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Original Research Article

Nutraceutical Iridoid Glycoside Monotropein Induces Apoptosis and Suppresses PI3K/Akt/mTOR Signaling in Breast Cancer Cells: An *In Vitro* Evaluation

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Abstract

Background: The rising global burden of breast cancer, marked by increasing incidence and mortality rates, has intensified the pursuit of anti-cancer agents that are both effective and mechanistically targeted while minimizing systemic toxicity. In this context, nutraceuticals are being explored for their therapeutic potential due to their capacity to influence multiple oncogenic and survival pathways, their favorable safety profiles, and their potential to complement or enhance conventional chemotherapeutic approaches. Monotropein, a plant-derived iridoid glycoside, has garnered considerable interest owing to its diverse pharmacological activities, including anti-inflammatory, antioxidant, and cytoprotective effects. Despite these documented bioactivities, the specific anti-cancer mechanisms of monotropein, particularly in the context of breast carcinoma, remain inadequately explored.
Objectives: The present study aims to elucidate the anti-cancer potential of monotropein in a breast adenocarcinoma cell line.
Materials and Methods: The anti-cancer potential of monotropein was assessed using an *in vitro* breast cancer model. Cytotoxicity was assessed in MCF-7 breast adenocarcinoma cells and normal Vero epithelial cells using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay, and the IC_{50} value of monotropein was determined. Nuclear morphological alterations induced by monotropein were examined through DAPI (4′,6-diamidino-2-phenylindole) staining. Apoptosis was further validated by quantifying caspase activation and the expression of key apoptotic regulators in monotropein-treated MCF-7 cells. In addition, phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling proteins were measured to elucidate the compound's mechanistic effects.
Results: Our findings demonstrated that monotropein exhibited selective anti-cancer activity against breast cancer cells. Increased caspase activity and elevated Bax levels, accompanied by a decline in the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2), were observed in the MCF-7 cells treated with monotropein. Furthermore, monotropein treatment significantly downregulated PI3K, Akt, and mTOR protein expression. Collectively, these findings demonstrate that monotropein exerted an anti-cancer effect in the breast adenocarcinoma cell line through the activation of the apoptotic cascade and suppression of PI3K/Akt/mTOR signaling.
Conclusion: These findings highlight monotropein's potential as a nutraceutical-based therapeutic candidate, although further investigations are required to validate its efficacy and underlying mechanisms in advanced pre-clinical models.

Keywords

Anti-cancer drug, apoptosis, *in vitro*, monotropein, nutraceutical, PI3K/Akt/mTOR signaling

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Introduction

Nutraceuticals have emerged as a prominent class of health-promoting products that bridge the gap between conventional nutrition and therapeutic interventions. These bioactive compounds, derived from natural food sources, are recognized for offering physiological benefits and contributing to disease prevention and management beyond foundational nutritional support (Arshad et al., 2025; Ruby et al., 2021; Sachdeva et al., 2020). The category encompasses a diverse range of

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substances, including essential nutrients, herbal derivatives, phytochemicals, dietary fibers, probiotics, and prebiotics, as well as fortified and recombinant formulations developed through modern biotechnological processes (AlAli et al., 2021). Compared with synthetic pharmaceuticals, nutraceuticals are widely valued for their favorable safety profiles, reduced risk of side effects, accessibility, and lower cost (Puri et al., 2022).

The therapeutic relevance of nutraceuticals has broadened substantially, with numerous studies demonstrating their potential to modulate biological pathways associated with chronic disease onset and progression (Bergamin et al., 2019; Fatima et al., 2025). They have been investigated as alternatives or adjuncts to conventional pharmacological therapies for a wide spectrum of conditions, including cardiovascular disorders, cancer, diabetes, and other neurological or metabolic dysfunctions (Chopra et al., 2022; Nasri et al., 2014). Their efficacy is attributed to a variety of mechanisms, such as antioxidant and anti-inflammatory actions, immune modulation, regulation of metabolic homeostasis, and the presence of unique phytoconstituents capable of exerting biochemical effects not typically observed in conventional drugs (Krishan & Sarvesh, 2015).

Globally, the nutraceutical sector continues to expand at an accelerated pace. Recent estimates value the market at approximately $117 billion, with projections indicating a rise to nearly $404.8 billion by 2025 (Habeeba, 2022; Sachdeva et al., 2020). Among the fastest-growing segments are dietary supplements and natural or herbal formulations, which exhibit annual growth rates of 19.5% and 11.6%, respectively (Ruby et al., 2021). Market expansion is driven by increasing consumer preference for preventive healthcare strategies, rising disposable income, and growing investments in wellness-oriented products, particularly across regions such as the USA, India, and Europe (Precedence Research, 2025). Collectively, these trends highlight the growing scientific and economic significance of nutraceuticals and underscore their potential as valuable agents in promoting long-term health and mitigating disease risk.

