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Targeting Epigenetic Silencing: Nanocurcumin Upregulates ESR1 and Suppresses KRAS and CyclinD1 in TNBC Cells

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ABSTRACT

Hormone receptor-positive (HR+) breast cancer accounts for approximately 70% of all breast cancers, with tamoxifen being a key therapeutic option for estrogen receptor-positive (ER+) cases. However, triple-negative breast cancers (TNBC), lacking ER expression, remain unresponsive to this treatment. Nanocurcumin, a bioactive compound with epigenetic-modulating properties, has shown potential in reactivating ESR1 expression by inhibiting DNA methyltransferases. This study investigates the effect of nanocurcumin on ESR1, CyclinD1, and KRAS gene expression in MDA-MB231 cells, a tamoxifen-resistant TNBC cell line. The IC50 of nanocurcumin was determined through MTT assay. Gene expression levels were analyzed using qRT-PCR, and apoptosis and cell cycle distribution were assessed via flow cytometry and Annexin V assays. Our results show a significant increase in ESR1 expression and a concurrent decrease in CyclinD1 and KRAS expression in nanocurcumin-treated cells compared to controls. Apoptosis rates were higher, and cell cycle analysis revealed G1 phase arrest. These findings suggest that nanocurcumin may reverse epigenetic silencing of ESR1, enhance tamoxifen sensitivity, and suppress downstream oncogenic pathways by inhibiting KRAS and CyclinD1.

Keywords: nanocurcumin, triple-negative breast cancer, ESR1, epigenetic reprogramming, apoptosis

INTRODUCTION

Breast cancer is a multifactorial disease driven by both genetic mutations and epigenetic dysregulation [1-3]. Epigenetic changes, including DNA methylation, histone modifications, and non-coding RNAs, play a pivotal role in tumor progression, immune evasion, and therapeutic resistance [4-7]. Recent advances in “Epi-drugs” have targeted these alterations, offering promising new directions in cancer therapy [8, 9]. In hormone receptor positive (HR+) breast cancer, estrogen receptor alpha (ERα), encoded by the ESR1 gene, regulates cell proliferation and survival through downstream pathways, including the KRAS and CyclinD1 oncogenic cascades [10, 11]. Tamoxifen, a selective estrogen receptor modulator (SERM), is a standard therapy that blocks estrogen signaling, effectively inhibiting ER+ breast cancer growth [12]. However, triple-negative breast cancers (TNBCs), which lack ERα, progesterone receptor (PR), and HER2

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expression, remain unresponsive to tamoxifen [13]. Curcumin, a polyphenolic compound derived from Curcuma longa, has demonstrated anticancer properties by modulating key signaling pathways, inducing cell cycle arrest, and promoting apoptosis [13, 14]. Nanocurcumin is synthesized using a dendrosomal delivery system, which consists of dendrosomes, nanocarriers with a stable structure, high loading capacity, and biodegradable properties [15, 16]. These nanoparticles are electrically neutral, enhancing curcumin's cellular uptake and antitumor effects without causing toxicity to normal cells [17, 18]. The dendrosomal structure improves curcumin's bioavailability and stability, facilitating effective drug delivery specifically to cancer cells [19]. Notably, nanocurcumin has been shown to inhibit DNA methyltransferases (DNMTs), potentially reversing epigenetic silencing of tumor suppressor genes such as ESR1 [20, 21].

This study explores nanocurcumin's ability to restore ESR1 expression in MDA-MB231 TNBC cells, thereby enhancing sensitivity to tamoxifen. Additionally, we examine the expression of CyclinD1 and KRAS, two key oncogenes associated with cell cycle progression and survival, to determine whether nanocurcumin modulates these pathways to induce apoptosis and G1 phase arrest.

MATERIALS AND METHODS

Nanocurcumin Preparation

In a previous study, the synthesis of the nanocarrier was described in detail. Briefly, the nanocarrier was produced through an esterification reaction involving octyl chloride (Sigma-Aldrich), polyethylene glycol 400 (Merck), triethylamine (Merck), and chloroform (Merck) as the solvent, conducted at 25 °C. To obtain nanocurcumin, appropriate amounts of curcumin (Sigma-Aldrich) and the nanocarrier were mixed in a 1:25 (w/w) ratio, followed by subsequent formulation steps to yield the final nano system [22-24].

