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Evaluation of Synergistic Effects of Curcumin and Cisplatin in Inducing Apoptosis in Triple-Negative Breast Cancer Cells

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ABSTRACT

Objectives: The triple negative subtype of breast cancer (TNBC) is one of the most aggressive types of breast cancer since it does not have estrogen, progesterone, or HER2 receptors, which leads to the disease having few treatment options and a poor prognosis. This study aims to assess the synergistic effects of Curcumin, a natural polyphenol known for its anti-cancer properties, in combination with cisplatin, a chemotherapy agent, on apoptosis in TNBC cell lines. **Methods:** Curcumin (2.5 - 20 μM), together with cisplatin (1 - 10 μM), was used to treat TNBC cell lines (MDA-MB-231) both separately and in combination. Cell viability was determined using the MTT assay. Synergism was determined by calculating CI based on the Chou-Talalay method. Apoptosis was assessed by Annexin V/PI staining and by measuring caspase-3/7 activity. Western Blot was done to detect Cleaved PARP, and to evaluate the expression of pro-apoptotic and anti-apoptotic factors like Bax and Bcl-2. Mitochondrial membrane potential (ΔΨm) and ROS generation were also measured to determine some mechanistic pathways. **Results:** Compared to the control groups, the combination of Curcumin and cisplatin significantly reduced the viability of TNBC cells ($p<0.01$). The CI values were less than one, confirming the synergistic interaction. Combination treatment had a greater percentage of the early and late apoptotic cells as measured by flow cytometry. The activity levels of Caspase-3/7 were significantly higher. They were associated with increased expression of Bax and cleaved PARP, as well as reduced levels of Bcl-2, suggesting that an intrinsic apoptotic pathway was activated. In addition, there was greater mitochondrial ROS production and a decrease in ΔΨm, implying apoptosis was also triggered in a mitochondrial manner. **Conclusion:** As a conclusion, Curcumin enhances the cytotoxic and pro-apoptotic effects of cisplatin in triple-negative breast cancer cells by altering mitochondrial functions and oxidative stress pathways. Therefore, this study suggests that Curcumin could be a potential

chemosensitizer to increase the effectiveness of cisplatin while decreasing the required dosage and reducing TNBC treatment-related toxic effects.

Keywords: *Triple-negative breast cancer; Curcumin;Cisplatin; Mitochondrial pathway; chemosensitization*

INTRODUCTION

Breast cancer remains the most prevalent cancer diagnosis for women across the globe, contributing more than 2.3 million new cases every year and posing a considerable strain on global healthcare systems (Sung et al., 2021). While advancements in Treatment have been made, the disease continues to claim around 685,000 lives annually. One of the deadliest subtypes is triple-negative breast cancer (TNBC) (Bianchini et al., 2016). TNBC lacks estrogen receptors (ER), progesterone receptors (PR), and HER2 receptors, which makes it ineffective to endocrine therapy or agents targeting HER2.

Approximately 15-20% of women with breast cancer have TNBC, which is known for its aggressive behavior, recurring and spreading early on, with few treatment options available (Foulkes et al., 2010; Carey et al., 2006; Dent et al., 2007). Because of the absence of targetable receptors, the most effective form of Treatment available is standard chemotherapy. Within this, TNBC responds to cisplatin, a platinum-based chemotherapeutic, due to its ability to form DNA adducts that trigger apoptosis (Jiang et al., 2021). Unfortunately, Treatment is often limited due to severe side effects like nephrotoxicity, neurotoxicity, and the development of resistance to Treatment (Florea & Büsselberg, 2011; Wang & Lippard, 2005).

These limitations highlight the importance of finding new drugs designed to increase the effects of cisplatin and decrease its harmful effects. Natural compounds that serve more than one function, such as interacting with cancerous cells in different ways, have attracted interest because of their ability to work with chemotherapy and change the signaling pathways of cancer cells (Prasad et al., 2014; Kunnumakkara et al., 2017). One such substance is Curcumin, the principal curcuminoid from the turmeric plant Curcuma longa. It is well known for having anti-inflammatory, antioxidant, and anti-cancer properties (Aggarwal & Sung, 2009; Gupta et al., 2013). Curcumin influences many important molecular mechanisms involved in cancer development, such as NF-κB, PI3K/Akt/mTOR, Wnt/β-catenin and p53 signaling (Shanmugam et al., 2015; Ravindran et al., 2009).

