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The effect of Tamoxifen on the expression of antioxidant genes Superoxide Dismutase 2 and Glutathione Peroxidase 1 in the presence and absence of antioxidants

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Abstract

Background: Tamoxifen (TAM) is a first-line therapy for estrogen receptor-positive breast cancer, exerting part of its anticancer effect through the induction of oxidative stress. Despite its widespread clinical use, the precise impact of TAM on the cellular antioxidant defense system remains incompletely understood.

Objectives: This study aimed to investigate the effect of TAM on the expression of key antioxidant genes, Superoxide Dismutase 2 (SOD2) and Glutathione Peroxidase 1 (GPx1), and to assess whether the antioxidants Vitamins C and E can modulate this response.

Methods: Human MCF-7 breast cancer cells were treated with 2 µM TAM, either alone or in combination with Vitamin C (Vit C, 50 µM) and/or Vitamin E (Vit E, 16 µM), for 6 and 24 hours. Total Antioxidant Capacity (TAC) was measured using the FRAP assay. The mRNA expression of SOD2 and GPx1 was quantified by real-time polymerase chain reaction (qRT-PCR).

Results: Exposure to TAM for 24 hours significantly reduced TAC while simultaneously upregulating SOD2 and GPx1 mRNA expression. Co-treatment with Vit E effectively attenuated the TAM-induced suppression of SOD2 and restored TAC to near baseline levels. Vit C demonstrated a similar, though less pronounced, effect. Interestingly, the combined administration of both vitamins did not produce a synergistic benefit and was not superior to Vit E alone in mitigating TAM-induced oxidative stress.

Conclusion: TAM induces notable oxidative stress in MCF-7 cells within 6 hours, yet upregulation of antioxidant enzymes contributes to a partial recovery in TAC after 24 hours. Vit E, and to a lesser extent Vit C, can counteract TAM-induced oxidative stress, while the absence of synergy between the two antioxidants suggests that a single, well-chosen antioxidant may suffice to mitigate these effects. These findings have potential implications for optimizing adjuvant antioxidant therapy in patients undergoing TAM treatment.

Keywords: Tamoxifen, Superoxide Dismutase 2 (SOD2), Glutathione Peroxidase 1 (GPx1), Vitamin E, Vitamin C, Breast cancer.

Introduction

Breast cancer (BC) is among the most prevalent malignancies and remains the leading cause of cancer-related mortality among women worldwide.[1] It is characterized by the uncontrolled proliferation of breast epithelial cells and is associated with clinical manifestations such as palpable breast lumps, nipple abnormalities, breast pain, and, in some cases, unintended weight loss.[2,3] In Iran, the age-standardized incidence of BC is reported at 34.5 per 100,000 women, with a corresponding mortality rate of 10.8 per 100,000.[4]

Molecular classification categorizes BC into five intrinsic subtypes; Luminal A, Luminal B, HER2-enriched, Basal-like (triple-negative), and normal-like; based on gene expression profiles and receptor status. Estrogen receptor (ER)-positive subtypes generally respond well to hormonal therapies, whereas triple-negative breast cancer (TNBC), which lacks ER, progesterone receptor (PR), and HER2 expression, is more aggressive and exhibits resistance to conventional treatments.[5]

The primary therapeutic strategies for BC include chemotherapy, radiotherapy, surgery, targeted therapy,

and hormone therapy, often employed in combination depending on tumor subtype and disease stage.[6] While chemotherapy can substantially reduce mortality, its use is frequently limited by severe adverse effects such as myalgia, headache, gastrointestinal disturbances, and cytotoxicity.[7] Consequently, safer and more targeted therapeutic approaches are under active investigation.