Cell culture and viability assay

MDA-MB231 cells, a triple-negative breast cancer cell line, were cultured at a density of 2×10^5 cells per well in DMEM medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. Cells were incubated at 37°C with 5% CO_2 for 48 hours prior to treatment. Nanocurcumin was prepared in serial dilutions ranging from 5 to 60 μM and added to the cells. Cell viability was assessed using the MTT assay after 48 hours of incubation. The IC50 was determined using GraphPad Prism 6 software, and results were expressed as a percentage of viable cells compared to untreated controls.

Cell cycle analysis (Flow Cytometry)

Cells were seeded in 6-well plates, trypsinized, and washed with PBS. Following fixation in 75% ethanol, cells were stained with propidium iodide (PI) and analyzed via flow cytometry using a BD FACSCalibur system. Data were processed with FlowJo software to evaluate cell cycle distribution across G1, S, and G2/M phases.

Apoptosis detection

The Annexin V-FITC apoptosis detection kit (Invitrogen) was used to measure apoptotic rates. Cells were stained with Annexin V and PI, and apoptosis was assessed using flow cytometry. Early apoptotic, late apoptotic, and necrotic cell populations were distinguished based on staining patterns.

Gene expression analysis (qRT-PCR)

Total RNA was extracted using TRIzol reagent, and cDNA synthesis was performed using a high-capacity cDNA reverse transcription kit (Applied Biosystems) [25]. Gene expression of ESR1, CyclinD1, and KRAS was analyzed using SYBR Green-based qRT-PCR. GAPDH was used as an internal control. The $2^{-}\Delta\Delta Ct$

method was employed to calculate relative gene expression. Primers used for gene amplification are listed in Table 1.

Table 1. Primers used in the study for gene expression analysis.

Product Length (Bp)	Transcriptase Reaction Primer	Chromosome Number	F/R	Genes
201	5'-CAGTAGACACAAAACAGGCTCAG -3'	12	F	*KRAS*
	5'-TGTCGGATCTCCCTCACCAATG-3'		R	
172	5'-TCTACACCGACAACTCCATCCG-3'	11	F	*CCND1*
	5'-TCTGGCATTTTGGAGAGGAAGTG-3'		R	
160	5'-TGGAGTCCACTGGCGTCTTC -3'	12	F	*GAPDH*
	5'-TTGCTGATGATCTTGAGGCTGT -3'		R	
180	5'-CCCACTCAACAGCGTGTCTC -3'	1	F	*ESR1*
	5'-CGTCGATTATCTGAATTTGGCCT-3'		R	

Statistical analysis

All experiments were performed in triplicate. Data were presented as mean ± standard deviation (SD). Statistical significance was determined using an unpaired Student's t-test, with p-values <0.05 considered statistically significant.

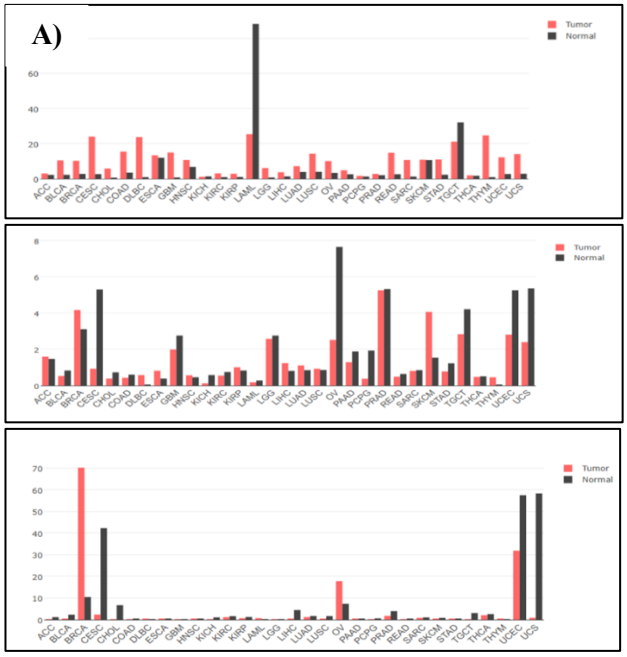
RESULTS

Confirmation of estrogen receptor-deficient MDA-MB 231 cells and expression analysis of KRAS, CyclinD1, and ESR1 genes