Monotropein, an iridoid glycoside primarily derived from *Morinda officinalis*, has emerged as a noteworthy nutraceutical and pharmaceutical candidate owing to its diverse pharmacological activities (Wu et al., 2023; Zhao et al., 2018). Experimental evidence demonstrates that monotropein exhibits significant anti-inflammatory (Choi et al., 2005; Jiang et al., 2020), antioxidant (Shi et al., 2020), anti-osteoporotic (Wang & He, 2020), and cytoprotective effects (Zhu et al., 2019), largely mediated through the regulation of critical molecular pathways, including nuclear factor kappa B (NF-κB), phosphoinositide 3-kinase/protein kinase B (PI3K/Akt), and intrinsic apoptotic signaling networks (Jiang & Lin, 2025; Wu et al., 2023; Zhu et al., 2016). Its plant-derived origin, coupled with a favorable safety profile and desirable pharmacokinetic characteristics, positions monotropein within the growing class of nutraceutical agents capable of conferring therapeutic benefits with reduced adverse effects relative to conventional chemotherapeutics.

Breast cancer is the most frequently occurring malignancy in women and continues to be a major contributor to cancer mortality worldwide (Cai et al., 2025). Despite advancements in screening, diagnosis, and therapeutic strategies, the disease imposes a substantial public health burden, particularly in regions with constrained healthcare resources (World Health Organization, 2025). Epidemiological forecasts further underscore the urgency of developing novel and effective therapeutic agents; by the year 2050, global breast cancer incidence is projected to escalate by nearly 38%, while mortality rates are expected to increase by approximately 68%. Notably, these increases are predicted to disproportionately impact populations in countries with a low Human Development Index (HDI), where limited access to early detection, specialized care, and advanced treatment modalities contributes to poorer clinical outcomes (Kim et al., 2025). Given these rising trends, the exploration of bioactive compounds such as monotropein offers promising prospects for developing safer, more accessible, and mechanistically targeted interventions for breast cancer management. In this context, the current investigation utilized an *in vitro* experimental model to comprehensively analyze the anti-cancer potential of monotropein in a breast adenocarcinoma cell line.

Materials and Methods

Chemicals

Monotropein (purity: ≥95.0%) was purchased from Sigma-Aldrich, USA. The assay kits were commercially purchased from Abcam and MyBioSource, USA, respectively.

Cell Culture

MCF-7 breast adenocarcinoma cells and Vero kidney epithelial cells were obtained from a certified repository and cultured in high-glucose Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS), 1% penicillin-streptomycin, and 2 mM l-glutamine. Cells were maintained at 37 °C in a humidified 5% CO_2 incubator. Frozen stocks were thawed at 37 °C, transferred to warm complete medium, centrifuged, and seeded into T-25 flasks. Cultures were refreshed every 2–3 days and passaged at 70%–80% confluence using 0.25% trypsin-ethylenediaminetetraacetic acid (EDTA). Detached cells were collected, centrifuged, and reseeded at the required density. Routine monitoring was performed to ensure normal morphology and contamination-free cultures.

Cytotoxicity Assay

Cell viability in MCF-7 and Vero cells following monotropein treatment was evaluated using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Mosmann, 1983). Cells were seeded in 96-well plates

(MCF-7: 5 × 10^3 cells/well; Vero: 1 × 10^3 cells/well) and allowed to adhere for 24 h. Monotropein, dissolved in dimethyl sulfoxide (DMSO) (final DMSO ≤0.1%), was added at concentrations of 0, 5, 10, 25, 50, and 100 µM, and the cells were incubated for 24 h at 37 °C in 5% CO_2. Following treatment, 10 µL of MTT solution (5 mg/mL) was added, and plates were incubated for 3 h. The medium was removed, formazan crystals were dissolved in 100 µL DMSO, and absorbance was recorded at 570 nm. Blank and vehicle controls were included for normalization. Cell viability was expressed relative to the vehicle group, and IC_{50} values were obtained through non-linear regression analysis.

DAPI Nuclear Staining Assay

MCF-7 cells were plated on sterile coverslips in 24-well plates (5 × 10^3 cells/well) and allowed to adhere for 24 h. Cells were then exposed to monotropein (25 µM), doxorubicin (2 µg; positive control), or vehicle (≤0.1% DMSO) for 24 h. After treatment, coverslips were rinsed with phosphate-buffered saline (PBS) and fixed in 4% paraformaldehyde for 10 min. Cells were washed, permeabilized with 0.1% Triton X-100 when required, and stained with DAPI (4′,6-diamidino-2-phenylindole) (1 µg/mL) for 5 min in the dark. Excess stain was removed with saline, and coverslips were mounted using an anti-fade medium. Nuclear morphology was visualized using a fluorescence microscope with a DAPI filter set under identical exposure conditions. For each experiment, a minimum of five randomly selected fields per coverslip were imaged.