Among hormonal therapies, Tamoxifen (TAM) has emerged as one of the most effective and widely used agents for ER-positive BC. TAM is a selective estrogen receptor modulator that competitively binds to ERs, exerting either agonistic or antagonistic effects depending on the tissue context.[8] Originally synthesized in 1962 as ICI 46,474 by Dora Richardson and later developed by Arthur Walpole's team as an anti-estrogenic agent, TAM has been extensively evaluated in clinical trials since the 1980s, establishing its efficacy as adjuvant therapy in both early and advanced ER-positive BC.[9]

At the molecular level, TAM inhibits tumor proliferation through both ER-dependent and ER-independent mechanisms. It suppresses the activity of protein kinase C (PKC) and phospholipase C/D (PLC/D) while modulating key signaling molecules, including p53, p21, cyclin D, and c-Myc.[10] Additionally, TAM induces apoptosis by activating caspases (6, 7, and 9), altering mitochondrial membrane permeability, and promoting the generation of reactive oxygen species (ROS).[11]

Objectives

Our previous study demonstrated that TAM markedly increases oxidative stress parameters in breast cancer cells.[12] Building on this observation, the present study aimed to explore the mechanisms underlying TAM-induced oxidative stress in MCF-7 cells. We hypothesized that TAM-mediated oxidative stress leads to the upregulation of key antioxidant enzymes, including Superoxide Dismutase 2 (SOD2) and Glutathione Peroxidase 1 (GPx1). Moreover, we evaluated the modulatory effects of two major antioxidants, Vitamins C and E, on oxidative stress and antioxidant enzyme expression, providing further insight into TAM's cellular mechanisms of action.

Methods

Cell culture

Human breast cancer MCF-7 cells were maintained in RPMI-1640 medium supplemented with 10% fetal bovine serum (FBS) and 100 U/mL penicillin–streptomycin. Cultures were incubated at 37 °C in a humidified atmosphere containing 5% CO_2. To synchronize metabolic activity and minimize basal signaling, cells were gradually adapted to reduced serum conditions and serum-starved for 12 hours in medium containing 0.3% FBS prior to treatment.

Drug and Antioxidant Treatments

Based on prior dose–response and time-course studies, TAM was applied at a final concentration of 2 µM, which preserves approximately 75% cell viability while effectively inducing ROS generation. Vitamin C (Vit C) and Vitamin E (Vit E) were administered at 50 µM and 16 µM, respectively. Vit C was added simultaneously with TAM and allowed to react for approximately 10 minutes to account for its rapid oxidative kinetics. Hydrogen peroxide (H_2O_2, 1%) served as a positive control for oxidative stress.

Cells were seeded into eleven culture flasks and treated for 6 and 24 hours according to the following groups: Vit C alone, Vit E alone, TAM alone, Vit C + Vit E, TAM + Vit C + Vit E, TAM + Vit C, TAM + Vit E, untreated control, and H_2O_2-treated positive control. At the end of each treatment period, cells were harvested. All experiments were independently repeated at least three times. A schematic representation of the treatment groups is provided in Figure-1.

Figure-1. Schematic representation of MCF-7 cell treatments at 6 and 24 hours across different drug and vitamin combinations.

Cell lysis, RNA extraction, and Quantitative Real-Time PCR (qRT-PCR)

After treatment, cells were lysed using the buffer provided in the RNA extraction kit. Total RNA was isolated from all nine treatment groups as well as negative and positive controls, following the manufacturer's protocol. RNA purity and concentration were determined using a NanoDrop spectrophotometer, and integrity was assessed via agarose gel electrophoresis. Only high-quality RNA samples, exhibiting sharp 28S and 18S rRNA bands and an A_{260}/A_{280} ratio between 1.8 and 2.0, were used for downstream applications.

Complementary DNA (cDNA) was synthesized from 1 µg of total RNA using a reverse transcription kit, following the supplier's instructions. Gene-specific primers for SOD2 and GPx1 were purchased from Origene. Gene expression analysis was performed using SYBR® Green-based qRT-PCR, with all reactions conducted in triplicate, including no-template controls. Relative mRNA expression levels were calculated using the $2^{\wedge-\Delta\Delta Ct}$ method, with normalization to the housekeeping gene β-actin [Table-1].

Table-1. Primer sequences for antioxidant enzyme gene expression

Genes	Forward Primer	Reverse Primer
SOD2	GGCCTACGTGAACAA CCTGAA	CTGTAACATCTC CCTTGGCCA
GPx1	GTGCTCGGCTTCCCG TGCAAC	CTCGAAGAGCA TGAAGTTGGGC
β-actin	AGAGCTACGAGCTGC CTGAC	AGCACTGTGTTG GCGTACAG

Total Antioxidant Capacity assay

The total antioxidant capacity (TAC) of cell supernatants was measured using the Ferric Reducing Antioxidant Power (FRAP) assay, as described by Benzie et al (1996). The assay is based on the reduction of ferric ions (Fe^{3+}) to ferrous ions (Fe^{2+}) under acidic conditions. The ferrous ions form a colored complex with 2,4,6-Tris(2-pyridyl)-s-triazine (TPTZ; Sigma-Aldrich, USA), which exhibits maximum absorbance at 593 nm.