Quantitative real-time PCR (qRT-PCR) analysis demonstrated significant alterations in the expression profiles of KRAS, CyclinD1, and ESR1 genes in MDA-MB231 cells compared to normal breast epithelial cells (Figure 1C). A notable upregulation of KRAS was observed in MDA-MB231 cells, consistent with its established role as an oncogene driving tumorigenesis through MAPK and PI3K-AKT signaling pathways. This increased expression likely contributes to enhanced proliferation and reduced apoptosis in MDA-MB231 cells. A significant increase in CyclinD1 expression was detected, indicating dysregulated cell cycle progression. CyclinD1's role in promoting the G1/S transition supports its involvement in uncontrolled cell proliferation in MDA-MB231 cells. Downregulation of ESR1 was confirmed, aligning with the ER-negative phenotype of MDA-MB231 cells. The reduced expression suggests epigenetic silencing of ESR1, contributing to hormone therapy resistance, particularly tamoxifen unresponsiveness.

These findings emphasize the pro-oncogenic role of KRAS and CyclinD1, alongside ESR1 suppression, in maintaining the aggressive phenotype of MDA-MB231 cells. The observed reduction in ESR1 supports the hypothesis of promoter methylation or chromatin remodeling as potential mechanisms underlying its silencing, warranting further investigation into epigenetic reactivation strategies.

Control experiments using dendrosome alone (without curcumin) showed no significant changes in cell viability, apoptosis, or ESR1 expression compared to untreated cells ($p>0.05$). This indicates that the observed effects are specific to nanocurcumin and not the dendrosome carrier.



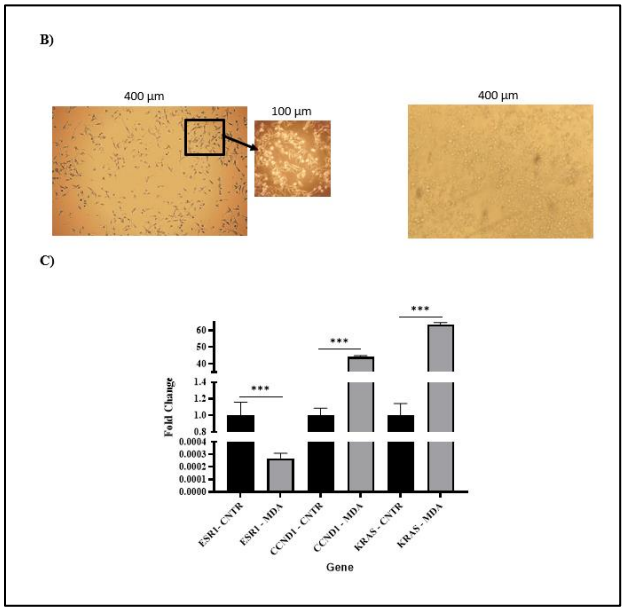


Figure 1. A) Comparative expression profiles of KRAS, CyclinD1 and ESR1 genes in tumor and normal tissue samples, showing the influence of the genes involved. **B)** The image on the left shows a dead MDA-MB231 cell and on the right a live one, confirming the MDA-MB231 cells that lack estrogen receptors. **C)** Graph of changes in the expression of CyclinD1, KRAS and ESR1 genes in normal cells and MDA-MB231 cell line.

MDA-MB231 cell treatment and MTT assay were performed to investigate the effects of nanocurcumin

MTT assay results demonstrated a dose-dependent decrease in cell viability. The IC50 value for nanocurcumin was approximately 22 µM after 48 hours ($p < 0.0001$ compared to untreated controls) (Figure 2A). Morphological changes in treated cells, including cell shrinkage and membrane blebbing, were observed under a fluorescence microscope (Figure 2B).

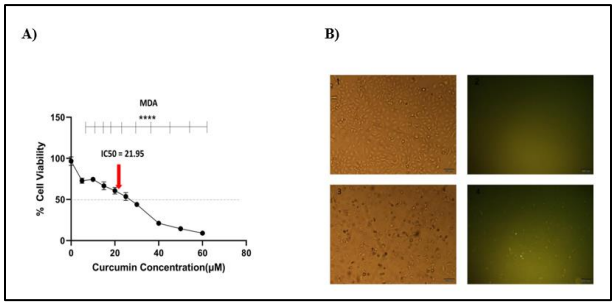


Figure 2. A) The evaluation of MDA-MB231 cell survival after 48 hours of dendrosome nanocurcumin treatment is shown. The P value for each concentration was measured relative to the control (P value <0.0001). **B)** The images display MDA-MB231 cells before and after 48 hours of nanocurcumin treatment. 1- Control MDA cells, 2- Control fluorescence microscope image, 3- MDA-MB231 cells treated with nanocurcumin, 4- Fluorescence microscope image of cells treated with nanocurcumin.