Enzyme-linked Immunosorbent Assay for Apoptotic Proteins

MCF-7 cells were seeded in 6-well plates (2 × 10^3 cells/well) and allowed to attach for 24 h before treatment with monotropein (25 µM), doxorubicin (2 µg), or vehicle (≤0.1% DMSO) for an additional 24 h. All experiments were performed in biological triplicates. Following treatment, cells were washed with cold PBS and lysed on ice using radioimmunoprecipitation assay (RIPA) buffer containing protease and phosphatase inhibitors. Lysates were clarified by centrifugation (12,000 × *g*, 15 min, 4 °C), and protein content was quantified using a bicinchoninic acid (BCA) assay. Caspase-3, caspase-9, Bcl-2-associated X protein (BAX), and B-cell lymphoma 2 (Bcl-2) levels were measured using Abcam enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions. Standards and samples were added to antibody-coated wells, incubated for 2 h, washed, and treated with horseradish peroxidase (HRP)-conjugated detection antibodies for 1 h. After additional washing, 3,3′,5,5′-tetramethylbenzidine (TMB) substrate was added, and color was allowed to develop for 10 min before adding stop solution. Absorbance was recorded at 450 nm.

Quantification of PI3K/Akt/mTOR

The PI3K/Akt/mammalian target of rapamycin (mTOR) signaling axis is among the most commonly altered pathways in malignant cells. To assess its modulation, PI3K, Akt, and mTOR protein levels were measured in control, monotropein-treated, and doxorubicin-treated MCF-7 cells using ELISA kits from MyBioSource. All procedures followed the manufacturer's protocol, with analyses performed in triplicate. Absorbance values were recorded at 450 nm using a microplate reader.

Statistics

All experiments were performed in at least three independent biological replicates to ensure data reliability. Quantitative outcomes were analyzed using one-way analysis of variance (ANOVA), followed by Tukey's *post hoc* test for comparisons among treatment groups using GraphPad software (version 10.2.0). Data are expressed as mean ± standard deviation (SD), and differences were considered statistically significant at $*p < .05$.

Results

Cytotoxic Effect of Iridoid Glycoside Monotropein in Adenocarcinoma and Normal Epithelial Cells

Figure 1 depicts the selective cytotoxic effect of iridoid glycoside monotropein on human breast adenocarcinoma (MCF-7) cells. Treatment of MCF-7 breast cancer cells with monotropein for 24 h resulted in a clear concentration-dependent reduction in cell viability as assessed by the MTT assay. Compared with the untreated control group, monotropein at 5 µM produced a slight decrease in viability, whereas more pronounced cytotoxicity was observed at 10, 25, 50, and 100 µM. Viability declined progressively from approximately 92 ± 0.4% at 5 µM to nearly 27 ± 0.2% at 100 µM, indicating substantial growth inhibition at higher concentrations. The calculated IC_{50} value for MCF-7 cells was 25 µM, consistent with the marked reduction in viability observed at this concentration. In contrast, monotropein demonstrated negligible cytotoxicity in Vero cells across all tested concentrations. Cell viability remained close to control levels, with no significant reduction even at the highest concentration of 100 µM, indicating a favorable selectivity profile toward cancer cells over normal cells.

Effect of Iridoid Glycoside Monotropein and Doxorubicin on Nuclear Integrity in MCF-7 Cells

Figure 2 illustrates the nuclear morphological alterations in MCF-7 cells following iridoid glycoside monotropein and standard chemotherapeutic drug doxorubicin treatment. DAPI staining revealed distinct differences in nuclear density among the treatment groups. Vehicle-treated MCF-7 cells displayed a

