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CYTOTOXICITY OF CURCUMIN, TAURINE AND ALPHA TOCOPHEROL ACETATE ON ZR-75-1 CELL LINE

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Abstract

Breast cancer continues to be one of the major contributors to cancer-related illness and death across the globe. Although current therapies are effective, they are often associated with significant side effects and invasive treatment protocols. This study explores the cytotoxic potential of three phytochemicals-Taurine, Alpha Tocopherol Acetate (α-TEA), and Curcumin-on ZR-75-1 human breast cancer cell lines, aiming to identify natural compounds that could serve as safer, adjunctive therapeutic options. Using the MTT assay, the effects of varying concentrations of each compound were assessed. Taurine and α-TEA exhibited cytotoxic effects at millimolar concentrations, while Curcumin demonstrated strong anticancer potential at low nanomolar concentrations. These findings support the role of phytochemicals in breast cancer treatment and underscore the need for further research into their mechanisms of action and therapeutic applicability

***Keywords*:** *ZR-75-1cellline, Taurine, Alpha-tocopherol acetate, curcumin, Cytotoxicity.*

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INTRODUCTION

Cancer is a pathological condition characterized by the dysregulated proliferation of abnormal cells with the ability to invade surrounding tissues and metastasize to distant organs. A primary driver of oncogenesis is the accumulation of genetic and epigenetic alterations in genes that regulate essential cellular processes, including proliferation, apoptosis, DNA repair, and differentiation. Given the global increase in cancer incidence and the growing challenge of resistance to conventional therapies, there is an intensified scientific focus on the development of multifaceted strategies for cancer prevention and early intervention [1].

Breast cancer management typically involves a combination of therapeutic modalities, including chemotherapy to target systemic disease, surgical removal of the tumor when operable, radiation therapy to eliminate residual cancer cells in the affected area, and hormone therapy for tumors that express hormone receptors. The selection and sequencing of these treatments depend on tumor-specific factors such as stage, molecular profile, and receptor status, as well as the patient's overall health, with the objective of maximizing therapeutic efficacy while minimizing recurrence [2].

Although conventional cancer therapies are often effective initially, they are associated with several limitations, including tumor recurrence, the development of drug resistance, and cytotoxic effects on healthy tissues. These challenges can significantly reduce treatment effectiveness and adversely impact patients' quality of life. In response, ongoing research is focused on identifying novel anticancer compounds with improved efficacy and reduced toxicity. Among these, plant-derived bioactive compounds-commonly referred to as phytochemicals-have gained considerable attention due to their potent biological activities and promising anticancer potential. The present study explores selected phytochemicals that exhibit anticancer effects through diverse and complementary molecular mechanisms, thereby contributing to the inhibition of cancer progression [3].

Among the phytochemicals investigated, **curcumin, taurine, and alpha-tocopherol acetate** were selected due to their extensive mechanistic involvement in regulating key oncogenic pathways in breast cancer.

Phytochemicals

Curcumin

Curcumin, a polyphenolic compound derived from the rhizome of *Curcuma longa*, exhibits strong anticancer properties by modulating multiple oncogenic signaling pathways in breast cancer cells. It has been shown to downregulate key oncogenic and proliferative markers, including vascular endothelial growth factor (VEGF), nuclear factor-kappa B (NF-κB), mitogen-activated protein kinase (MAPK), Akt, human epidermal growth factor receptor 2 (HER2), and recepteur d'Origine Nantais (RON). Curcumin also reduces the phosphorylation of Src and STAT3 through the downregulation of PRL-3 expression.

Furthermore, curcumin suppresses the expression of enhancer of zeste homolog 2 (EZH2), AIP-1/Alix, Bcl-2, proliferating cell nuclear antigen (PCNA), Ki-67, and several genes involved in the Wnt/β-catenin signaling pathway. By simultaneously targeting these molecular pathways, curcumin inhibits tumor cell proliferation, angiogenesis, and survival, supporting its potential role as a complementary therapeutic agent in breast cancer treatment (4).

Taurine

Taurine is a β-amino sulfonic acid synthesized primarily in the liver and abundantly distributed in various tissues. It plays a vital role in maintaining the function of the central nervous system, retina, heart, and skeletal muscle. Taurine contributes to cellular osmoregulation, membrane stabilization, calcium homeostasis, and antioxidant defense mechanisms [5].