Nanocurcumin induces ESR1 expression and downregulates KRAS and CyclinD1

qRT-PCR analysis revealed a significant upregulation of ESR1 expression in nanocurcumin-treated cells, accompanied by a substantial reduction in CyclinD1, and KRAS expression compared to untreated cells (Figure 3).

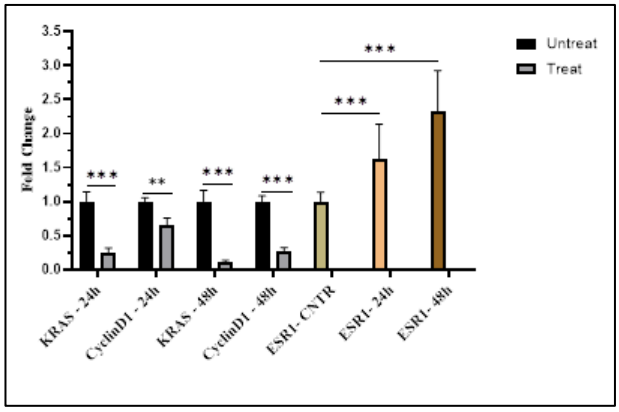
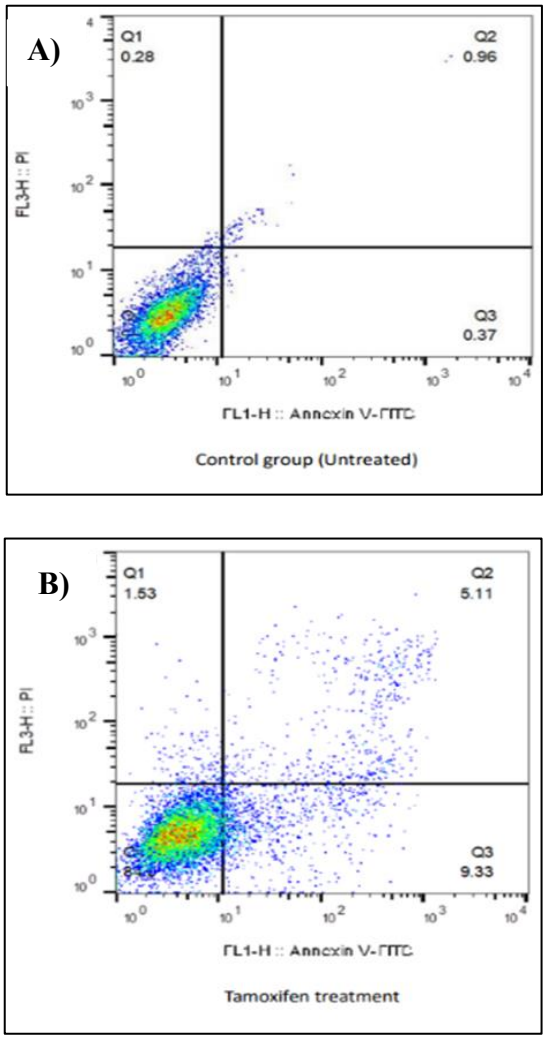


Figure 3. Graph showing changes in the expression of CyclinD1, KRAS, and ESR1 genes in normal cells and the MDA-MB231 cell line.

Enhanced apoptosis in nanocurcumin-treated cells

Annexin V staining demonstrated a significant increase in apoptotic cells following nanocurcumin treatment compared to controls (Figure 4). The inhibition of DNA methyltransferases by nanocurcumin could be due to the downregulation of KRAS and CyclinD1 expression, which alters ESR1, leading to the observed G1 arrest and increased apoptosis. The apoptosis results indicate the

therapeutic potential of nanocurcumin, as it led to the re-expression of ER, accompanied by the downregulation of KRAS and CyclinD1 expression, and drove the cells towards programmed cell death.



