raut, and P. T. Giri, "A Review on Carbazole and Its Derivatives as Anticancer Agents From 2013 to 2024," Chirality, vol. 37, no. 2, p. e70021, 2025.
42. R. Colomer et al., "Biomarkers in breast cancer 2024: an updated consensus statement by the Spanish Society of Medical Oncology and the Spanish Society of Pathology," Clin. Transl. Oncol., vol. 26, no. 12, pp. 2935–2951, 2024.
43. H. Hua, H. Zhang, J. Chen, J. Wang, J. Liu, and Y. Jiang, "Targeting Akt in cancer for precision therapy," J. Hematol. Oncol., vol. 14, no. 1, p. 128, 2021.
44. Z. Feng et al., "Iterative Design of a Prodrug Nanocarrier for Cell Cycle Arrest, Immune Modulation, and Enhanced T Cell Infiltration for Colon Cancer Therapy," Nano Lett., vol. 25, no. 7, pp. 2820–2830, 2025.
45. A. Al Shoyaib, S. R. Archie, and V. T. Karamyan, "Intraperitoneal route of drug administration: should it be used in experimental animal studies? Al Shoyaib, Archie and Karamyan," Pharm. Res., vol. 37, no. 1, p. 12, 2020.
46. H. Singhai, S. Raikwar, S. Rathee, and S. K. Jain, "Emerging combinatorial drug delivery strategies for breast cancer: a comprehensive review," Curr. Drug Targets, vol. 26, no. 5, pp. 331–349, 2025.
47. D. Bose, S. Shetty, A. Udupi, and K. Srinivasan, "Murraya koenigii as a Phytotherapeutic Agent in Breast Cancer: A Comprehensive Review," Pharmacol. Res. Prod., p. 100487, 2025.