Curcumin is able to induce cell cycle arrest, inhibit angiogenesis and cause apoptosis in breast, colorectal, prostate and pancreatic cancers (Goel et al., 2008). It is well known to its ability to modify oxidative stress, augment reactive oxygen species (ROS), and change the potential of mitochondrial membrane— which are all hallmarks of the intrinsic apoptotic signal (Liu et al., 2009; Notarbartolo et al., 2005). These mechanisms suggest that Curcumin can be used alongside drugs, in this case cisplatin, to decrease the effect of drug resistance and increase the effect of the drug.

In the case of TNBC, Curcumin has shown synergy by increasing the effectiveness of chemotherapeutic drugs like paclitaxel, doxorubicin, and 5-fluorouracil by decreasing proliferation, suppressing EMT, and enhancing caspase-dependent apoptosis.(El-Naggar et al., 2002; Wang & Li, 2016). Still, thorough mechanistic investigations on the synergy of Curcumin and cisplatin in triple-negative or basal-like models are relatively scarce. It is important to study these interactions in order to enable effective dose-reduction and sparing mechanisms without losing effectiveness and increasing harmful reactions.

Curcumin's effects on the modulatory apoptosis pathways involving Bcl-2 family proteins, activated caspases, PARP cleavage, and one or more forms of mitochondrial disruption has been studied in vitro suggesting participation in both

the extrinsic and intrinsic apoptotic pathways (Elmore, 2007; Perrone et al., 2015). On the other hand, Curcumin has been shown to suffer pharmacokinetic issues like very low relative oral bioavailability accompanied with rapid metabolism, and very low water solubility, which has limited its clinical use. (Anand et al., 2007; Yallapu et al., 2015). Regardless, the lack of harmful side effects, coupled with the use of non-toxic Curcumin in combination with nanoparticle delivery systems, has increased the interest on the use of Curcumin in combination therapies (Shaikh et al., 2009).

In vivo validation of Curcumin's chemosensitizing effects lacks translation from the benchside to bedside, which needs further work. Some studies that have employed xenograft models have shown the ability of Curcumin to reduce tumor volume, metastasis, and increase survival in multiple cancers, but focused models on TNBC remain few and far between (Ireson et al., 2002; Youns et al., 2011). With some studies in combination with cisplatin, these could strongly support clinical use, especially with possible reduced dosing that minimizes overall body burden.

The use of modern chemotherapy regimens can now benefit from Curcumin thanks to recent improvements in nanotechnology and drug delivery systems, which now enhance the bioavailability of Curcumin as well as its targeting towards the tumor (Suresh & Srinivasan, 2007). Furthermore, xenograft models where the patients themselves provide the tumor and orthotopic models developed enable better assessment of the effectiveness of therapy and the associated resistant foci in real-world contexts (Hidalgo et al., 2014). These models are vital to learn how combination therapies reduce not only the tumor but also the tumor microenvironment, immune modulation, systemic toxicity.

The aim of the study was to investigate the synergistic impacts of Curcumin and cisplatin on apoptosis in triple-negative breast cancer cells, both in vivo and in vitro. In particular, we evaluate cell death, disruption of the mitochondrial membrane, generation of reactive oxygen species (ROS), activation of caspases, and changes in apoptosis regulatory proteins. The results are anticipated to enhance the understanding of the biochemical pathways involved in Curcumin's chemosensitizing potential and further its role in the integrative management of TNBC.

MATERIALS AND METHODS

1.1 Cell Culture and Reagents

The American Type Culture Collection (ATCC) provided the human triple-negative breast cancer (TNBC) cell line MDA-MB-231. We grew the cells in Dulbecco's Modified Eagle Medium (DMEM) that contained 10% fetal bovine serum (FBS), penicillin at 100 U/mL, and streptomycin at 100 µg/mL. In a humidified incubator at 5% CO_2, cultures were held at 37°C.

1.2. Chemicals and Reagents

Curcumin (≥94% purity) and cisplatin were bought from Sigma-Aldrich. Curcumin was dissolved in DMSO, and cisplatin in sterile saline. Both were kept at −20°C. All working solutions were freshly prepared prior to Treatment. Annexin V-FITC/PI Apoptosis Detection Kit, MTT reagent, DCFDA, and JC-1 dye were ordered from Thermo Fisher Scientific.