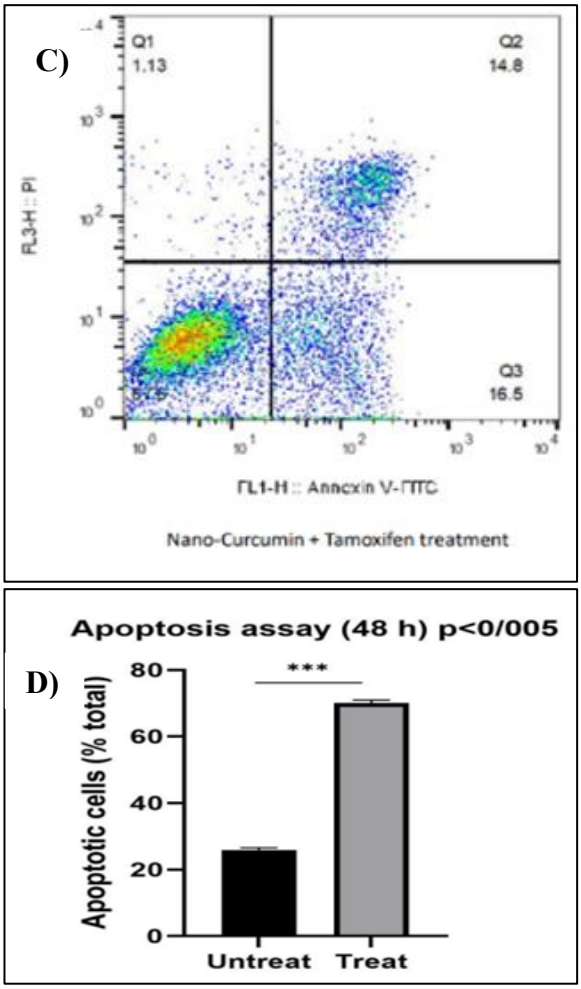


Figure 4. Cell death rate for MDA-MB231 cells. A) Untreated. B) Tamoxifen treated. C) Nanocurcumin and Tamoxifen treated. D) MDA-MB231 cell death rate before and after treatment with nanocurcumin.

Cell cycle arrest at G1 phase

Flow cytometry analysis showed a significant increase in the G1 population, alongside a reduction in S phase (Figure 5).

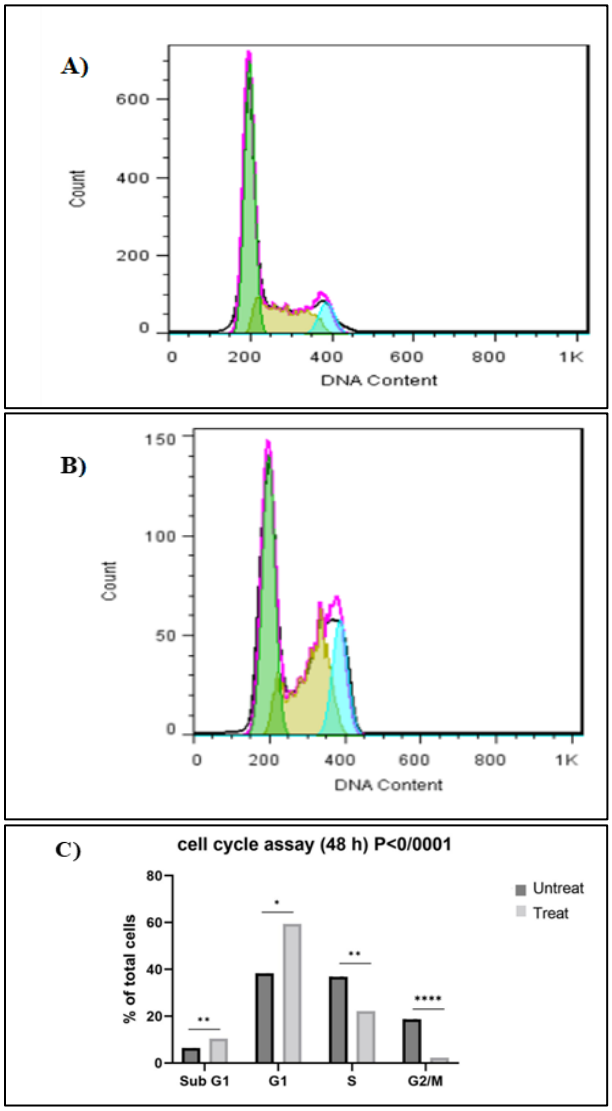


Figure 5. Cell cycle for MDA-MB231 cells. A) Untreated. B) Tamoxifen treated. C) Quantitative graph of MDA-MB231 cell cycle before and after treatment with nanocurcumin and Tamoxifen.

