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Original Article

Inhibitory Effects of Diosgenin on Breast Cancer Cell Progression through Regulation of Metastatic Gene Expression

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Abstract

Background: As a steroidal saponin found in numerous plants historically used in traditional healing systems, diosgenin exhibits promising activity against multiple types of cancer. While its anticancer properties are documented, its molecular mechanisms remain incompletely characterized. Accordingly, this study investigated whether diosgenin can enhance the efficacy of doxorubicin (DOX) in MCF-7 breast carcinoma cells.

Methods: Following treatment with DOX, diosgenin, or their combination, MCF-7 viability was quantified using the MTT method. Then, the expression patterns of metastatic regulators (matrix metalloproteinase 2 [MMP-2], MMP-9, c-Myc, and K-Ras) were analyzed by quantitative real-time polymerase chain reaction and immunoblotting.

Results: DOX demonstrated concentration-dependent growth inhibition. Moreover, combined diosgenin-DOX treatment produced superior antiproliferative effects compared to individual agents ($P<0.05$). Additionally, diosgenin could substantially suppress metastatic potential by downregulating MMP-2, MMP-9, c-Myc, and K-Ras expression. Ultimately, diosgenin amplified DOX-triggered programmed cell death.

Conclusion: Our findings indicated that this plant-derived compound potentiates DOX anticancer activity through enhancing apoptotic response while suppressing metastasis-associated gene networks. These observations support investigating diosgenin as a complementary agent in breast malignancy management and warrant expanded biological evaluations.

Keywords: Apoptosis, Breast cancer, Diosgenin, Natural product-based adjuvant therapy, Doxorubicin, Metastasis

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Introduction

Among women, breast malignancies represent the second most common cause of cancer mortality worldwide.[1] Although substantial progress has been achieved in deciphering disease mechanisms and developing therapeutic interventions, incidence rates continue increasing, with approximately 2.3 million new diagnoses recorded in 2020.[2] Genetic alterations constitute major risk determinants for developing this malignancy.[3] This disease exhibits remarkable heterogeneity, with histological categorization dependent on hormonal receptor profiles (including progesterone and estrogen receptors and human epidermal growth factor receptor 2 [HER2]).[4] Molecular classification identifies five distinct subtypes: HER2-enriched, luminal estrogen receptor-positive (subdivided into A and B), normal breast-like, and triple-negative phenotypes.[5] Contemporary therapeutic selection integrates multiple parameters, encompassing tumor architecture, dimensions, receptor expression patterns, metastatic status, and histological grade.[6,7] Understanding the molecular circuitry governing malignant transformation and dissemination remains essential for developing innovative treatment paradigms.

Recent investigations have focused on diosgenin, a steroidal sapogenin derived from natural sources, for the treatment of various pathological conditions.[8] This compound, structurally resembling estrogen, derives from Dioscoreaceae and Leguminosae plant

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families, many species of which feature prominently in Ayurvedic, Unani, and traditional healing practices for inflammatory and metabolic conditions.[9] Comprehensive pharmacological studies have confirmed its anti-inflammatory, antioxidant, antiproliferative, organ-protective, cholesterol-lowering, and antitumor activities, validating traditional applications while establishing contemporary biomedical significance.[8, 9]

Given its growth-inhibitory and pro-apoptotic properties, diosgenin may synergize with established chemotherapeutics, such as doxorubicin (DOX), to enhance treatment efficacy. It is hypothesized that diosgenin would amplify DOX anticancer effects through suppressing proliferation, downregulating metastasis-related gene networks, and promoting programmed cell death in MCF-7 cells. This investigation aims to evaluate the individual and combined effects of these agents on MCF-7 cells, generating insights into their potential as a combination therapy to inhibit malignant progression and dissemination, while connecting traditional medicinal knowledge with modern cancer therapeutics.

Methods

Cell Culture Conditions

MCF-7 human breast adenocarcinoma cells (Pasteur Institute Cell Bank, Tehran, Iran) were maintained in RPMI-1640 medium (Gibco) supplemented with 10% fetal bovine serum and 100 units/mL penicillin-streptomycin under standard conditions (37°C, humidified atmosphere with 5% CO_2).