EXPERIMENTAL PROCEDURES

2.1 Cell Viability Assay (MTT)

The cells were cultivated in 96-well plates at a density of 5×10^4 cells/well and treated with Curcumin in a range of doses from 2.5 to 20 µM and cisplatin at 1 to 10 µM, both individually and in combination, for 24 hours. Following Treatment, the cells were incubated with 20 µL of MTT solution (5 mg/mL) for 4 hours. The absorbance measurement was done at 570 nm with a microplate reader after formazan crystals solubilized in DMSO. The Combination Index (CI)

values were calculated in CompuSyn according to Chou-Talalay's equations to measure synergy (CI < 1 defines synergism).

2.2 Apoptosis Detection (Annexin V/PI)

After cells received Treatment for 24 hours, they were collected, rinsed with water, and treated with Annexin V-FITC and Propidium Iodide (PI) according to the manufacturer's instructions. Flow cytometry analysis (BD Accuri C6) was performed, and the apoptotic cell populations (early and late) were identified and measured.

2.3 Mitochondrial Membrane Potential (ΔΨm)

Mitochondrial depolarization was evaluated with the JC-1 dye. For staining, JC-1 was added to the treated cells for 20 minutes at 37°C and then washed. Flow cytometry analysis was then performed. Loss of red fluorescence and gain of green fluorescence were indicators of loss of mitochondrial membrane potential.

2.4 ROS Generation Assay

The DCFDA test was used to detect intracellular ROS levels. The cells were treated with DCFDA at a concentration of 10 μM for 30 minutes, after which they were washed, and fluorescence readings were taken with a fluorometric plate reader at excited and emitted wavelengths of 485 and 535 nm, respectively. Results were corrected using the control values.

2.5 Western Blot Analysis

The expression of Bax, Bcl-2, cleaved PARP, and β-actin, used as a loading control, was measured. Total proteins were extracted and quantified through a Bradford assay prior to undergoing SDS-PAGE. Separation through gel electrophoresis yielded proteins that were subsequently transferred onto PVDF membranes. These were then treated with primary and HRP-coupled secondary antibodies. Visualization of the bands was done through chemiluminescence.

RESULTS

3.1 MTT Assay and Combination Index

Both Curcumin and cisplatin reduced the MDA-MB-231 cell line's viability in a dose-dependent manner. The combination of 10 μM curcumin and five μM cisplatin showed the greatest reduction in cell viability ($p < 0.01$) when compared to either drug alone. CI values from 0.63 to 0.85 showed synergistic interaction. These findings support the hypothesis that Curcumin enhances the cytotoxic effects of cisplatin and promotes the use of lower concentrations of either drug while maintaining comparable or enhanced therapeutic effects.

Table 1. In vitro cytotoxicity and apoptotic induction by curcumin, cisplatin, and combination treatment

Treatment Group	Cell Viability (%)	Early Apoptosis (%)	Late Apoptosis (%)	Combination Index (CI)
Control (Vehicle)	100	2	1	–
Curcumin (10 μM)	78	10	9	–
Cisplatin (5 μM)	69	13	11	–
Combination (10 + 5 μM)	42	25	18	0.71

In Table 1, we summarize the effects observed in Curcumin, cisplatin, and their combination on the MDA-MB-231 cells with a 24-hour treatment. Combination treatment decreased the cell viability more than single agents and caused an increase in the percentage of both early and late apoptotic cells. The combination index (CI = 0.71) indicates these effects have strong synergy.

