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Research Article

# Cytotoxic effects of cisplatin, curcumin, and a lipid-based vitamin E formulation on MCF-7 breast cancer cells

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## ABSTRACT

**Aim:** To characterize, for each agent individually, the dose-dependent cytotoxic activity of cisplatin, curcumin, and a lipid-based vitamin E formulation in MCF-7 breast cancer cells, as groundwork for subsequent combination research.

**Methods:** MCF-7 cells were exposed to a range of escalating concentrations of cisplatin, or of curcumin and vitamin E, over an extended exposure period, after which viability was determined using the MTT colorimetric assay. For curcumin, background absorbance arising from its intrinsic pigmentation was corrected using acellular compound-only wells. Statistical comparisons were performed using the Mann-Whitney U test.

**Results:** Both cisplatin and curcumin significantly lowered MCF-7 viability relative to untreated controls in a dose-dependent fashion across all concentrations tested. A pronounced drop in viability was already evident with cisplatin at its lowest tested concentration. After correcting for background absorbance, curcumin still showed a marked cytotoxic effect. The lipid-based vitamin E formulation, however, showed no such concentration-dependent decline; at several doses, apparent viability was actually higher than in controls, an effect more consistent with the formulation's poor aqueous solubility than with a true biological response.

**Conclusion:** Both cisplatin and curcumin exhibited consistent, reproducible cytotoxicity toward MCF-7 cells, whereas the tested lipid-based vitamin E formulation proved unsuitable for assessment under conventional aqueous culture conditions. Collectively, these single-agent concentration-response data lay the methodological groundwork for future studies combining cisplatin, curcumin, and more water-compatible vitamin E formulations in breast cancer models.

**Keywords:** breast neoplasms, cisplatin, curcumin, vitamin e, mcf-7 cells, cell survival

## Introduction

According to GLOBOCAN 2022 data, breast cancer is the most commonly diagnosed cancer in women and the leading cause of female cancer mortality worldwide (1). Despite progress in systemic treatment, breast cancer continues to impose a substantial global burden, underscoring the need for more effective, better-tolerated therapies (2).

Among platinum-based coordination compounds, cisplatin occupies a central place in chemotherapy regimens for its strong antineoplastic action against solid tumors, including breast cancer, exerted primarily

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through intrastrand DNA cross-link formation that blocks replication and triggers apoptosis (3,4). Nonetheless, its clinical use is limited by dose-dependent adverse effects- kidney damage, nerve toxicity, hearing loss, and vestibular impairment- together with the development of resistance over time (3,5). These limitations have fueled interest in combination approaches capable of sustaining or boosting cisplatin's anticancer effect while lowering the required dose (5).

Interest in naturally occurring bioactive molecules as chemotherapy adjuncts has grown considerably. Curcumin, a polyphenolic compound from *Curcuma longa*, was first reported to possess antitumor activity in 1985 (6) and has since been investigated extensively across cancer cell lines and animal models (7). In breast cancer, curcumin acts through multiple mechanisms, modulating proliferative and apoptotic signaling and elevating reactive oxygen species (ROS) levels, while also sensitizing cells to agents such as doxorubicin and allowing apoptosis to occur at reduced concentrations (8), making it a rational candidate for cisplatin-sparing combinations.

A related line of investigation concerns vitamin E, a family of lipid-soluble tocopherols and tocotrienols known for context-dependent antioxidant and pro-oxidant activity and for their capacity to modulate cancer-related gene pathways (9,10). In breast cancer cell models, combining vitamin E with doxorubicin enhanced the drug's antiproliferative effect while sparing normal cells, although no formal synergism was established (10). This dual profile supports a rationale for including vitamin E in cisplatin-based protocols while underscoring the need for careful validation.

Although cisplatin, curcumin, and vitamin E have each been studied individually, and curcumin has previously been paired with various chemotherapeutic agents as well as with vitamin C (11,12), no prior study has evaluated combinations of all three agents together in breast cancer cells. Notably, vitamin C has featured far more prominently than vitamin E in this line of research, leaving the latter's antitumor potential comparatively underexplored (9-13). Establishing dependable single-agent dose-response data for each compound is a necessary precondition for meaningfully evaluating their combined effects.