FRAP solution was prepared by dissolving 10 mM TPTZ in 40 mM HCl and mixing with 300 mM acetate buffer (Merck, Germany). One milliliter of FRAP solution was combined with 50 µL of cell supernatant and incubated at 37 °C for 30 minutes. Following incubation, absorbance at 593 nm was measured, and TAC values were calculated accordingly.

Statistical analysis

All experiments were conducted in triplicate using independently treated samples. Statistical analyses were performed using Prism software (version 7). Data normality was confirmed via Q-Q plots. Differences between groups were assessed using Student's t-test or one-way ANOVA, followed by appropriate post-hoc tests. A p-value < 0.05 was considered statistically significant.

Results

Effect of tamoxifen and vitamins on total antioxidant capacity

TAC in MCF-7 cells was measured following treatment with TAM, Vitamin C (Vit C), Vitamin E (Vit E), and their combinations at 6 and 24 hours [Figure-2]. Statistical comparisons were conducted using one-way ANOVA followed by post-hoc analyses. Treatment with TAM for 6 hours did not significantly alter TAC relative to the control group (mean difference=3.116 µM, p=0.157). In contrast, 24-hour TAM exposure significantly reduced TAC compared with control (mean difference=–6.860 µM, p<0.001). Vit C treatment for 24 hours caused a marked decrease in TAC (mean difference=–20.938 µM, p<0.001), while Vit E treatment also significantly reduced TAC (mean difference=–12.346 µM, p<0.001).

Combinatorial treatments revealed differential effects. TAM + Vit C at 6 hours significantly reduced TAC (mean difference=–15.998 µM, p<0.001), whereas TAM+Vit E at 6 hours showed no significant change (mean difference=–2.648 µM, p=0.354). The positive control, H_2O_2, significantly decreased TAC compared with untreated cells (mean difference=5.946 µM, p < 0.001). At 24 hours, TAM+Vit C treatment continued to significantly reduce TAC (mean difference=–5.998 µM, p<0.001), while TAM + Vit E did not differ from control (mean difference=–1.932 µM, p=0.776). The triple combination of TAM+Vit C+Vit E at 24 hours significantly affected TAC (mean difference=–7.676 µM, p<0.001) but was not superior to the effect of TAM+Vit E alone.

Antioxidant vitamins modulate tamoxifen-induced oxidative stress and gene expression in MCF-7 cells

To examine the interplay between TAM-induced oxidative stress and the cellular antioxidant defense system, we evaluated mRNA expression of the antioxidant enzymes SOD2 and GPx1, alongside TAC, following 24-hour treatments. Our results demonstrate that TAM induces oxidative stress, evidenced by its significant impact on antioxidant enzyme expression. This response was both biphasic and concentration-dependent. Specifically, treatment with 2 µM TAM for 24 hours (TAM24) resulted in significant downregulation of SOD2 and GPx1 mRNA levels (p<0.001), while the positive oxidative-stress control, H_2O_2, induced a robust suppression of both enzymes (p<0.001) [Figure-3].

Co-treatment with antioxidant vitamins attenuated the TAM-induced changes. Vit E exhibited a particularly strong protective effect. In the TAM + Vit E group, SOD2 suppression was significantly less pronounced than with TAM alone (p<0.001), and TAC was restored to near-control levels (p<0.01). In contrast, the simultaneous administration of both Vit C and Vit E (TAM+Vit C+Vit E) did not produce a synergistic or additive effect. For SOD2, the triple combination restored expression to a

level comparable to control but did not surpass the protective effect of Vit E alone. For GPx1, suppression remained statistically significant despite co-treatment. Similarly, TAC restoration in the TAM + Vit C + Vit E group was not significantly greater than that achieved with TAM + Vit E alone [Figure-4].

