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Effects of Cisplatin and Caffeic Acid on MDA-MB-231 Breast Cancer Cells

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Abstract
Triple-negative breast cancer (TNBC) is a highly aggressive subtype of breast cancer that lacks all three essential receptors. This aggressive characteristic makes it harder to treat with standard targeted therapy and necessitates novel treatment strategies. This study aims to evaluate the effects of cisplatin and caffeic acid (CA) on the MDA-MB-231 cells. CellTiter-Blue® assay was used to assess cell viability while morphological changes upon solo and combined treatment were observed using inverted microscopy. Both cisplatin and CA reduced cell viability in a concentration-dependent manner with cisplatin demonstrating higher potency (IC_{50} = 9.364 µM) compared to CA (IC_{50} = 104.1 µM). Microscopic observation revealed the morphological appearance including cell rounding, membrane blebbing, detachment and apoptotic-like body formation across all treatments. Importantly, preliminary morphological observations suggested that the combined cisplatin-CA treatment (at a sub-cytotoxic 5 µM cisplatin baseline) likely resulted in greater cytotoxic effect than either agent alone. Conclusively, this study demonstrated the individual potency of cisplatin and CA against TNBC cells while highlighting the therapeutic potential of their combination qualitatively.
Keywords: Cisplatin; Caffeic acid (CA); Triple-negative breast cancer (TNBC); MDA-MB-231 cell lines; Cell viability

Introduction

Breast cancer is a leading malignancy worldwide among women. Triple-negative breast cancer (TNBC) represents a highly aggressive and heterogeneous subtype that accounts for 15-20% of all breast cancer cases (Harahap et al., 2025). The majority of them are invasive ductal carcinomas, which arise in the milk ducts (Zagami & Carey, 2022). It is characterized by the absence of estrogen, progesterone and HER2 receptors. This profile hinders the effectiveness of targeted hormonal therapies, leaving systemic chemotherapy as the mainstay for TNBC treatments.

Platinum-based chemotherapeutics, particularly cisplatin, have been used extensively in TNBC treatment due to their potent ability to form DNA crosslinks that disrupt cellular DNA replication (Sahoo et al., 2024). In addition, a study by Bakar et al. (2023) demonstrated its potency of inducing the differentiation of cancer stem cells (CSCs), which effectively targets a key vulnerability of TNBC. Nevertheless, its clinical application is highly restricted by severe toxicities and the rapid acquired chemoresistance development. These clinical challenges are exacerbated in TNBC models such as MDA-MB-231 cell line as it exhibits high metastatic potential, overexpression of epithelial-mesenchymal transition (EMT) and enrichment of CSCs populations (Witt & Tollefsbol, 2023; Hero et al., 2019).

To overcome these limitations, interest in exploring natural bioactive compounds to be used alongside as chemosensitizers has increased recently. Caffeic acid (CA), a natural phenolic acid that is found in vegetables, fruits and coffees possesses established antioxidant, anti-inflammatory and anticancer properties (Mirzaei et al., 2021). Recently, CA have been found to have the ability to inhibit CSCs self-renewal by disrupting mitochondrial membrane potential and suppressing cancer stemness (Xie et al., 2024). Despite the extensive study of individual anticancer profiles of both cisplatin and CA, their specific comparative and combination interaction on TNBC as well as detailed morphological changes remain poorly explored. Therefore, this study aims to evaluate individual and combined effects of cisplatin and CA on MDA-MB-231 cells.

Materials and methods

Cell culture

MDA-MB-231 cell was taken from -80°C freezer at Cancer Research Laboratory (CRL) and cultured in a T25 flask using complete medium containing DMEM/F12 supplemented with 10% fetal bovine serum (FBS) and 1% antibiotics solution containing penicillin-streptomycin. The culture was then incubated in a CO_2 incubator under conditions of 37℃ and 5% CO_2 to grow. The cells were passaged at least twice a week when it reached 70%-80% cell confluency.