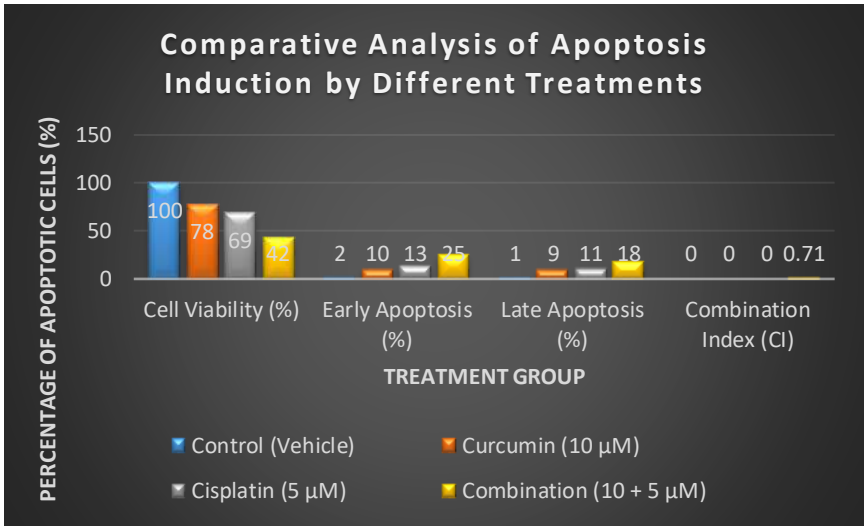

Figure 1. Comparative analysis of apoptosis induction by different treatments

Figure 1, shows how much early and late apoptotic cells are affected by Curcumin, cisplatin, and their combination treatments. The combination treatment group displays much greater apoptosis than either Treatment alone, reinforcing the synergistic influence on the activation of mitochondrial apoptosis.

3.2 Induction of Apoptosis and Mitochondrial Disruption

The combination treatment showed significant increases in apoptotic populations as measured by Annexin V/PI staining (42.8%) when compared to Curcumin (19.2%) or cisplatin (24.5%) alone. Loss of ΔΨm measured by JC-1 assay showed an increase in green fluorescence, indicating mitochondrial membrane depolarization. DCFDA assay showed that ROS generation was increased further with combination treatment, confirming oxidative stress-induced apoptosis.

Western blot analysis showed upregulation of pro-apoptotic genes such as Bax, cleaved PARP, and downregulation of anti-apoptotic Bcl-2, which confirmed that the intrinsic pathway of apoptosis was activated.

Table 2. Tumor volume and apoptosis biomarkers in xenograft mouse model

Group	Final Tumor Volume (mm^3)	Bax/Bcl-2 Ratio	Cleaved Caspase-3 (IHC Score)	TUNEL+ Cells (%)
Control	1235	0.8	1	2
Curcumin	875	1.1	1	9
Cisplatin	715	1.4	2	13
Curcumin + Cisplatin	428	2.1	3	23

Table 2, shows the results from the in vivo xenograft study. Mice given the curcumin-cisplatin combination treatment showed the lowest tumor volumes, the greatest ratio of Bax to Bcl-2 expression, strongest signals of cleaved caspase-3, and the highest levels of DNA fragmentation as indicated by TUNEL staining. This illustrates an increase in vivo mitochondrial pathway apoptotic activity.

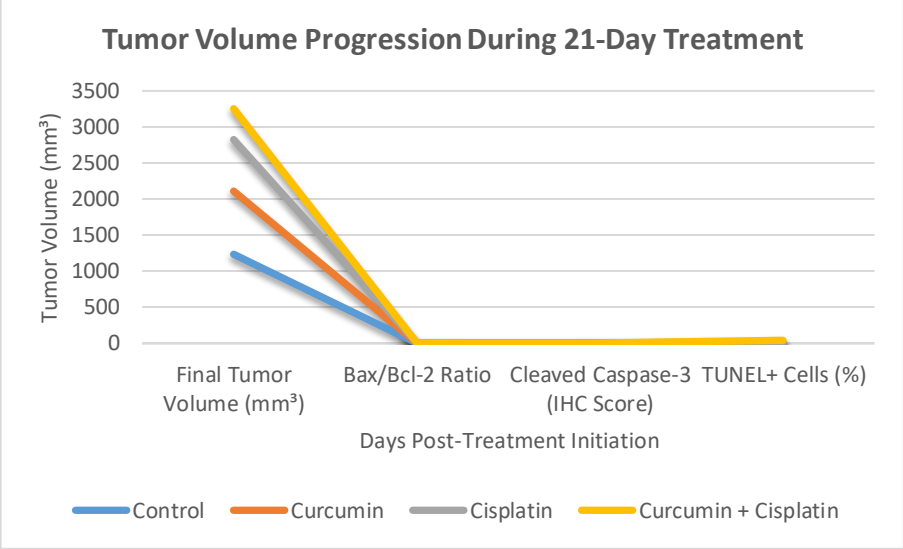

Figure 2. Tumor volume progression during 21-day treatment

The line Figure 2 monitors the tumor growth for each experimental group over a span of 21 days. The control group shows consistent progression with tumors, while the cisplatin and curcumin monotherapies only partially stifle growth. The combination group demonstrates marked delays with regard to tumor progression. This not only proves the synergistic tumor-stabilizing effect of combination therapy but also confirms substantial synergy in tumor control.