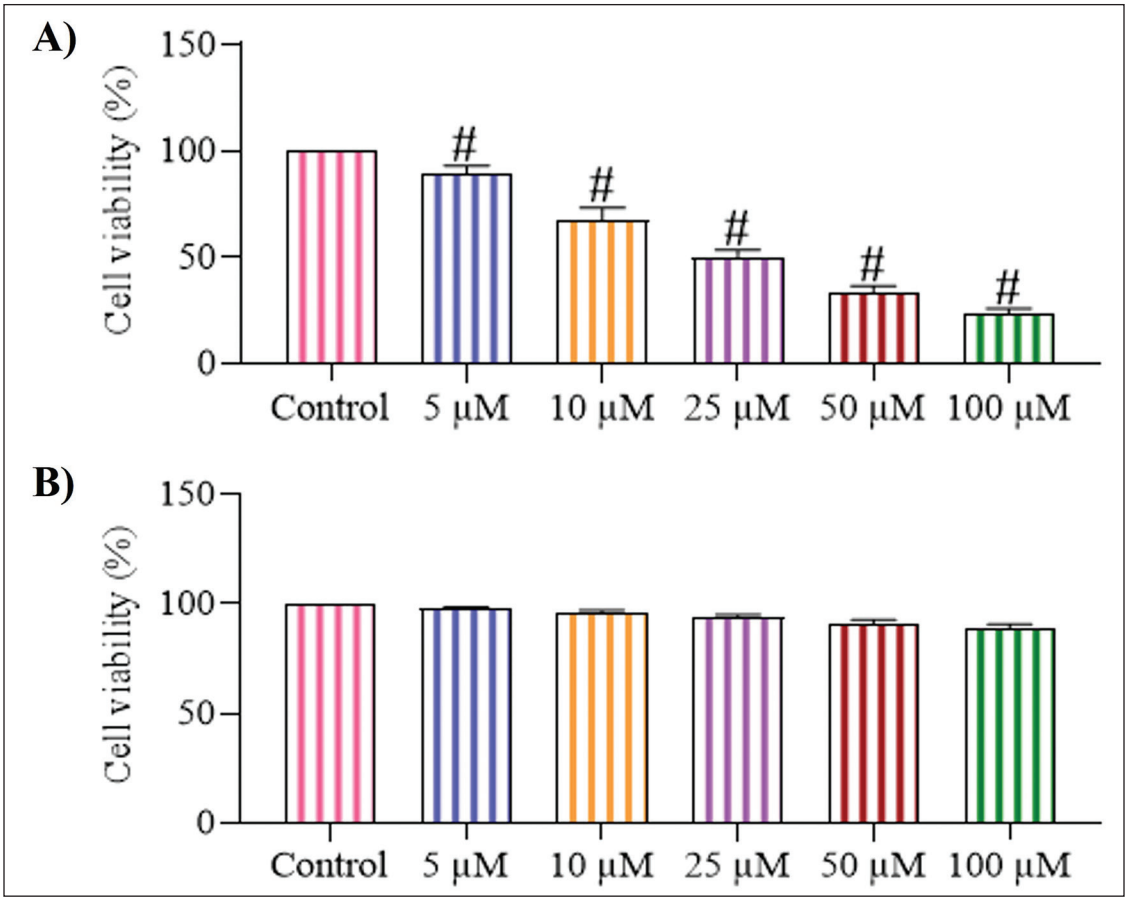


Figure 1. Cytotoxic Effect of Iridoid Glycoside Monotropein on MCF-7 and Vero Cells Assessed by MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium Bromide) Assay. (A) MCF-7 Adenocarcinoma Cells and (B) Vero Epithelial Cells Were Treated With Increasing Concentrations of Monotropein (5–100 μM) for 24 h, and Cell Viability Was Quantified Using the MTT Assay. Monotropein Induced a Dose-dependent Reduction in Viability in MCF-7 Cells, With IC_{50} Value of 25 μM. Vero Cells Maintained >90% Viability Across All Concentrations Tested. Data are Presented as Mean ± Standard Deviation (SD). A Value of $^{\#}p < .05$ Was Considered to Indicate Statistically Significant Differences Among the Groups.

moderate number of intact nuclei, consistent with normal cell growth. Exposure to monotropein (25 μM) for 24 h resulted in a pronounced reduction in nuclear count, indicating substantial loss of viable cells and suggesting cytotoxic activity at the IC_{50} concentration. Doxorubicin-treated cells exhibited the most marked decrease in DAPI-positive nuclei, accompanied by evident nuclear condensation and fragmentation, which are characteristic of advanced apoptotic changes.

Effects of Iridoid Monotropein on Caspase Activation and Bcl-2 Family Proteins in MCF-7 Cells

Figure 3 signifies the apoptotic signaling responses induced by iridoid glycoside monotropein in MCF-7 cells. Bax-mediated mitochondrial permeabilization and caspase activation represent a central strategy for promoting programmed cell death in malignant cells. Monotropein (25 μM) and doxorubicin significantly modulated the expression of key apoptotic regulators in MCF-7 cells compared with the untreated control. Caspase-9 activity increased from 98 ± 0.5 units in control cells to 169 ± 0.9 units following monotropein treatment and further to 187 ± 0.4 units in the doxorubicin group. A comparable trend was observed for caspase-3, with activity rising from 102 ± 0.5 units in the control to 182 ± 0.3 units in monotropein-treated cells and 194 ± 0.4 units with doxorubicin, demonstrating robust activation of the intrinsic apoptotic cascade. The pro-apoptotic protein Bax also showed a marked elevation, increasing from 23 ± 0.4 units in the control to 72 ± 0.4 units after monotropein treatment and 78 ± 0.5 units following doxorubicin exposure. In contrast, the anti-apoptotic protein Bcl-2 declined substantially, decreasing from 74 ± 0.9 units in control cells to 57 ± 0.7 units with monotropein and to 32 ± 0.5 units in the doxorubicin group.