Cell Treatment and Viability Assay

MDA-MB-231 cells were seeded into 96-well plates at a density of 3500 cells/well and incubated overnight to allow for attachment. Before treatment, the initial cell morphology was recorded for later comparison.

For solo treatment, cells were treated with various concentrations of cisplatin (0-50 μM) and CA (0-200 μM) separately for 24 hours. For combined treatment, cells were treated with varying concentration of CA (0-200 μM) and fixed sub-IC_{50} concentration of cisplatin (5 μM) for 24 hours. All the experiments were performed in triplicate.

Cell viability was then evaluated using the CellTiter-Blue® assay. Following treatment, 10μL of CellTiter-Blue® reagent were added into each well and incubated for 3 to 4 hours in the CO_2 incubator. Absorbance was measured at 570 nm (reference wavelength 600 nm) using a microplate reader. Additionally, cellular morphological changes were documented using an inverted microscope at 4x, 10x and 20x magnifications.

Statistical Analysis

Data were presented as mean ± standard deviation (SD) of three independent experiments. Statistical analysis was performed using GraphPad Prism (version 10.6) and nonlinear regression analysis were performed to obtain the IC_{50} for both agents. Differences between treatment groups and the control were evaluated using one-way ANOVA followed by multiple comparisons using Dunnett's post-hoc test.

Results and discussion

Solo cisplatin and caffeic acid (CA) reduced viability of MDA-MB-231 cells

To evaluate the cytotoxic profiles, MDA-MB-231 cells were exposed to varying concentrations of cisplatin and CA for 24 hours. According to Figure 1, both compounds reduced viability of MDA-MB-231 cells in a concentration-dependent manner.

Cisplatin treatment showed a significant reduction at 7.5 μM with viability dropping to 62.99% ($p \leq 0.0001$) and achieved near-complete inhibition above the concentration of 20 μM. This steep decline most likely reflects the mechanism of action exerted by cisplatin. Cisplatin allowed the DNA adduct formation via crosslinking the N7 atom of purine bases, halting DNA replication (Dasari & Tchounwou, 2014). When the DNA damage exceeds the capacity of cellular DNA repair mechanisms such as nucleotide excision repair (NER) pathway, it will trigger apoptosis (Kopacz-Bednarska & Król, 2022). Furthermore, cisplatin also induces the generation of reactive oxygen species (ROS), which may activate pro-apoptotic protein in response to DNA damage to cause the release of cytochrome c, initiating the intrinsic caspase-3 apoptotic pathway (Kopacz-Bednarska & Król, 2022).

Likewise, significant cytotoxicity induced by CA began to be observed at 75 μM (72.47% viable cells), with pronounced suppression beyond 125 μM (45.70% viable cells). This phenomenon may be associated with CA's multifaceted mechanisms. As study by Xie et al. (2024) described, CA has the ability of modulating FOXO1 activity and upregulating mitochondrial fission proteins which could disrupt the mitochondrial membrane potential and reduce ROS generation. This mechanism suppresses cancer of its ability to self-renew, targeting the stem-cell-like properties of TNBC cells (Xie et al., 2024) The altered FOXO1 expression may also lead to G2/M cell cycle arrest (Parvizi et al., 2022). In addition, Alam et al. (2022) mentioned CA's ability to inhibit anti-apoptotic proteins like Bcl-2, which effectively activates intrinsic apoptosis.

Non-linear regression determined the IC_{50} value for cisplatin and CA at 24 hours are 9.364 μM (95% CI: 8.586–10.16 μM) and 104.1 μM (95% CI: 94.62 - 113.2 μM), respectively. For cisplatin, the resulting IC_{50} value showed a similar trend with previous study by Toh et al. (2024). However, the resulting IC_{50} value of CA was comparatively lower than those published in the literatures. For example, a 24-hour IC_{50} of 253.04 μM for CA treatment was reported by Xie et al. (2024) and 40.0μg/ml (~221.94 μM) by Parvizi et al. (2022). Such variations may probably be due to several biological and experimental variables including different initial seeding density, assay methods and culture conditions (Femina et al., 2022).