This study was therefore designed to characterize the dose-dependent cytotoxic effects of cisplatin, curcumin, and vitamin E in the MCF-7 breast cancer cell line using the MTT viability assay, as a preliminary step toward future combination work. We report concentration-response profiles for cisplatin and curcumin, together with a methodological observation regarding the technical limitations of a lipid-based vitamin E formulation under standard cell culture conditions, a finding with direct practical relevance for future *in vitro* combination studies involving this vitamin.

## Materials and Methods

### *Cell line and culture conditions*

MCF-7 human breast cancer cells were maintained in Dulbecco's Modified Eagle Medium (DMEM) containing 10% fetal bovine serum (FBS), 1% penicillin-streptomycin (10,000 U/mL penicillin, 10 mg/mL streptomycin), and 1% L-glutamine, at 37°C under a humidified atmosphere with 5% $CO_2$.

### *Drugs and treatment groups*

The dose-dependent cytotoxic effects of cisplatin, curcumin, and vitamin E on MCF-7 cells were each evaluated separately. Vitamin E was administered as a commercially available lipid-based preparation (Vi-Plex E, OSEL İlaç Sanayi ve Ticaret A.Ş., Istanbul, Turkey), with the tested concentrations expressed relative to the total formulation rather than to its $\alpha$-tocopherol content alone. Each agent was

tested at four concentrations: 0.95, 1.9, 3.8, and 7.6 μg/mL for cisplatin, and 12.5, 25, 50, and 100 μg/mL for curcumin and vitamin E. Cisplatin was applied directly in its ready-to-use liquid form. Curcumin was dissolved in dimethyl sulfoxide (DMSO) to prepare stock solutions, while vitamin E (Vi-Plex E) was dissolved in ethanol before being added to the cultures. All intermediate dilutions were prepared in FBS-free DMEM; for vitamin E, this corresponded to final in-well ethanol concentrations of 0.0083%, 0.0167%, 0.0333%, and 0.0667% (v/v), respectively, remaining well within levels generally considered non-cytotoxic for cultured cells. For curcumin, this corresponded to final in-well DMSO concentrations of 3.125%, 6.25%, 12.5%, and 25% (v/v), respectively. A DMSO-only vehicle control was tested at each of these matched concentrations, including the highest (25%), and showed no cytotoxicity at any concentration; it was therefore not presented as a separate figure. No corresponding ethanol-only vehicle control was prepared for the vitamin E experiments. Each treatment condition was tested in quadruplicate wells (n=4) within each plate, across 4 independent experiments. The control condition consisted of an untreated MCF-7 group.

### *Cell viability (MTT) assay*

Cell viability was determined with the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) colorimetric assay, which relies on the conversion of MTT into insoluble formazan crystals by mitochondrial dehydrogenase enzymes present in viable cells (14). Cells were plated in 96-well dishes at $1\times10^4$ cells per well and allowed to attach for at least 1 h at 37°C in 5% $CO_2$, with attachment verified before proceeding (typically reaching approximately 80% cell adherence within 1–4 h), before being exposed to the test agents for 72 h. At the end of this exposure period, each well received 10 μL of MTT solution (5 mg/mL), and the plates were kept at 37°C in 5% $CO_2$ for 4 h in the dark. After removing the supernatant, 100 μL of DMSO was added to dissolve the formazan crystals that had formed. Absorbance readings were then taken at 570 nm with a microplate spectrophotometer, and percentage viability and cytotoxicity values were calculated as shown in Equations 1 and 2:

$$\%\ \text{Viability} = (\text{A}_{\text{sample}}/\text{A}_{\text{control}}) \times 100 \quad (1)$$

$$\%\ \text{Cytotoxicity} = 100 - [(\text{A}_{\text{sample}}/\text{A}_{\text{control}}) \times 100] \quad (2)$$

in which $A_{sample}$ and $A_{control}$ denote the absorbance values recorded for treated and untreated control wells, respectively (14).

Since curcumin's inherent yellow pigmentation can interfere with absorbance measurements at 570 nm, cell-free wells containing curcumin alone at each test concentration were also included as negative controls. The absorbance recorded in these compound-only wells was then subtracted from that of the matching cell-containing wells, isolating the true cell-viability signal from compound-related background absorbance.