Inhibitory Effects of Iridoid Glycoside Monotropein on PI3K/Akt/mTOR Signaling Proteins in MCF-7 Cells

Figure 4 depicts the iridoid glycoside monotropein treatment-induced PI3K/Akt/mTOR survival signaling modulation in MCF-7 cells. The PI3K, Akt, and mTOR signaling axis is

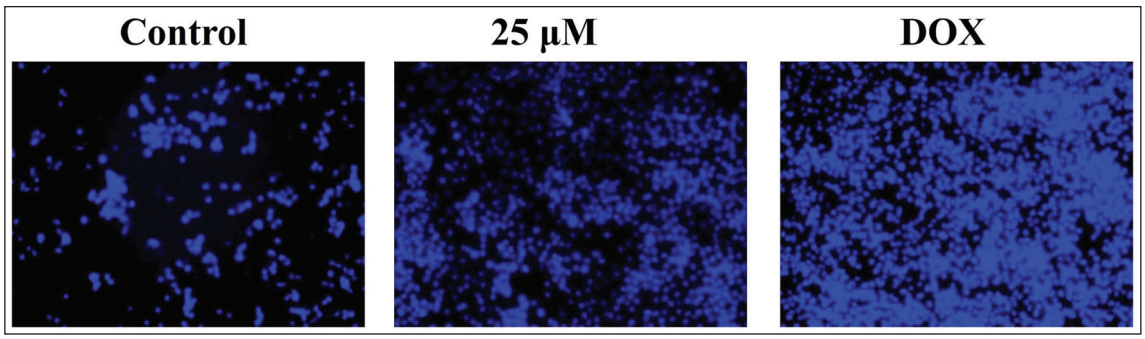


Figure 2. Effect of Iridoid Glycoside Monotropein on Nuclear Morphology in MCF-7 Cells. MCF-7 Cells Were Treated with Monotropein (25 µM) and Doxorubicin for 24 h, Followed by DAPI (4′,6-Diamidino-2-phenylindole) Staining to Assess Nuclear Integrity. Results Showed That Monotropein Treatment Induced Apoptosis in MCF-7 Cells.