Crucially, the cytotoxic effects on the normal and non-cancerous cells are vital to consider when evaluating therapeutic potential of a compound. A study by Tetikoglu et al. (2024) reported that the 24-hour IC_{50} of cisplatin against non-tumorigenic MCF-10A breast epithelial cells is 25 μg/mL (~ 83 μM). While the data regarding CA on MCF-10A is limited, caffeic acid phenethyl ester (CAPE) as its derivatives has been reported to have no adverse effect on the viability of MCF-10A cells at concentrations up to 100 μg/mL (~351.73 μM) (Poyraz et al., 2023). These literatures provide preliminary and indirect support for the safety of the therapeutic dosages evaluated in this study.

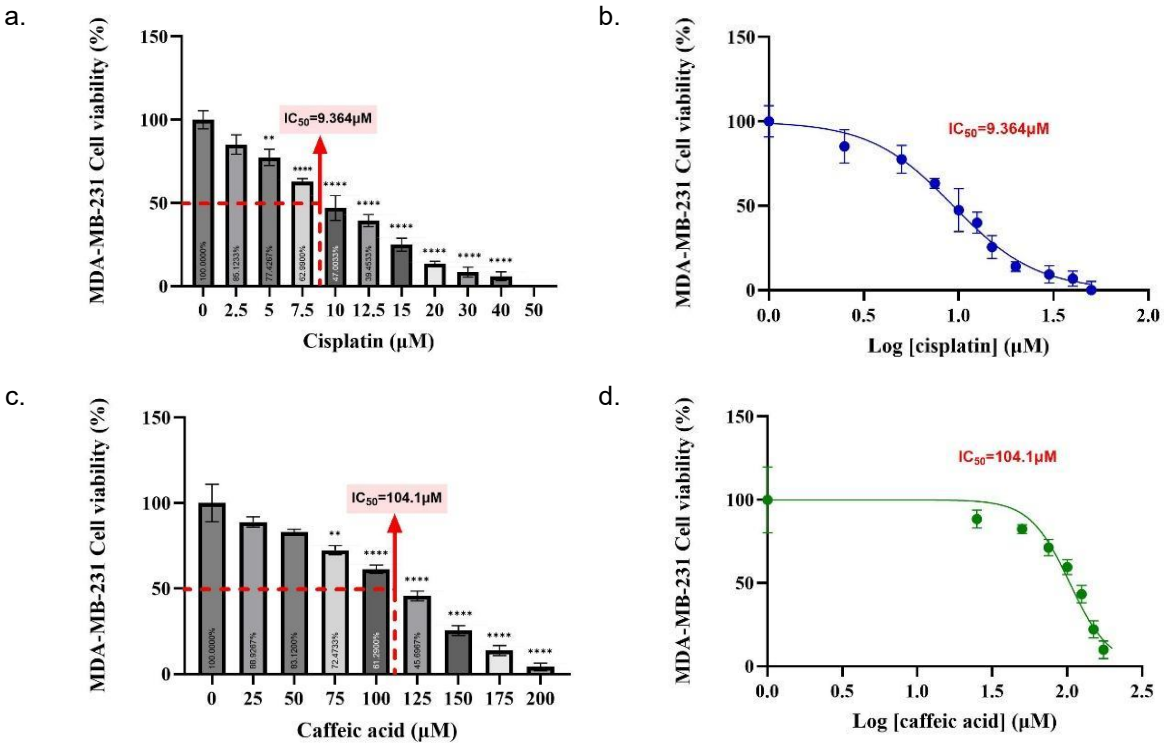

Figure 1 Cell viability of MDA-MB-231 after 24-hour individual treatment with cisplatin and CA. Dose-dependent viability reduction and corresponding non-linear regression curves for (a,b) cisplatin (IC_{50}=9.364 μM) and (c,d) CA (IC_{50}=104.1 μM). Data represent mean ± SD (n=3). *p ≤ 0.05, **p ≤ 0.01, ***p ≤ 0.001, and ****p ≤ 0.0001, while bars without indicators represent non-significant differences