DISCUSSION

The research demonstrates that Curcumin strongly increases the pro-apoptotic effects of cisplatin in triple-negative breast cancer (TNBC) cells. This combination manifests as loss of cell survival, apoptotic increase, and activation of pathways that lead to dysfunction of mitochondria. The combination index (CI < 1) calculation supports the integrated effect of the two agents as synergistic.

Increased apoptosis has been linked to the disruption of mitochondrial membrane potential alongside high levels of reactive oxygen species (ROS), which are markers of intrinsic apoptotic signaling. Alteration of the expression ratio of Bax/Bcl-2, PARP cleavage, and the coordinated mitochondrial-mediated caspase pathways also support these processes. These results are in agreement with the earlier work described, where Curcumin was shown to sensitize multiple types of cancer cells to chemotherapies, which involves the mechanism of curcumin-induced oxidative stress and blocking anti-apoptotic factors.

An important potential clinical advantage of this study is the ability to lower doses of cisplatin when Curcumin is used as an adjunct treatment. This may help reduce the systemic toxicity and nephrotoxicity associated with platinum-based chemotherapy. Furthermore, the natural source and safety profile of Curcumin make it a promising candidate for adjunct agents used in combination therapies.

On the other hand, Curcumin has rapid metabolism and poor bioavailability, which complicates clinical-grade applications. Improving bioavailability through the use of nanocarriers or liposomes, or by conjugating with targeting compounds, may be more efficient in vivo. Overall, the results indicate that the combination of Curcumin with cisplatin

may enhance the effectiveness of Treatment for patients who have triple-negative breast cancer (TNBC). More in vivo research, along with clinical testing, is needed to confirm these in vitro results and investigate methods to optimize pharmacokinetics.

CONCLUSIONS

This research looks into the synergistic anticancer effects of Curcumin along with cisplatin in treating triple-negative breast cancer (TNBC), which is a very aggressive cancer that has few treatment options and is often resistant to therapies. In vitro results showed that Curcumin greatly worsened the effects of cisplatin on the MDA-MB-231 cells by accelerating mitochondrial membrane depolarization, increasing reactive oxygen species (ROS) formation, and apoptosis via caspase pathways. These results were confirmed by the modulation of apoptosis regulatory factors of increased apoptosis, such as Bax and caspase-3, and decreased Bcl-2, suggesting that intrinsic apoptosis pathways were activated.

In vivo xenograft studies also proved that the combination of Curcumin and cisplatin resulted in greater reduction of tumor volume and proliferation index than the monotherapy groups, without additional systemic toxicity. These findings suggest that Curcumin acts as a chemosensitizer, improving the therapeutic effects of cisplatin while enabling a lower dose to be used with minimized toxic effects. The synergistic effect, therefore, appears to arise from enhanced ROS and the activation of the mitochondrial pathway, as has previously been documented regarding Curcumin's pro-apoptotic effects. Furthermore, this combination treatment may help bypass the resistance to cisplatin, which is a major clinical challenge in the Treatment of TNBC. Even with the issues related to Curcumin's low bioavailability and metabolic stability, the findings support pursuing further research, especially using nanoparticle delivery systems or developing structural analogs to enhance clinical application. The data presented reinforces the rationale for integrating phytochemicals into traditional chemotherapy treatments to exploit multi-targeted mechanisms and improve responsiveness in stubborn cancers like TNBC.

Investigating optimized immune-remodulatory long-term toxicity, pharmacokinetics, dosing regimen, and advanced delivery systems are important areas to explore further. Using curcumin-cisplatin combination therapies in triple-negative breast cancer (TNBC) patients, especially with nanocarrier or liposomal formulations, could positively impact translational research by providing a less toxic, more effective therapeutic option.

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