Taurine exerts cytotoxic effects by increasing the expression of c-Jun N-terminal kinases (JNK1/2), leading to apoptosis in human breast cancer cells (6). It also enhances the expression of tissue inhibitors of metalloproteinases (TIMPs) while inhibiting VEGF and matrix metalloproteinases (MMPs), thereby preventing the migration of MCF-7 and MDA-MB-231 breast cancer cells (7). Additionally, taurine regulates the expression of genes, proteins, and enzyme systems associated with breast cancer progression, including p53, caspases, PCNA, membrane-bound enzymes, and drug-metabolizing enzymes (8,9). Animal studies have demonstrated that taurine suppresses breast cancer development induced by dimethylbenz[a]anthracene (DMBA) in rats (8). Collectively, these findings suggest that taurine effectively inhibits breast cancer progression [5].

Alpha-Tocopherol Acetate

Alpha-tocopherol acetate (α-TEA) is a stable synthetic analog of RRR-α-tocopherol, characterized by the presence of an acetic acid moiety attached via an ether bond to the C-6 phenolic group on the chroman ring. α-TEA has been shown to induce apoptosis in both estrogen-sensitive and estrogen-insensitive human breast cancer cells. Studies using MDA-MB-435 and MCF-7 cell lines have demonstrated that α-TEA induces apoptosis in a time- and concentration-dependent manner.

At the molecular level, α-TEA activates key signaling pathways involved in programmed cell death, including transforming growth factor-beta (TGF-β), Fas (CD95), and JNK pathways. These signaling cascades play a critical role in mediating α-TEA–induced apoptosis. Moreover, α-TEA causes sustained activation of MAP kinase JNK and prolonged phosphorylation of c-Jun, a downstream transcription factor, further supporting its pro-apoptotic effects. These findings suggest that α-TEA possesses strong potential to suppress breast cancer progression [10–15].

MATERIALS AND METHODS

1. Cell Line

The human breast cancer cell line **ZR-75-1** was used in this study. This cell line was originally derived from the malignant ascitic fluid of a 63-year-old female patient diagnosed with infiltrating ductal carcinoma of the breast. ZR-75-1 cells are classified as the luminal A subtype, characterized by the expression of estrogen receptor (ER^+) and progesterone receptor (PR^+), with minimal or absent HER2/neu expression. The cells exhibit epithelial morphology and grow as adherent monolayers under standard in vitro conditions.

ZR-75-1 cells were procured from the National Centre for Cell Science (NCCS), Pune, India. The cells were cultured in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 1% penicillin–streptomycin. Cultures were maintained in T25 vented flasks at 37 °C in a humidified incubator with 5% CO_2. All experiments were performed in triplicate using cells in the exponential growth phase, with routine subculturing conducted to ensure optimal cell viability and morphology.

2. Chemicals

RPMI-1640 culture medium, fetal bovine serum (10%), trypsin–EDTA solution, and antibiotic–antimycotic solution (1%) containing penicillin, streptomycin, and amphotericin B were procured from HiMedia Laboratories Pvt. Ltd., India. All reagents were aliquoted and stored at −20 °C until use.

The phytochemicals **curcumin, taurine, and alpha-tocopherol acetate (vitamin E acetate)** were obtained from HiMedia Laboratories Pvt. Ltd., India, to ensure consistency in purity and solubility for in vitro applications. Curcumin was used at concentrations ranging from **300 nM to 800 nM**, while taurine and alpha-tocopherol acetate were administered at concentrations ranging from **100 mM to 1000 mM** during experimental treatments.

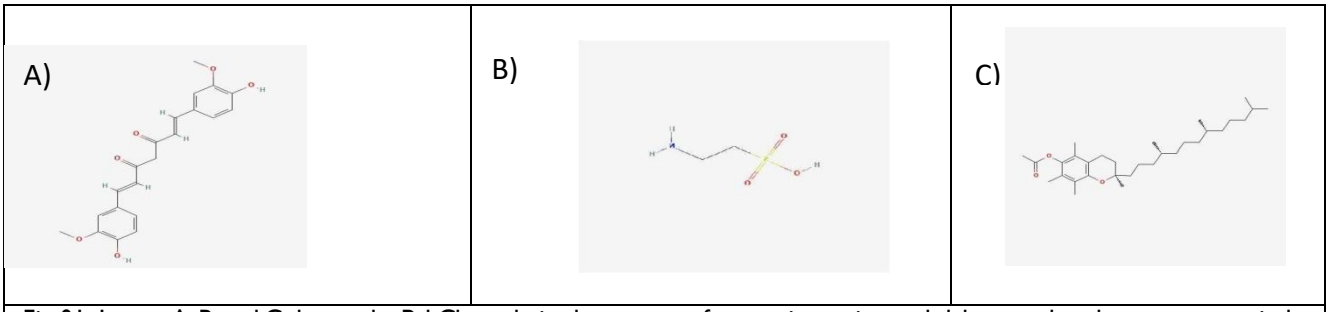

Fig 01- Images A, B, and C denote the PubChem-derived structures of curcumin, taurine, and alpha-tocopherol acetate, respectively. (Source-PubchemWebsite)