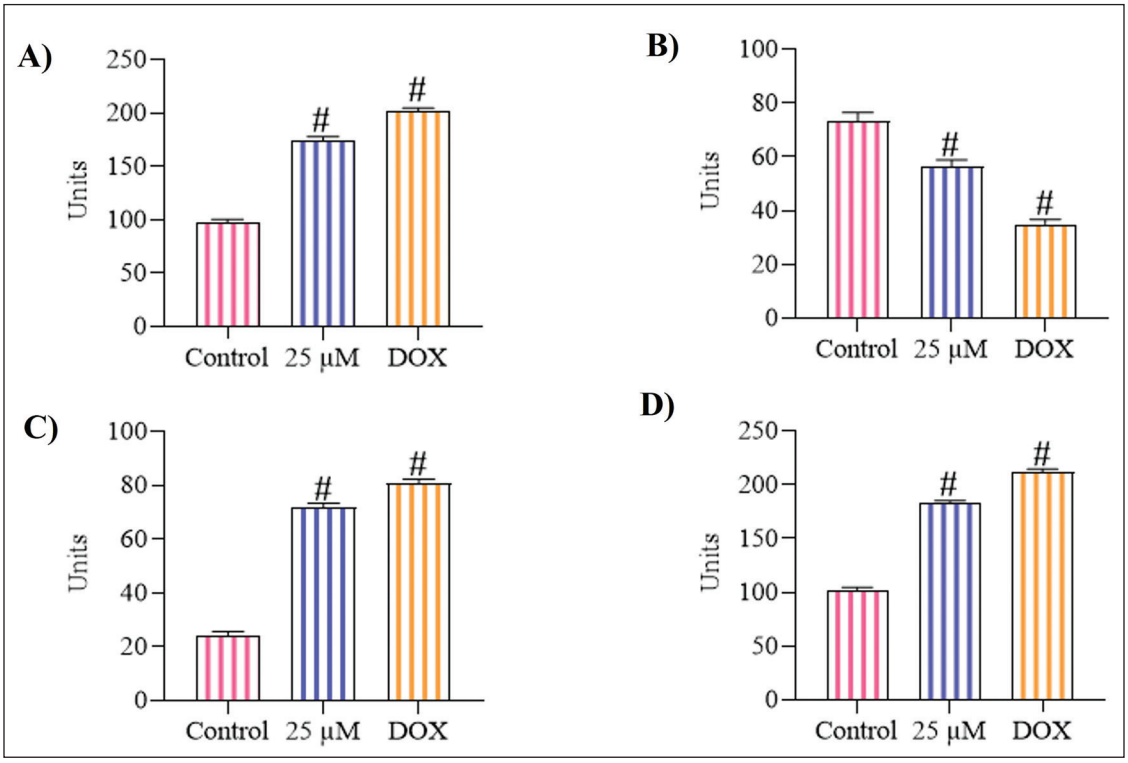


Figure 3. Modulation of Intrinsic Apoptotic Markers by Iridoid Glycoside Monotropein in MCF-7 Cells. Cells Were Treated With Vehicle, Monotropein (25 µM), or Doxorubicin for 24 h. (A) Caspase-9, (B) B-cell Lymphoma 2, (C) Bcl-2-associated X Protein, (D) Caspase-3 Levels Were Quantified Using Enzyme-linked Immunosorbent Assay (ELISA) Technique. Data Represent Mean ± Standard Deviation (SD). A Value of $p < .05$ Was Considered to Indicate Statistically Significant Differences Among the Groups.

pivotal in the regulation of cancer cell survival, proliferation, metabolic reprogramming, and resistance to therapy. Overactivation of the PI3K/Akt/mTOR pathway is a well-established hallmark of many cancers, including breast carcinoma. Monotropein (25 µM) and doxorubicin produced a substantial inhibitory effect on the PI3K/Akt/mTOR signaling cascade in MCF-7 cells evaluated against the control group. PI3K levels decreased from 26 ± 0.9 units in the control to 17 ± 0.6 units following monotropein treatment and further to 15 ± 0.3 units in doxorubicin-treated cells. Akt expression showed a similar downward pattern, declining from 8.7 ± 0.009 units in the control group to 7.2 ± 0.003 units with monotropein and 6.5 ± 0.003 units with doxorubicin. mTOR levels also dropped from 8.3 ± 0.007 units in control cells to 6.8 ± 0.004 units after monotropein exposure and 4.7 ± 0.005 units in the doxorubicin group.

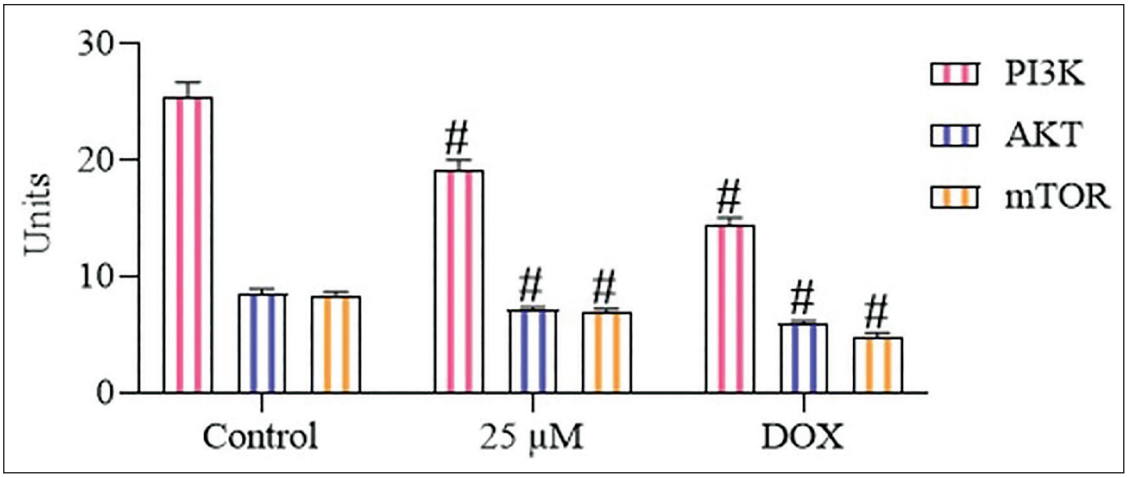


Figure 4. Inhibitory Effect of Monotropein on Phosphoinositide 3-kinase/Protein Kinase B/Mammalian Target of Rapamycin (PI3K/Akt/mTOR) Signaling in MCF-7 Cells. Protein Levels of (A) Phosphatidylinositol 3-kinase, (B) Protein Kinase B, and (C) Mechanistic Target of Rapamycin Were Quantified After 24 h Treatment with Vehicle, Monotropein (25 µM), or Doxorubicin Using Enzyme-linked Immunosorbent Assay (ELISA) Technique. Data Represent Mean ± Standard Deviation (SD). A Value of $p < .05$ Was Considered to Indicate Statistically Significant Differences Among the Groups.