Table 1: Comparative summary of cisplatin and CA against MDA-MB-231 cells

Characteristics	Cisplatin	Caffeic acid (CA)
Concentration range	2.5-50 μM	25-200 μM
IC_{50} value	9.364 μM	104.1 μM
Potency	High potency	Lower potency
Primary mechanism of action	DNA crosslinking; ROS generation; intrinsic caspase-3 pathway activation	FOXO1 modulation; stemness suppression; G2/M cell cycle arrest

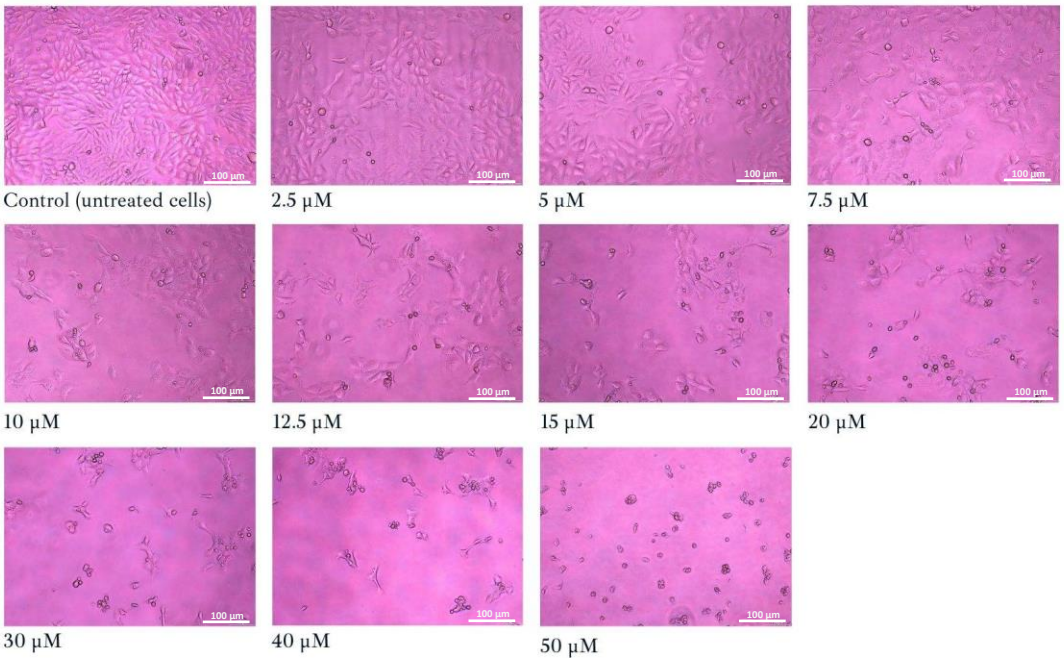

Figure 2 Microscopic image of control (untreated) and Cisplatin-treated MDA-MB-231 cells after 24 hours at 10x magnification