3. CytotoxicityAssay (MTT assay)

This assay was performed to evaluate the cytotoxic effects of the selected phytochemicals on the ZR-75-1 human breast cancer cell line. The method is based on the reduction of the yellow tetrazolium dye MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] to insoluble purple formazan crystals by mitochondrial succinate dehydrogenase in metabolically active (viable) cells. For the assay, 100 µL of MTT-containing medium was added to each well. The plates were covered with aluminum foil to protect from light and incubated at 37 °C for 4 hours to allow formazan formation. After incubation, the medium containing residual MTT was carefully removed, and 100 µL of dimethyl sulfoxide (DMSO) was added to each well to dissolve the formazan crystals. Absorbance was measured immediately at 570 nm using a microplate reader. All experiments were conducted in triplicate. This assay enabled the determination of the effective concentrations of individual phytochemicals required to induce cytotoxic effects in ZR-75-1 cells [17].

DATA ANALYSIS

The data from the MTT assay was statistically analyzed usingAnalyse-it (version 6.16.2), a powerful Excel add-in commonly used for statistical analysis in clinical and biomedical research. One-way ANOVA was performed and statistical significance was defined as a P-value < 0.05.

RESULTS AND DISCUSSION

1. Effect of Curcuminon ZR-75-1

Curcumin exhibited cytotoxic effects across the tested concentration range (300-800 nM). A concentration-dependent increase in cytotoxicity was observed in curcumin-treated groups. The highest cytotoxic effect was recorded at 400 nM (90.11%), followed closely by 800 nM (89.05%); both concentrations showed statistically significant differences compared with lower concentrations (denoted by superscript "c"). In contrast, treatments with 300 nM, 350 nM, and concentrations ranging from 450 nM to 750 nM produced comparable levels of cytotoxicity, ranging from 83.99% to 86.93%, with no statistically significant differences among these groups (denoted by superscript "b"), as presented in Table 01. These findings indicate that 400 nM represents the optimal concentration for inducing maximal cell death with minimal variability, highlighting both the potency and consistency of curcumin's cytotoxic effect. Overall, the differences observed among the tested concentrations were statistically significant ($p < 0.05$), underscoring the strong anticancer potential of curcumin even at low nanomolar concentrations.

Table 01: Percentage of cell inhibition (mean ± standard error) for the corresponding curcumin treatments. Different superscript letters indicate statistically significant differences between groups ($p < 0.05$).

Treatment	% Inhibition±SE	CLD
Control	0.00	a
Control-300nM	83.99±0.17	b
Control-350nM	86.48±1.21	b
Control-400nM	90.11± 0.73	c
Control-450nM	85.80±0.51	b
Control-500nM	86.93±0.92	b
Control-550nM	85.05±0.28	b
Control-600nM	85.42±1.11	b
Control-650nM	85.57±0.51	b
Control-700nM	86.03±0.24	b
Control-750nM	85.12±0.67	b
Control-800nM	89.05±0.99	c

2. Effect of Taurineon ZR-75-1

In Table 02, all taurine treatments ranging from 100 mM to 1000 mM were statistically similar to one another (denoted by superscript "b"), indicating no significant differences among these treatment levels. The percentage of cell inhibition increased steadily from 29.71% at 100 mM to a maximum of 77.77% at 700 mM, followed by a plateau between 700 mM and 1000 mM, suggesting saturation of the treatment effect at higher concentrations. A slight decline was observed at 800 mM (72.75%), with values remaining relatively stable up to 1000 mM (75.2%).

These results indicate that 700 mM is the most effective concentration among those tested, achieving maximal cell inhibition. However, it does not exhibit a statistically significant advantage over adjacent concentrations such as 500 mM or 600 mM, suggesting that the maximal response is reached at 700 mM, and further increases in concentration do not produce significantly enhanced effects. Overall, the differences among concentrations were statistically significant ($p < 0.05$).