### *Statistical analysis*

All data were processed in GraphPad Prism (version 5.04) and are reported as mean ± standard error of the mean (SEM). Each treatment group was compared against the untreated control using the non-parametric Mann-Whitney U test, with statistical significance defined as $p<0.05$ (marked as * in the figures; ** denotes $p<0.005$). Each condition was tested in quadruplicate wells within a plate in each of 4 independent experiments; the mean of the quadruplicate wells from each independent experiment was treated as a single data point, and comparisons were performed on these experiment-level means (n=4 vs. n=4). Given this sample size, GraphPad Prism computed p-values using the asymptotic (Gaussian) approximation rather than the exact method.

## Results

### *Cisplatin reduces MCF-7 cell viability in a dose-dependent manner*

At every concentration tested, cisplatin significantly reduced MCF-7 cell viability relative to the untreated control ($p < 0.005$ for all doses), with viability declining progressively as the concentration increased (Figure 1). A roughly 50% loss of viability occurred at 0.95 μg/mL, making this an appropriate working concentration for subsequent experiments.

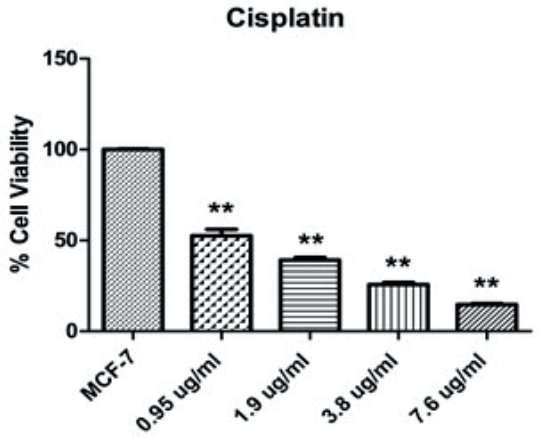


**Figure 1.** Cisplatin's effect on MCF-7 cell viability, as measured by the MTT assay. Cells were exposed to increasing concentrations of cisplatin (0.95, 1.9, 3.8, and 7.6 μg/mL), and viability values are shown relative to the untreated control.

**p < 0.005 versus untreated control. Values represent mean ± SEM from 4 independent experiments.

### *Curcumin reduces MCF-7 cell viability*

Curcumin likewise produced a significant reduction in MCF-7 viability at every concentration examined, relative to the untreated control ($p < 0.005$) (Figure 2A), with a pronounced decline evident across the whole concentration range. Although the resulting dose-response curve was not perfectly linear, all tested concentrations still showed a statistically significant cytotoxic effect compared with the control group. Given that curcumin's yellow pigmentation can interfere with 570 nm absorbance readings, acellular curcumin-only wells were used to correct for this compound-related background (see Section 2.3); after applying this correction, curcumin continued to show a clear cytotoxic effect across the concentrations tested (Figure 2B). Notably, at the lowest concentration examined (12.5 μg/mL), curcumin lowered cell viability to a greater extent than cisplatin did at its lowest tested concentration (0.95 μg/mL).

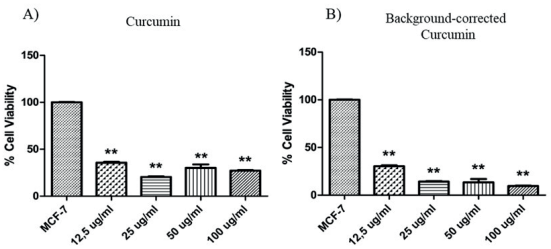


**Figure 2.** Curcumin's effect on MCF-7 cell viability, assessed via the MTT assay. (A) Cells were exposed to rising concentrations of curcumin (12.5, 25, 50, and 100 μg/mL); viability was measured by the MTT assay and is expressed relative to the untreated control. (B) Viability values after subtracting the absorbance recorded in acellular curcumin-only wells from that of the matching cell-containing wells, correcting for compound-related background.

Values represent mean ± SEM from 4 independent experiments; **p < 0.005 relative to the untreated control.

### *Vitamin E (lipid-based formulation) does not exhibit a cytotoxic effect in MCF-7 cells*

Unlike cisplatin and curcumin, the lipid-based vitamin E formulation (Vi-Plex E) produced no cytotoxic effect in MCF-7 cells. At several of the tested concentrations, apparent viability was actually higher than in the untreated control, and some of these differences reached statistical significance (Figure 3); nonetheless, no dose-dependent decline in viability was observed at any point. Given this outcome, the vitamin E formulation was not pursued further in the study.