Discussion

Breast cancer continues to represent a major global health burden, owing to its complex molecular heterogeneity and variable clinical behavior, which collectively hinder the development of universally effective therapeutic strategies (Bray et al., 2024; Giaquinto et al., 2022; Loibl et al., 2021; Siegel et al., 2024). Current treatment modalities, including endocrine therapy, anti-HER2-directed agents, chemotherapy, and radiotherapy, are applied based on tumor subtype and receptor status (Burguin et al., 2021). Although these approaches have substantially improved survival outcomes, their clinical utility is often constrained by treatment-related toxicities. Cardiotoxicity remains one of the most critical adverse effects, with radiotherapy shown to elevate the risk of myocardial injury and cardiovascular disease. Moreover, systemic therapies can precipitate additional complications such as reduced bone mineral density, osteoporosis, and ovarian dysfunction (Salata et al., 2021). Thus, despite advances in precision oncology, the persistence of long-term morbidities and therapy-induced physiological challenges underscores the need for safer, more targeted interventions. Continued research aimed at mitigating these adverse effects and enhancing therapeutic specificity is essential for improving overall patient outcomes (Habibi et al., 2025).

Nutraceuticals, which are bioactive constituents derived from natural dietary sources, are increasingly recognized as valuable adjuncts in oncology, complementing conventional modalities such as chemotherapy and radiotherapy (Augimeri et al., 2021; Cicero et al., 2019; Li et al., 2015). These compounds exert multifaceted anti-cancer effects, including modulation of oxidative stress, attenuation of inflammatory responses, inhibition of oncogenic cell growth, and apoptosis (Prakash & Bajpai, 2026). Evidence further suggests that specific nutraceuticals, such as flavonoids, omega-3 fatty acids, and various antioxidants, may enhance tumor cell sensitivity to standard therapies while improving overall treatment outcomes (Aggarwal et al., 2025; Krubaa et al., 2025). Among these agents, the iridoid glycoside monotropein, predominantly sourced from *M. officinalis* and related botanicals, has garnered attention for its broad pharmacological spectrum. Recent studies highlight its anti-inflammatory, antioxidant, anti-osteoporotic, and anti-cancer activities, underscoring its potential therapeutic relevance (Wu et al., 2023; Zhang et al., 2020). Given these findings, this study aimed to assess the anti-cancer efficacy of monotropein in breast adenocarcinoma cells, providing insight into its potential role as a supportive nutraceutical intervention.

Chemotherapeutic agents, although effective in suppressing tumor growth, are well-documented for their substantial toxicity toward normal tissues. Their mechanism of action relies on disrupting cell division and inducing cell death, yet this lack of specificity often results in considerable collateral damage to healthy proliferating cells (Anand et al., 2022; Mollaei et al., 2021). Cardiotoxicity remains one of the most serious adverse outcomes, with agents such as anthracyclines, alkylating drugs, and tyrosine kinase inhibitors (Morelli et al., 2022; Shyam Sunder et al., 2023). Widely used chemotherapeutics, including doxorubicin, cyclophosphamide, cisplatin, and paclitaxel, have been associated with impaired ovarian function, depletion of the primordial follicle pool, premature ovarian insufficiency, and early-onset menopause, adversely affecting long-term quality of life in survivors (Bhardwaj et al., 2023; Reynolds & McKenzie, 2023; Spears et al., 2019). Nutraceuticals have emerged as potential protective agents against chemotherapy-associated toxicities, owing to their intrinsic antioxidant, anti-inflammatory, and cytoprotective properties

(Farooq et al., 2021). In this context, our findings demonstrate that monotropein elicited significant cytotoxicity in MCF-7 breast adenocarcinoma cells while exhibiting minimal effects on normal epithelial Vero cells.

Aberrations in apoptotic signaling are fundamental to tumor initiation, progression, and resistance to therapy, making the apoptosis pathway a critical target in contemporary anti-cancer strategies. The evasion of apoptosis is a recognized cancer characteristic, enabling malignant cells to persist under metabolic and environmental stress (Mohammad et al., 2015; Tong et al., 2022). Phytochemicals have demonstrated the ability to modulate multiple cancer hallmarks, including disruption of cell-cycle regulators, inhibition of angiogenic signaling, interference with microtubule dynamics, and, importantly, activation of apoptosis (Bailon-Moscoso et al., 2017). By preventing the suppression of pro-apoptotic proteins, these compounds can sensitize cancer cells to therapeutic stressors such as ionizing radiation and cytotoxic drugs, thereby enhancing treatment efficacy (Sarkar et al., 2013; Wani et al., 2023). Based on this rationale, the present study evaluated the ability of monotropein to activate the apoptotic machinery in breast adenocarcinoma cells.