Table 02: Percentage of cell inhibition (mean ± standard error) for the corresponding taurine treatments. Different superscript letters indicate statistically significant differences between groups ($p < 0.05$).

Treatment	% Inhibition±SE	CLD
Control	0 ± 0.003	**a**
Control-100mM	29.71± 0.012	**b**
Control-200mM	44.77± 0.004	**b**
Control-300mM	64.04± 0.002	**b**
Control-400mM	74.28± 0.000	**b**
Control-500mM	76.23± 0.003	**b**
Control-600mM	76.13± 0.001	**b**
Control-700mM	77.77± 0.007	**b**
Control-800mM	72.75± 0.002	**b**
Control-900mM	73.57± 0.002	**b**
Control-1000mM	75.2±0.001	**b**

3. Effect of Alpha-Tocopherol Acetate on ZR-75-1

In Table 3, the 100 mM treatment exhibited a response (0.09, superscript "a") similar to the control, indicating no significant difference between these groups. From 200 mM onwards, α-Tocopherol Acetate treatments demonstrated significantly increased responses, with 200 mM showing 0.32 (superscript "b"), while treatments from 300 mM to 1000 mM were statistically grouped together (superscript "c"), with values ranging from 0.60 to 0.68. This pattern suggests a plateau in the measured response at concentrations ≥300 mM.

Table 3 also presents the corresponding percentages of cell inhibition. The control group exhibited negligible inhibition, while the 100 mM treatment displayed a slight negative inhibition value, suggesting a potential stimulatory effect at this lower concentration. Cell inhibition increased markedly from 200 mM (30.74%) and peaked between 500 mM and 700 mM, reaching a maximum of 65.67% at 500 mM, with comparable values observed at 600 mM and 700 mM. Beyond 700 mM, inhibition slightly declined but remained relatively high, ranging from 57.32% to 63.70%.

Collectively, these results indicate that α-Tocopherol Acetate exerts a concentration-dependent inhibitory effect on ZR-75-1 cells, with maximal responses observed between 300 mM and 700 mM. Among the concentrations tested, 500 mM represents the most effective dose, achieving the highest cytotoxicity. The overall differences among concentrations were statistically significant ($p < 0.05$).

Table 03: Percentage of cell inhibition (mean ± standard error) for the corresponding α-Tocopherol Acetate treatments. Different superscript letters indicate statistically significant differences between groups ($p < 0.05$).

Treatment	% Inhibition±SE	CLD
Control	0.00±0.02	a
Control-100mM	-8.86± 0.04	a
Control-200mM	30.74± 0.02	b
Control-300mM	61.73± 0.01	c
Control-400mM	63.70± 0.01	c
Control-500mM	65.67± 0.01	c
Control-600mM	63.93± 0.00	c
Control-700mM	64.05± 0.02	c
Control-800mM	61.42± 0.00	c
Control-900mM	57.32± 0.00	c
Control-1000mM	62.88± 0.01	c

CONCLUSION

Current therapies for breast cancer, though effective, are often associated with considerable side effects and invasive treatment regimens. This study supports the development of alternative, less toxic therapeutic strategies using natural compounds. The aim of the present work was to assess the cytotoxic potential of the phytochemicals Taurine, α-Tocopherol Acetate (α-TEA), and Curcumin on ZR-75-1 breast cancer cell lines and to evaluate their effectiveness across different concentration ranges.

The MTT assay revealed that at millimolar concentrations, Taurine and α-TEA significantly reduced cell viability, demonstrating strong cytotoxic activity. Interestingly, nanomolar concentrations of Curcumin showed a dose-dependent increase in cytotoxic response, indicating potential therapeutic benefits even at lower doses. These results suggest a biphasic response: high concentrations induce cytotoxicity, while lower concentrations may support cellular modulation. This dual behavior underscores the importance of dose optimization to maximize therapeutic benefits while minimizing toxicity.

Based on these findings, Curcumin, in particular, stands out as a promising candidate for supplementary therapy in breast cancer management. With further validation and mechanistic studies, these phytochemicals-alone or in combination-could be incorporated into non-invasive or adjunctive treatment strategies for breast cancer.

ABBREVIATIONS

CLD: Compact Letter Display

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

INFORMED CONSENT

Not Applicable

ETHICAL STATEMENT

Our institution does not require ethics approval for reporting individual cases or case series.

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