Viability Assessment

Cellular proliferation was quantified using the 3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide (MTT) metabolic assay. Following seeding at 5×10^3 cells per well in 96-well format, cells received escalating concentrations of DOX (0–5 µM) and diosgenin (0–20 µM) individually or in combination. Combination studies employed a fixed 1:8 ratio (DOX: diosgenin) based on individual half maximal inhibitory concentration (IC_{50}) determinations from dose-response experiments. After 48 hours of exposure, the MTT reagent (0.5 mg/mL) was added for 4 hours of incubation at 37°C. Next, absorbance measurements at 570 nm were performed in triplicate across three independent experiments. Finally, GraphPad Prism software (version 6) was used for IC_{50} calculations.

Gene Expression Analysis

Metastatic marker expression (matrix metalloproteinase 2 [MMP-2], MMP-9, c-Myc, and K-Ras) was evaluated via quantitative real-time polymerase chain reaction (RT-qPCR). Moreover, the TRIzol method was utilized for total RNA extraction according to the manufacturer's protocols. Then, complementary DNA synthesis was performed prior to RT-qPCR using SYBR Green chemistry on a Mic qPCR platform. It is noteworthy that β-actin served as the normalization reference, with relative expression calculated using the $2^{-\Delta\Delta CT}$ method.

Apoptosis Quantification

Flow cytometric evaluation assessed programmed cell death following diosgenin treatment of DOX-exposed MCF-7 cells. In addition, post-treatment cell harvesting was followed by dual staining with annexin V-FITC (5 µL) and propidium iodide (5 µL). After 15-minute dark incubation at ambient temperature, the samples underwent flow cytometric analysis.

Protein Expression Analysis

Cultured MCF-7 cells in six-well plates containing complete Dulbecco's modified Eagle medium underwent experimental treatments before protein extraction and Bradford quantification. Afterward, 20 µL of protein extract, combined with the sample buffer, underwent thermal denaturation (at 95°C for 5 minutes) before electrophoretic separation (10% sodium dodecyl-sulfate polyacrylamide gel electrophoresis, 100V) and semi-dry transfer to polyvinylidene difluoride membranes. Following blockade with 5% non-fat milk in Tris-buffered saline with 0.1% Tween 20 (for 1 hour at room temperature) and washing, the membranes received overnight primary antibody incubation at 4°C (targeting MMP-2, MMP-9, c-Myc, K-Ras, and glyceraldehyde-3-phosphate dehydrogenase). After additional washing steps, the horseradish peroxidase-conjugated secondary antibody was incubated for 2 hours at ambient temperature. Enhanced chemiluminescence visualization employed manufacturer-specified protocols with 5-minute substrate incubation and chemiluminescence imaging capture. It should be noted that the molecular weight standards provided reference markers.

Statistical Methodology

The obtained data were presented as means ± standard deviations from minimally triplicate independent experiments. SPSS software (version 26.0) and GraphPad Prism (version 6) were considered for statistical comparisons using t-tests or analysis of variance, with a significance threshold of $P < 0.05$.

Results

The Effect of Doxorubicin on MCF-7 Cell Line Proliferation

The MTT assay revealed dose-dependent DOX cytotoxicity against MCF-7 cells. Following 48 hours of exposure to varying concentrations, cytotoxicity calculations yielded an IC_{50} of 1.0 ± 0.1 µM (Figure 1), with higher concentrations producing proportionally greater growth inhibition.