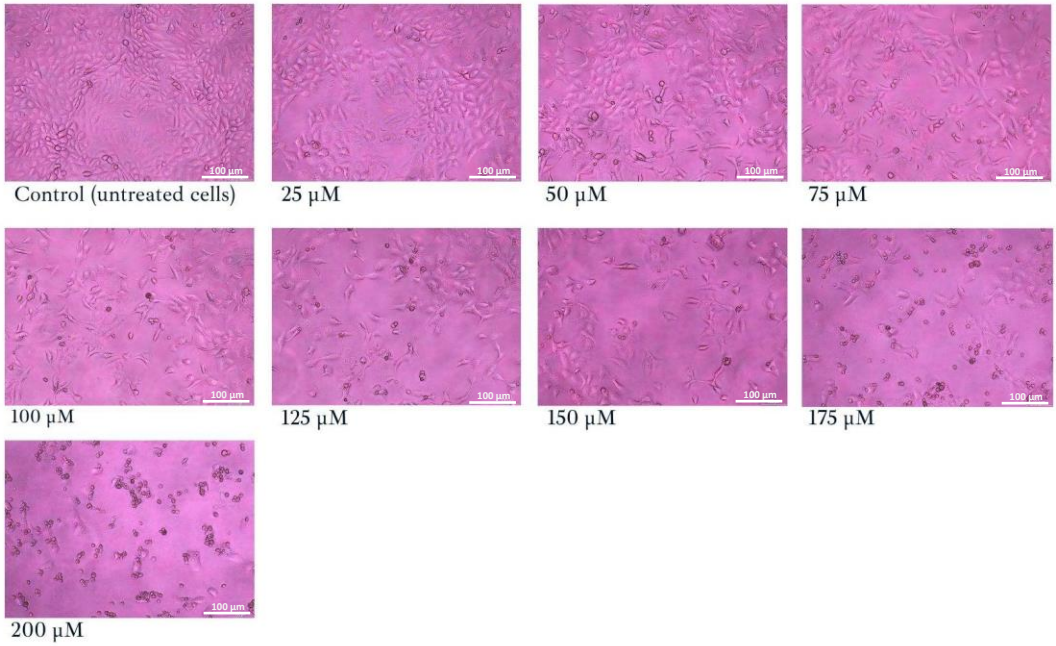

Figure 3 Microscopic image of control (untreated) and CA-treated MDA-MB-231 cells after 24 hours at 10x magnification

Cisplatin and CA induced morphological changes of MDA-MB-231 cells

The morphological changes of MDA-MB-231 cells was observed under an inverted microscope following a 24-hour treatment. Initially, MDA-MB-231 cell exhibits elongated and spindle-shaped appearance in a dense monolayer (Razak et al., 2019; Carneiro et al., 2023), serving as the morphological baseline. Upon 24-hour individual treatment, both cisplatin and CA induced concentration-dependent structural damage and progressive decrease in cell density (Figure 2 and 3), aligning to data obtained from viability assay. Figure 4 illustrated the 20x magnification of cisplatin-treated (a) and CA-treated (b) cells at selected concentrations.

For solo cisplatin treatment, cells were observed to start losing their spindle-like morphology and rounded up at the sub-cytotoxic levels (2.5 –5 μM), likely indicating the early stress responses (Cecati et al., 2026). It could be explained by the cytoskeletal stress from DNA adduct formation caused by cisplatin-induced DNA crosslinking (Povea-Cabello et al., 2017). As concentration increase to 7.5 μM (Figure 4a), a more pronounced effect was observed including dumbbell-shaped appearance, which could be explained by G2/M cell cycle arrest (Kopacz-Bednarska & Król, 2022), followed by more cells became smaller and irregular upon 10 μM. At the higher concentration (≥30 μM), cells were highly disrupted with fewer intact cells remaining and apoptotic body-like appearance, which was consistent with previous study by Ko et al. (2022). This could be related to the upregulation of pro-apoptotic proteins described in the study of Kopacz-Bednarska & Król (2022) due to the unrepairable DNA damage as accumulated cisplatin.

In contrast to cisplatin treatment, MDA-MB-231 cells did not see visible changes at the lower CA concentrations (25-50 μM). At the intermediate concentration (75-125 μM), cells exhibited significant detachment and began to appear membrane blebbing. These observed changes may be reflecting the ability of CA to downregulate anti-apoptotic Bcl-2 expression, which disrupt mitochondrial membrane integrity and subsequently induced apoptosis of cancer cells via the activation of caspase 3 pathway (Alam et al., 2022). This is followed by severe reduction in cell density alongside abundant apoptotic-like bodies formation at the higher concentrations (≥150 μM). This extensive cell death may be correlated with the completion of intrinsic apoptotic cascade which is accelerated by CA-induced FOXO1 modulation (Xie et al., 2024). However, the possible mechanism that is suspected to cause the observed morphological changes in both cisplatin and CA may require further molecular studies to validate.