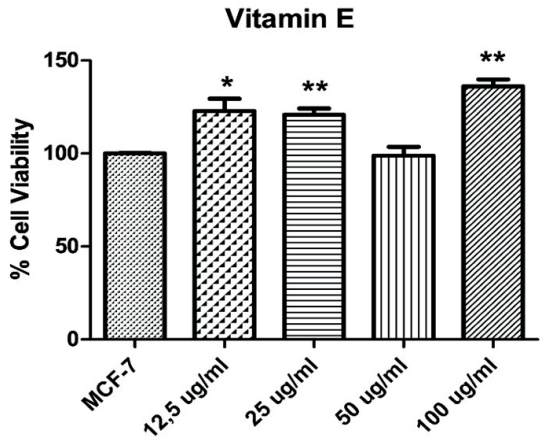


**Figure 3.** Effect of the lipid-based vitamin E preparation (Vi-Plex E) on MCF-7 cell viability, measured by the MTT assay. Cells were exposed to increasing concentrations of vitamin E (12.5, 25, 50, and 100 μg/mL), and viability, assessed by the MTT assay, is expressed relative to the untreated control. Values are given as mean ± SEM of 4 independent experiments.

*$p < 0.05$; **$p < 0.005$ versus untreated control.

## Discussion

In this work, we assessed how cisplatin, curcumin, and a lipid-based vitamin E preparation individually affect the viability of MCF-7 breast cancer cells, using the MTT assay as the readout. Both cisplatin and curcumin produced substantial declines in cell viability, while the vitamin E preparation failed to do so. Together, these single-agent concentration-response findings offer a working framework for subsequent combination experiments.

As a chemotherapeutic agent for solid tumors including breast cancer, cisplatin continues to be used extensively, largely because of its ability to generate DNA cross-links that trigger apoptotic cell death. In line with this mode of action, all tested cisplatin concentrations produced a significant drop in MCF-7 viability, and the 0.95 μg/mL dose was sufficient to reduce viability by roughly half, marking it as an appropriate concentration for subsequent work. While reported $IC_{50}$ figures differ between studies depending on exposure duration and assay setup, the response observed here is in line with the well-documented sensitivity of MCF-7 cells to cisplatin (4,5).

A similarly pronounced reduction in MCF-7 viability was seen with curcumin at every concentration examined, in agreement with existing evidence that curcumin restrains breast cancer cell growth through several routes—altering oxidative stress balance, blocking proliferative signaling, inducing cell-cycle arrest, and promoting apoptosis (6-8). Unlike cisplatin, the pre-correction concentration-response pattern was not strictly linear, an outcome most plausibly attributable to curcumin's strong yellow pigmentation, a recognized source of interference in colorimetric absorbance-based assays (15). To address this, acellular wells containing curcumin alone were included, allowing background absorbance attributable to the compound itself to be quantified and subtracted. Once this correction was applied, curcumin's cytotoxic effect remained clearly evident across the full concentration range, supporting the reliability of the compound-only control approach for pigmented substances. We note that this approach is an approximation; a more rigorous correction would require quantifying background absorbance directly from the formazan signal itself.

Notably, at their respective lowest tested doses (12.5 μg/mL for curcumin versus 0.95 μg/mL for cisplatin), curcumin caused a larger drop in viability than cisplatin did; these concentrations are not molar-equivalent, so cross-compound comparisons should be interpreted cautiously. Even so, this observation aligns with existing literature describing curcumin's strong antiproliferative activity in breast cancer models (6-8), as well as evidence that curcumin can potentiate chemotherapy-induced cytotoxicity, including that of cisplatin, by shifting oxidative stress balance and interfering with DNA repair processes such as FEN1 function (8,16).