The Effect of Diosgenin on MCF-7 Cell Line Proliferation

MTT evaluation demonstrated that diosgenin treatment significantly suppressed MCF-7 proliferation in a

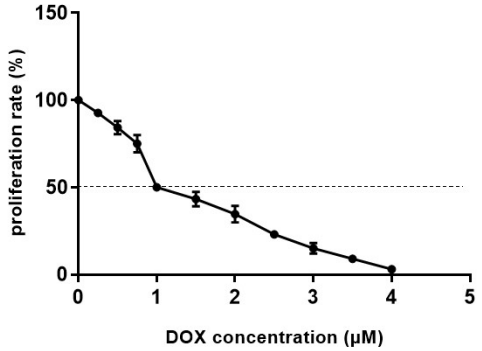

Figure 1. Effect of DOX on MCF-7 Cell Line Proliferation Rate
Note. DOX: Doxorubicin; SD: Standard deviation; MCF-7: Michigan Cancer Foundation-7. The results are expressed as means ± SDs after three repetitions of the experiments.

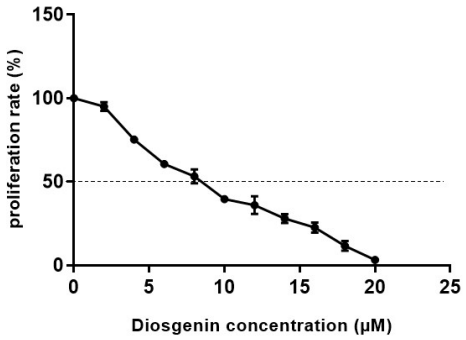

Figure 2. Effect of Diosgenin on MCF-7 Cell Line Proliferation Rate
Note. SD: Standard deviation. The results are demonstrated as means ± SDs after three repetitions of the experiments.

concentration-dependent manner after 48 hours of exposure compared with untreated controls. The calculated IC_{50} value was 8 ± 1 μM (Figure 2).

The Effect of Using the Combination of Doxorubicin and Diosgenin on the Proliferation Rate of the MCF-7 Cell Line

Combined DOX-diosgenin treatment had enhanced antiproliferative effects exceeding either monotherapy (Figure 3). Concentrations below 0.75 μM DOX combined with 8 μM diosgenin failed to achieve 50% growth inhibition. However, concentrations exceeding 0.75 μM showed synergistic interactions after 48 hours of incubation. Eventually, the combination reduced DOX IC_{50} values from 1.0 μM to 0.6 μM, with the 1:8 ratio selected based on individual IC_{50} determinations displaying optimal synergistic cytotoxicity enhancement.

The Effect of Using Doxorubicin and Diosgenin on the Expression of MCF-7 Cell Line Metastatic Genes

The expression of metastatic factors was examined at both messenger ribonucleic acid (mRNA) and protein levels. To investigate the changes in metastatic factors (including MMP2, c-Myc, K-Ras, and MMP9 in different groups treated with DOX, diosgenin, and a combination of them), the cells were divided into four groups as follows:
Group 1: MCF-7 cells without any treatment, and as a control group
Group 2: MCF-7 cells treated with 0.8 μM DOX (DOX)
Group 3: MCF-7 cells treated with 8 μM diosgenin (DIOS)
Group 4: MCF-7 cells treated with 0.8 μM DOX and 8 μM diosgenin (DOX + DIOS)

Following treatment, RNA extraction, complementary DNA synthesis, and qPCR quantification of metastasis markers proceeded using specific primer sets. Parallel protein extraction enabled Western blot analysis using antibodies against MMP-2, MMP-9, c-Myc, and K-Ras, with glyceraldehyde-3-phosphate dehydrogenase as a loading control.

Both MMP-2 and MMP-9 (critical metastatic regulators) represented reduced mRNA expression following either

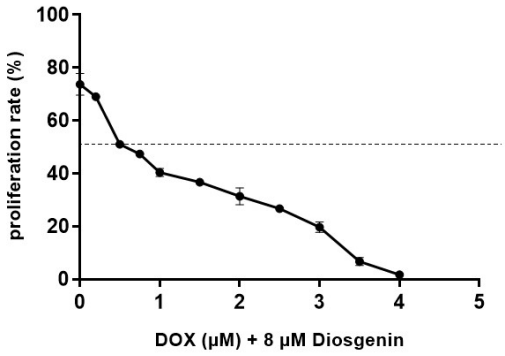

Figure 3. The Effect of DOX and Diosgenin Combination on MCF-7 Cell Line Proliferation
Note. DOX: Doxorubicin; SD: Standard deviation. The results are provided as means ± SDs after three repetitions of the experiments.