Based on these observations, 5 μM of cisplatin induced early morphological stress while maintaining high cell density, which acts as the sub-cytotoxic threshold. Hence, this specific concentration of cisplatin was selected to be fixed and combined with varying concentrations of CA (25-200 μM) to investigate the potential effects of combination treatment.

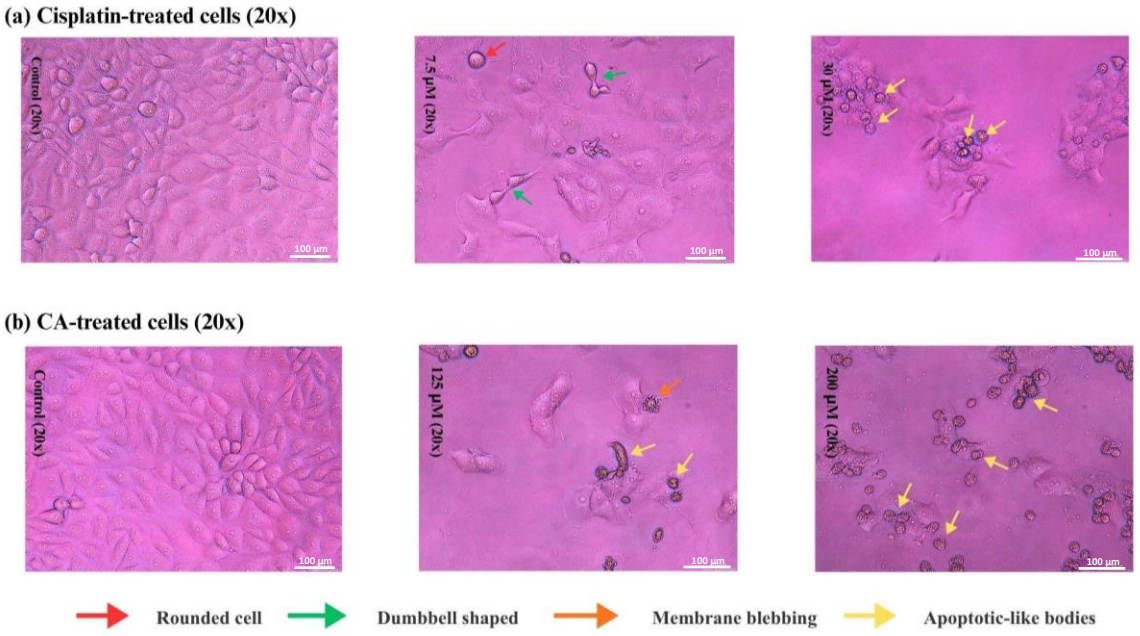

Figure 4 Microscopic image at 20x magnifications of control (untreated) and treated MDA-MB-231 cells after 24 hours (a) cisplatin-treated cells; (b) CA-treated cells

Combined cisplatin-CA treatment induced morphological changes on MDA-MB-231 cells

As illustrated in Figure 5, the full panel of 10x magnification microscopic images of cells upon the combined cisplatin-CA treatment revealed a progressive and concentration-dependent reduction in the number of viable cells across a range of combination concentrations.

Interestingly, the significant and visible reduction in cell density was observed even at the lowest concentration combining 5 µM cisplatin with 25 µM CA. At this concentration, many cells already exhibited a rounded appearance with apoptotic body-like structure, which were less dominant in either agent at these concentrations. As illustrated in Figure 6, treatment with 5 µM cisplatin alone resulted in only a moderate reduction in cell density while for 25 µM CA alone, cells were still largely intact with minimal changes. This finding was likely suggested that the combination could potentially produce a greater effect than single agent treatment at these concentrations. As the CA concentration increased to 50-100 µM, the number of viable cells declined further with fewer intact cells alongside an increase in rounded and apoptotic-like morphology. At the higher combination concentrations (5 µM cisplatin + 125-200 µM CA), the cell density was continued to be reduced gradually to near zero. The remaining cells appeared irregular morphology and increased cell debris, which was likely suggesting the hallmark of late-stage apoptosis.