Cancer cells employ several mechanisms to suppress apoptosis, particularly through dysregulation of the intrinsic pathway. These include mutations that impair caspase activity, increased anti-apoptotic Bcl-2 expression, enhanced inhibitor-of-apoptosis proteins, and loss or inactivation of the pro-apoptotic effectors BAX and Bcl-2 homologous antagonist/killer (BAK) (Gillissen et al., 2010; Lopez & Tait, 2015; Tian et al., 2024). Caspases—cysteine proteases central to apoptotic signaling—remain key therapeutic nodes, with initiator caspases activating downstream executioner caspases that orchestrate cellular dismantling (Boice & Bouchier-Hayes, 2020). Impaired caspase signaling contributes to tumorigenesis and treatment resistance; conversely, restoring or enhancing caspase activity represents an attractive therapeutic approach (Hensley et al., 2013). Consistent with this concept, monotropein treatment in our study significantly elevated initiator caspase-9 and executioner caspase-3 levels in MCF-7 cells, indicating robust activation of the caspase-dependent apoptotic cascade.

Dysregulation of the Bcl-2 family is another hallmark of apoptosis resistance in cancer (Weyhenmeyer et al., 2012; Zhang et al., 2021). Many tumors exhibit elevated levels of anti-apoptotic proteins such as Bcl-2, accompanied by reduced expression of pro-apoptotic members like BAX. This imbalance promotes cell survival, facilitates disease progression, and contributes to chemoresistance and radioresistance (Kaloni et al., 2023). Accordingly, strategies that inhibit Bcl-2 or enhance pro-apoptotic signaling have shown strong therapeutic potential, including the development of Bcl-2 homology 3 (BH3)-mimetics that antagonize pro-survival Bcl-2 family proteins (Qian et al., 2022; Weyhenmeyer et al., 2012). In alignment with previous evidence, our findings show that monotropein substantially elevated Bax expression while simultaneously reducing Bcl-2 levels in breast adenocarcinoma cells, indicating a shift toward a pro-apoptotic profile. This shift in the Bax/Bcl-2 ratio further supports the pro-apoptotic efficacy of monotropein and underscores its potential as a nutraceutical candidate capable of modulating key regulators of programmed cell death in cancer therapy.

Targeting the PI3K/Akt/mTOR (PAM) signaling cascade has become a major focus in breast cancer therapy because of its pivotal involvement in cell proliferation, survival, and resistance to treatment. This pathway regulates essential cell-cycle components such as cyclin D1, which partners with cyclin-dependent kinases 4 and 6 (CDK4/6) to phosphorylate the retinoblastoma (Rb) protein, ultimately enabling E2F-driven transcription and progression into the S phase (Piezzo et al., 2020; Stanciu et al., 2023; Vinciguerra et al., 2022). Genetic and functional alterations in the PAM pathway are reported in a large proportion of breast cancers, making it a key driver of tumor growth and a central target for therapeutic intervention (Miricescu et al., 2020). As a result, several PI3K, Akt, and mTOR inhibitors have been developed and integrated into clinical practice, often in combination with endocrine therapies to improve responses in hormone-resistant disease (Liu et al., 2020; Sirico et al., 2023; Yu et al., 2023). Despite the advancement of FDA-approved agents, drug toxicity, drug resistance, and variable patient responses highlight the need for safer and more effective modulators of this pathway (Hudes et al., 2007; Mao et al., 2022; Turner et al., 2023). In this context, our findings provide new insight into the potential of the nutraceutical monotropein, which markedly downregulated PI3K, Akt, and mTOR signaling in MCF-7 breast adenocarcinoma cells. The observed inhibition of this pathway aligns with its established role in controlling tumor growth and survival, offering a mechanistic explanation for the reduced proliferation and enhanced apoptosis seen with monotropein treatment, and it is also evident with our DAPI results.

Conclusion

In conclusion, monotropein demonstrated selective anti-cancer activity against MCF-7 breast adenocarcinoma cells by activating caspase-dependent apoptosis, modulating the Bax/Bcl-2 ratio, and suppressing the PI3K/Akt/mTOR survival pathway. Its ability to target key regulators of cell death and proliferation, while sparing normal cells, highlights its promise as a safe and effective nutraceutical candidate. Further pre-clinical and *in vivo* investigations are required to confirm its therapeutic effectiveness and support its development as an adjunct in breast cancer management.

Abbreviations

Akt: Protein kinase B; BAX: Bcl-2-associated X protein; Bcl-2: B-cell lymphoma 2; DAPI: 4′,6-Diamidino-2-phenylindole; DMEM:

Dulbecco's Modified Eagle Medium; DMSO: Dimethyl sulfoxide; FBS: Fetal bovine serum; mTOR: Mammalian target of rapamycin; PI3K: Phosphoinositide 3-kinase.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Not applicable.

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Informed Consent

Not applicable.

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