DOX or diosgenin treatment compared with controls ($P < 0.05$, Figure 4). Moreover, combined treatment produced more pronounced suppression ($P < 0.05$). Likewise, protein-level analysis mirrored these patterns, with monotherapies decreasing expression ($P < 0.05$) and combination therapy exerting stronger inhibitory effects ($P < 0.05$).

The oncogenic transcription factor c-Myc exhibited significantly reduced mRNA expression with individual DOX or diosgenin treatment compared to controls ($P < 0.05$, Figure 4). Based on the results, combined therapy could produce greater suppressive effects ($P < 0.05$). Western blot confirmed these findings at protein levels, with monotherapies reducing expression ($P < 0.05$) and combination treatment further enhancing suppression ($P < 0.05$).

K-Ras expression analysis revealed similar patterns. Individual treatments decreased mRNA levels compared with controls ($P < 0.05$; Figure 4), and combination therapy produced greater suppression ($P < 0.05$). In addition, protein quantification demonstrated comparable trends, showing reductions with single agents ($P < 0.05$) and synergistic decreases with combined treatment ($P < 0.05$).

Overall, both agents suppressed metastatic gene networks at transcriptional and translational levels, thereby suggesting potential synergistic mechanisms in

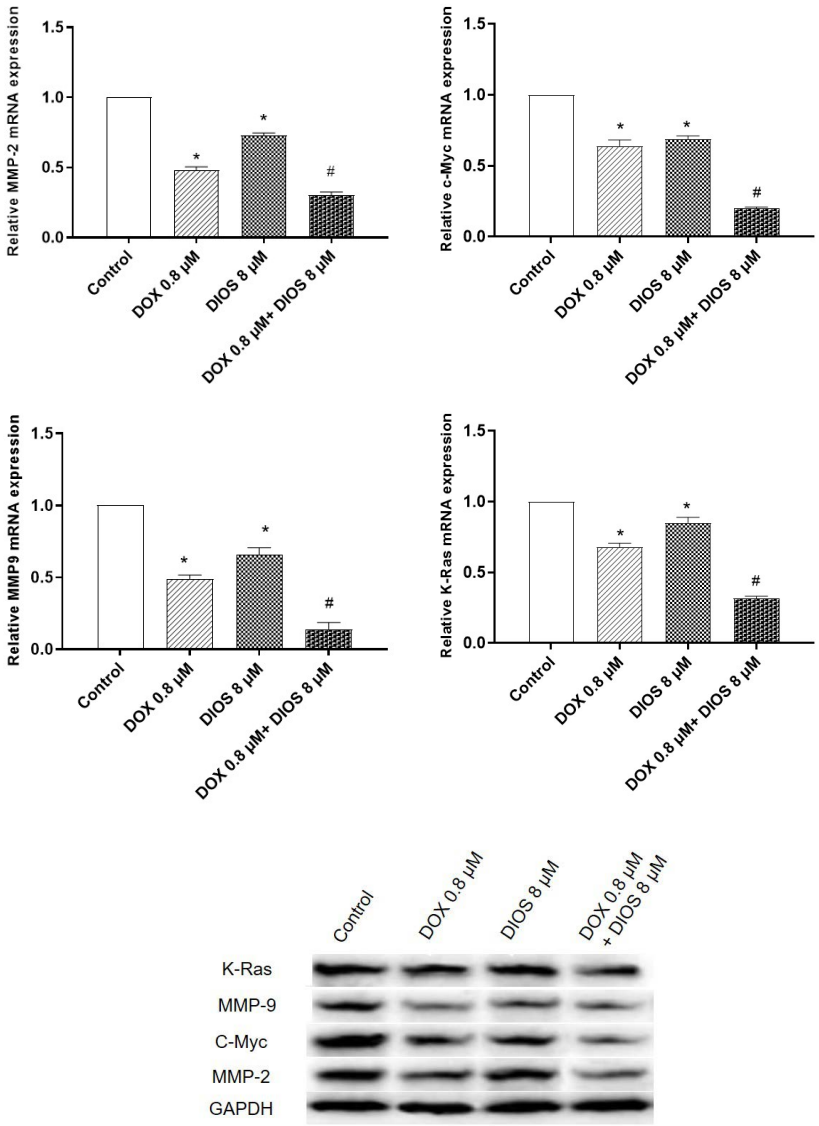

Figure 4. An Example of Changes in *MMP-2*, *MMP-9*, *c-Myc*, and *K-Ras* Gene Expression in the Treated Group at mRNA and Protein Levels
Note. mRNA: Messenger ribonucleic acid; SD: Standard deviation. The results are shown as means ± SDs after three repetitions of the experiments.

metastasis inhibition.

The Effect of Doxorubicin and Diosgenin on MCF-7 Cell Line Apoptosis

Flow cytometric quantification revealed that DOX and diosgenin monotherapies induced apoptosis in 60% and 20% of cells, respectively, compared to 4% of cells in untreated controls (Figure 5). Combined treatment led to stronger apoptotic induction (80%) versus either single agent. These data confirm that diosgenin enhances MCF-7 sensitivity to DOX-mediated programmed cell death.

Discussion