The lipid-based vitamin E preparation (Vi-Plex E) behaved quite differently: rather than showing a dose-dependent decline in viability, several tested concentrations produced apparent viability values above those of the control wells. We interpret this as more likely a technical artifact than a genuine biological effect. Given that $\alpha$-tocopherol is a highly lipophilic molecule with poor water solubility (17), lipid-based preparations of this kind may not disperse evenly within aqueous culture medium, which could distort assay readings. It should also be noted that, because an ethanol-only vehicle control was not included, some contribution from the ethanol solvent itself to these results cannot be ruled out. In addition, redox-active compounds such as $\alpha$-tocopherol can nonenzymatically reduce the MTT tetrazolium salt independent of cell viability, which, alongside solubility, may further contribute to the above-control readings observed in Figure 3. Furthermore, vitamin E's antitumor efficacy is known to vary considerably depending on the specific isoform and formulation used; tocotrienols and derivatives such as $\alpha$-tocopheryl succinate, for example, have demonstrated stronger antiproliferative and pro-apoptotic activity than native $\alpha$-tocopherol in breast cancer models (9,10,13,18,19). These results do not argue against vitamin E's anticancer potential broadly, but indicate that this specific lipid-based $\alpha$-tocopherol formulation did not generate an interpretable cytotoxic signal under the tested conditions.

All experiments described here were performed in the MCF-7 line, a commonly used and well-characterized luminal A model of hormone receptor-positive breast cancer. Like any single-cell-line system, it cannot capture the full molecular and phenotypic heterogeneity seen across breast cancer subtypes; so applying these results to other subtypes - triple-negative disease, for instance- will require confirmation in additional cell models. In addition, each dose group was compared against the untreated control using a separate Mann-Whitney U test without correction for multiple comparisons, which may inflate the type I error rate; the reported p-values should therefore be interpreted with appropriate caution. Absorbance was recorded at a single wavelength (570 nm) without a paired reference/background wavelength (typically 630-690 nm); background from curcumin's intrinsic pigmentation was instead addressed through the acellular compound-only wells described in Section 2.3, but the absence of a reference-wavelength subtraction step is acknowledged as an additional methodological limitation. Because agents differing markedly in physicochemical behavior (e.g., pigmentation versus lipophilicity) require optimized solubilization and co-culture conditions for reliable combination in an aqueous system, we first established single-agent concentration-response profiles as necessary groundwork. While this approach does not allow us to draw conclusions about synergistic or additive drug interactions, the individual-agent data we generated supply the reference profiles needed to design future combination experiments on a rational basis.

Building on this work, later studies could broaden the scope to additional breast cancer cell lines covering other molecular subtypes-triple-negative models such as MDA-MB-231 among them - so that luminal and triple-negative responses can be compared directly. Substituting the lipid-based vitamin E formulation used here with alternatives better suited to aqueous environments, such as D-$\alpha$-tocopheryl polyethylene glycol succinate (TPGS) or tocotrienol-based preparations, may allow for a more dependable assessment of vitamin E-based approaches (19,20). Once an appropriate formulation has been identified, two-drug (cisplatin-curcumin) and eventually three-drug combinations could be examined using the Chou–Talalay combination index approach (21), supplemented by assays targeting apoptosis and other modes of cell death.

## Conclusion

Taken together, this work characterizes the dose-dependent cytotoxicity of cisplatin and curcumin in MCF-7 breast cancer cells, establishing both as suitable candidates for future combination studies. Cisplatin's viability-reducing effect followed a clear dose-dependent pattern consistent with its known DNA cross-linking mechanism, and curcumin's antiproliferative activity proved reproducible once an appropriate background-correction step was applied to account for its natural pigmentation. The lipid-based vitamin E formulation examined here, by contrast, did not produce an interpretable cytotoxic signal, an outcome attributable primarily to its limited aqueous solubility rather than to any absence of biological activity; formulations such as TPGS or tocotrienol derivatives, better suited to aqueous systems, merit consideration in subsequent work. Although combination experiments fell outside the scope of the present study, the concentration-response data presented here provide a basis for subsequent investigations of cisplatin-curcumin-vitamin E combinations in MCF-7 and other breast cancer cell models.

## Acknowledgements

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## Ethical approval

This study did not require ethics committee approval, as it involved only in vitro experiments on an established human breast cancer cell line (MCF-7) and did not involve human participants, patient data, or animal subjects.

## Author contribution

The authors confirm contribution to the paper as follows: Study conception and design: GEC; data collection: GEC and ÇB; analysis and interpretation of results: GEC and ÇB; draft manuscript preparation: GEC. All authors reviewed the results and approved the final version of the article.

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## Conflict of interest

The authors declare that there is no conflict of interest.

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