These findings indicate that combining 5 µM cisplatin with CA can potentially sensitize the MDA-MB-231 cells toward the treatment. It is aligned with previous studies that demonstrated the chemo sensitizing effects of cisplatin with natural compounds. For example, Pauzi et al. (2016) reported the significant enhanced apoptosis induction in MDA-MB-231 cells via the co-treatment of cisplatin and bromelain, which is a natural proteolytic enzyme derived from pineapple and Yang et al. (2021) found the synergistic effect of cisplatin with resveratrol in the same cell line. In addition, specific combinations of cisplatin and CA have shown enhanced therapeutic efficacy in CaSki and HeLa cell lines through the suppression of cell growth and survival (Alam et al., 2022).

The observed greater effect in morphological changes induced by co-treatment of cisplatin and CA may be attributed to the cisplatin-induced DNA damage and intrinsic apoptotic pathway combined with the ability of CA in disrupting mitochondrial membrane potential and suppressed cancer stemness (Kopacz-Bednarska & Król, 2022; Xie et al., 2024). Notably, MDA-MB-231 cell line is classified as claudin-low TNBC subtype with the enriched cancer stem cell features which could contribute to the poor prognosis outcome (Prabhakaran et al., 2013). These features may cause MDA-MB-231 cells responsive to the CA's ability in reducing cancer stemness, could potentially limit the cell proliferation capacity and be more susceptible to cell death when combined cisplatin-CA treatment.

Importantly, the combination treatment conducted in this study was a preliminary investigation based on the qualitative morphological observation without the quantitative cell viability and combination index (CI) analysis involved. Therefore, the preliminary observation of morphological changes and proposed potential mechanisms of action still require more comprehensive studies to validate and confirm.

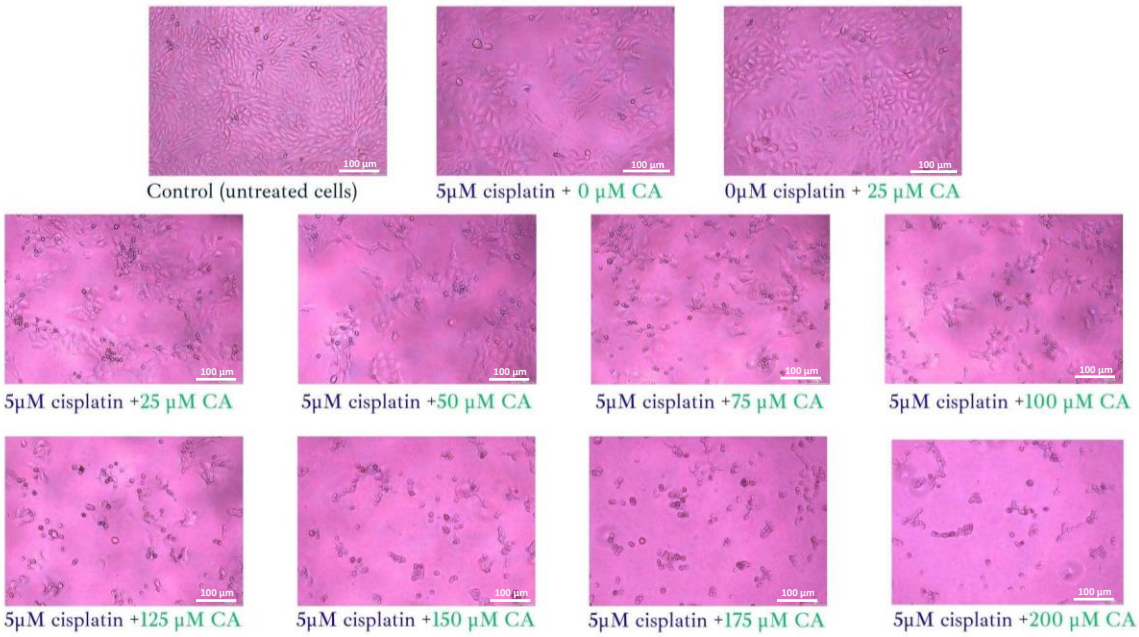

Figure 5 Microscopic image of control (untreated) and combined cisplatin-CA-treated MDA-MB-231 cells after 24 hours at 10x magnification