Breast malignancy ranks among the leading cancer-related mortality causes globally.[10] Despite diagnostic and therapeutic advances, the overall prognosis remains suboptimal.[11] Multiple risk determinants of breast malignancy include lifestyle patterns, advancing age, and inherited genetic defects.[12] This disease represents a multi-stage process wherein normal cells progress through adenomatous transformation to malignant and metastatic phenotypes via accumulated genetic and epigenetic alterations.[13] While numerous molecular events have been identified, thousands of contributing molecules remain uncharacterized. Their identification is crucial for early detection and the development of therapeutic strategies. A deeper understanding of molecular pathways and genetic networks governing initiation and progression will enhance diagnostic and therapeutic approaches.

Chemotherapeutic agents function through diverse mechanisms, enabling multi-level tumor targeting through combination strategies. DOX inhibits the rapid division of cell proliferation by preventing cell division. However, current therapies face limitations, including poor efficacy in high-risk patients and low metastatic survival rates. Resistance development leads to recurrence and progression in some patients. Approximately 25% of good responders experience recurrence, while poor responders

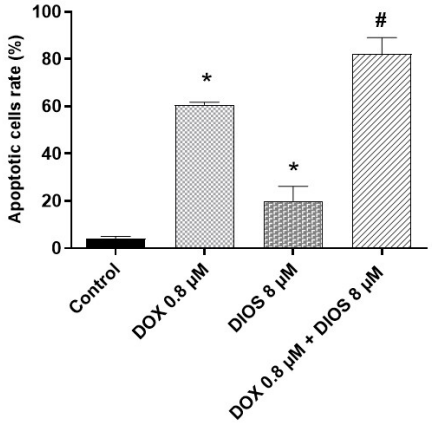

Figure 5. The Effect of the DOX and Diosgenin Combination on the Apoptosis Rate in the Treated Group
Note. DOX: Doxorubicin; SD: Standard deviation. The results are presented as means ± SDs after three repetitions of the experiments.

may rapidly develop metastases. Resistance manifests as either the intrinsic (pre-existing within tumors) or acquired (developing during treatment) type.[14] Intrinsic resistance involves pre-existing resistant cell populations that can proliferate despite chemotherapy due to genetic mutations or activated signaling cascades. On the other hand, acquired resistance emerges during treatment as tumor cells adapt through proto-oncogene activation, mutational changes, or alterations in drug targets and transporters. It is noteworthy that both resistance forms stem from genomic instability that favors the selection of resistant clones.[15] Resistance remains a principal therapeutic failure factor, necessitating more effective immediate interventions. Accordingly, understanding the molecular mechanisms of chemotherapy resistance is essential for developing novel strategies and improving patient outcomes. Despite chemotherapeutic progress, only 50–60% of tumors respond to treatment.[16]