DISCUSSION

Triple-negative breast cancer (TNBC) remains one of the most challenging subtypes of breast cancer due to its lack of estrogen receptor (ER), progesterone receptor (PR), and HER2 expression [3, 26, 27]. This molecular profile renders TNBC resistant to targeted hormonal therapies such as tamoxifen. Our study demonstrates that nanocurcumin can reprogram TNBC cells by upregulating ESR1 (Figure 3 and 1C), restoring ER expression, and enhancing cellular sensitivity to apoptosis.

The significant increase in ESR1 expression observed after nanocurcumin treatment supports its potential role as an epigenetic modulator. This finding aligns with previous studies indicating that curcumin inhibits DNA methyltransferases (DNMTs), potentially reversing promoter methylation at the ESR1 locus [7, 28, 29]. By restoring ER expression, nanocurcumin may convert ER-negative cells into an ER-positive phenotype, allowing tamoxifen to exert its therapeutic effects [30-32].

Similarly, reported that curcumin can restore ER expression in ER-negative breast cancer cells, making them more responsive to endocrine therapies [33]. The epigenetic modulation by nanocurcumin observed in our study aligns with these findings and extends them by confirming an actual increase in ESR1 expression at both mRNA and protein levels in TNBC cells [34]. Moreover, this re-expression of ER appears functional, as evidenced by increased sensitivity to tamoxifen-induced apoptosis, consistent with the hypothesis proposed, who suggested that curcumin could sensitize cancer cells to conventional therapies [35, 36].

Furthermore, the observed downregulation of CyclinD1 and KRAS genes provides insight into nanocurcumin's ability to suppress oncogenic signaling (Figure 3). CyclinD1, a key regulator of G1-to-S phase transition, is often overexpressed in breast cancer and associated with aggressive tumor behavior [37]. Its reduction, alongside G1 phase arrest, suggests that nanocurcumin disrupts cell cycle progression, limiting tumor cell proliferation (Figure 5). The decrease in KRAS expression is particularly noteworthy, given its role in activating downstream survival pathways such as MAPK and PI3K-AKT signaling. Several studies, have indicated that curcumin can inhibit KRAS-driven signaling cascades in various

cancers, including pancreatic and lung cancers [38-40].

These findings suggest that nanocurcumin not only restores ESR1 expression but also concurrently suppresses survival pathways driven by KRAS and CyclinD1.

The apoptosis results further reinforce nanocurcumin's therapeutic potential. Increased early and late apoptosis rates observed via Annexin V staining indicate that re-expression of ER, coupled with the downregulation of KRAS and CyclinD1, shifts cells toward programmed cell death (Figure 4). Similar apoptotic effects have been reported in prior studies where curcumin treatment led to mitochondrial pathway activation and increased caspase-3 activity [41-44].

The downregulation of KRAS and CyclinD1 may result from nanocurcumin's inhibition of DNA methyltransferases, which alters promoter methylation not only in ESR1 but also in oncogenes. Restored ESR1 expression re-establishes estrogen signaling, which can negatively regulate proliferative pathways such as RAS/MAPK and Cyclin D1/CDK4/6. This dual mechanism provides a plausible explanation for the observed G1 phase arrest and increased apoptosis.

This supports the hypothesis that nanocurcumin sensitizes MDA-MB231 cells to tamoxifen by reinstating estrogen receptor signaling while simultaneously weakening oncogenic pathways. Importantly, dendrosome alone did not induce ESR1 expression or alter oncogenic signaling, confirming that the therapeutic effect is attributable to curcumin's epigenetic activity rather than the carrier system.

Conclusions

Our study highlights nanocurcumin's potential as a promising therapeutic agent for triple-negative breast cancer (TNBC). By upregulating ESR1 expression, nanocurcumin may convert ER-negative TNBC cells into an ER-positive phenotype, thereby enhancing their responsiveness to tamoxifen. Concurrent downregulation of CyclinD1 and KRAS further suppresses oncogenic pathways, promoting G1 phase arrest and apoptosis. These findings propose a dual-action mechanism for nanocurcumin: (1) reactivation of ESR1 through epigenetic modulation, and (2) inhibition of downstream oncogenic targets involved in cell cycle progression and survival. While these results are promising, further in vivo studies and clinical evaluations are necessary to determine whether nanocurcumin can be integrated into standard TNBC treatment regimens — particularly as an adjuvant to enhance tamoxifen sensitivity in previously untreatable cases.

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