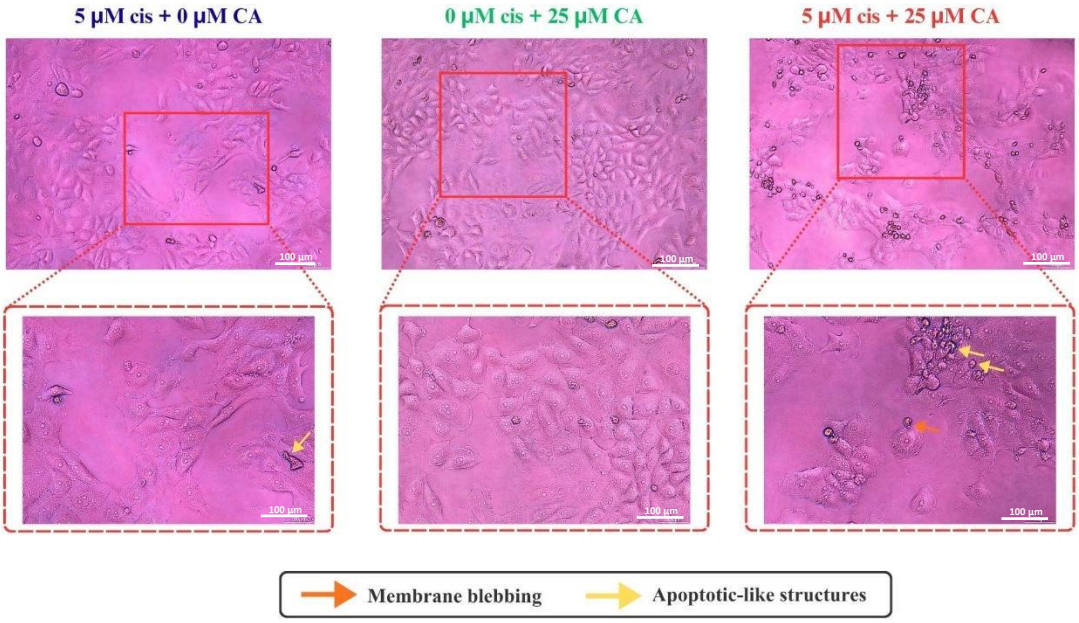

Figure 6 Morphological changes at 10x and 20x magnification of cisplatin (5µM) alone, CA (25µM) alone and combined cisplatin-CA (5µM cis + 25 µM CA) treated MDA -MB-231. The orange arrow indicates membrane blebbing; The yellow arrow indicates the apoptotic bodies formation

Conclusion

In summary, this study successfully demonstrated the concentration-dependent antiproliferative effects of cisplatin and caffeic acid (CA) both individually and combination against MDA-MB-231 triple-negative breast cancer cell lines. Based on the observations, cisplatin was found to have higher potency with a smaller IC_{50} value of 9.364 µM (95% CI: 8.586–10.16 µM) compared to CA with an IC_{50} value of 104.1 µM (95% CI: 94.62–113.2 µM). Both treatments independently induced morphological changes such as rounded and apoptotic-bodies formation, possibly associated with the mechanism of action exerted by both agents. Notably, the preliminary evaluation of combination treatment using a sub-cytotoxic baseline of cisplatin (5 µM) combined with varying concentrations of CA (25-200 µM) triggered a profound and dose-dependent morphological changes. This finding suggests that CA effectively chemo-sensitizes TNBC cells towards cisplatin treatment. Despite the qualitative morphological observation supporting the relevance of this combination, the further combination index (CI) analysis is essential to determine the specific interaction between cisplatin and CA whether is synergistic, additive or antagonistic. Furthermore, future analyses involving comprehensive molecular and in-vivo studies are also important to validate underlying mechanistic pathways and evaluate the overall clinical safety.

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