According to recent investigations, diosgenin possesses significant antiproliferative activity. One study synthesized two steroid compounds containing this molecule, which induced apoptosis and caspase-3 activation in cervical carcinoma cells and lymphocytes.[17] Another investigation reported antiproliferative effects against breast (HBL-100), colon (HCT-116 and HT-19), and lung (A549) cancer cell lines.[18] Diosgenin enabled the synthesis of 1α-hydroxysolasodin, thereby exhibiting potent anticancer activity against prostate (PC3), cervical (HeLa), and hepatic (HepG2) cancer cells.[19] Additionally, twelve diosgenin analogs with long-chain fatty acids demonstrated anticancer effects, with compound 16 showing potent activity against DU145 prostate cancer cells while inhibiting tumor necrosis factor alpha and interleukin 6 activation.[20] Furthermore, diosgenin-functionalized iron oxide nanoparticles inhibited breast cancer cell proliferation and migration and induced apoptosis.[21]

Our results align with the findings of these studies, demonstrating that the diosgenin-DOX combination enhanced cytotoxicity and apoptosis. Although we did not directly interrogate signaling cascades, the concurrent downregulation of MMP-2, MMP-9, c-Myc, and K-Ras, alongside marked increases in apoptosis following combined treatment, suggests the modulation of key pro-survival and pro-metastatic pathways. The evidence indicates that diosgenin can influence phosphatidylinositol 3-kinase/protein kinase B, mitogen-activated protein kinase/extracellular signal kinase, and nuclear factor-kappa B signaling pathways that regulate MMP expression, oncogene activity, and caspase-dependent apoptotic mechanisms. Therefore, diosgenin likely potentiates DOX cytotoxicity by inhibiting one or more pathways and decreasing c-Myc and MMP expression while enhancing apoptotic responses.[22-24] Nonetheless, validating this hypothesis requires future mechanistic studies, including pathway phosphorylation assessment, specific pharmacological inhibitors, and loss-of-function approaches (small interfering RNA/clustered regularly interspaced short palindromic repeats) across multiple breast cancer models.

Our study's limitations include the use of only MCF-7 cells, which limits the generalizability of results to other breast cancer subtypes (e.g., triple-negative or HER2-positive tumors). Additionally, mechanistic conclusions are largely inferential, based on correlative gene expression and phenotypic changes, without pathway-directed experiments (pathway inhibition, knockdown/rescue, or pharmacologic blockade) to causally validate proposed signaling mechanisms. No in vivo validation limits translational relevance. It is recommended that future studies (i) evaluate diosgenin-doxorubicin combinations across breast cancer cell panels, (ii) include pathway inhibition/rescue experiments for direct mechanistic testing, and (iii) employ appropriate in vivo models confirming efficacy and safety.

Conclusion

Preclinical research findings support the clinical application of diosgenin. Extensive data on molecular anticancer activity, drug toxicity, bioavailability, pharmacokinetics, and innovative delivery approaches provide a solid foundation for future applications. Our findings highlight the therapeutic potential of targeting both apoptosis and metastasis to improve DOX response in breast malignancy. However, appropriate drug selection for the DOX combination is critical.

Based on our findings, diosgenin enhanced DOX cytotoxicity while significantly promoting apoptosis and downregulating metastatic gene expression in MCF-7 cells, suggesting that diosgenin is highly promising in preclinical cancer models. Given its safety profile and broad biological activities, diosgenin can be a promising clinical trial candidate, offering opportunities to enhance breast cancer cell sensitivity to conventional chemotherapy and overcome resistance mechanisms.

Ethics statement
All experimental procedures were applied following the approval from the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1400.768).

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Conflict of interests declaration
The authors declare they have no conflict of interests.

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Data availability statement
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Methodology: Elham Jangi, Mehran Molavand.
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Software: Mehran Molavand, Amir Valizadeh.
Supervision: Bahman Yousefi.
Validation: Majid Montazer.
Visualization: Majid Montazer, Bahman Yousefi.
Writing–original draft: Elham Jangi.
Writing–review & editing: Majid Montazer.

Consent for publication
Not applicable.

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