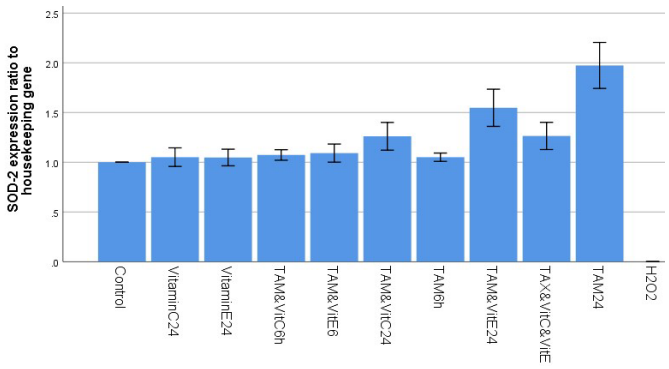

Figure-2. Total antioxidant capacity (TAC) in supernatants of MCF-7 cells treated with TAM, Vit C, Vit E, and combinations. Numbers indicate treatment duration in hours; H_2O_2 served as a positive control inducing complete cell death.

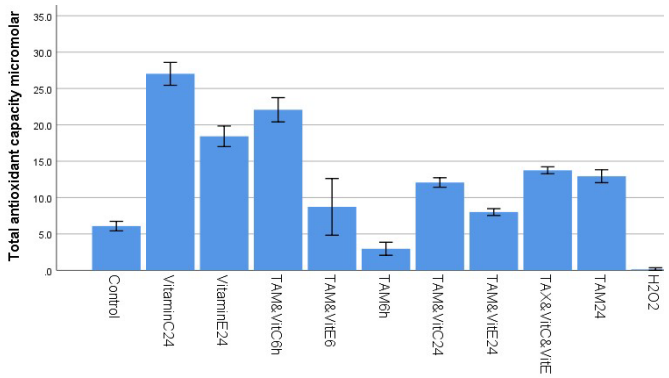

Figure-3. GPx1 mRNA expression in MCF-7 cells following treatment with TAM, Vit C, Vit E, and their combinations at 6 and 24 hours. H_2O_2 served as a positive control.

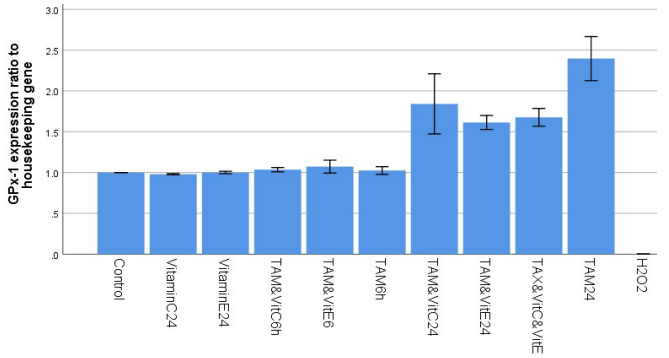

Figure-4. SOD2 mRNA expression in MCF-7 cells following treatment with TAM, Vit C, Vit E, and their combinations at 6 and 24 hours. H_2O_2 served as a positive control.

Discussion

Breast cancer remains one of the most prevalent malignancies in Iran and worldwide, with TAM widely used as an estradiol antagonist in ER-positive patients.[13] The oxidative effects of TAM have been documented in our previous study and other reports.[12] In parallel, the roles of antioxidant enzymes such as SOD2 and Glutathione Peroxidase 1 (GPx1) are complex and context-dependent. Overexpression of SOD2 has been associated with both tumor suppression and tumor promotion, depending on the cellular and cancer type context.[14,15] GPx1, a cytosolic selenoenzyme encoded on chromosome 3q49.36, catalyzes the reduction of hydrogen peroxide and lipid hydroperoxides to water and corresponding alcohols using reduced glutathione as an electron donor. It plays a protective role against oxidative stress-induced damage and modulates key immunological and stress-related pathways, including those involving tumor necrosis factor-alpha (TNF-α) and mitogen-activated protein kinases.[16] Increased GPx1 expression in breast cancer cells has been linked to apoptosis resistance and enhanced tumor cell survival.[17]

In our study, treatment with TAM led to a significant reduction in TAC at 6 hours, followed by an increase at 24 hours. This biphasic response confirms the oxidative stress-inducing properties of TAM. The initial decline in TAC likely reflects enhanced ROS production, whereas the subsequent increase after 24 hours may result from upregulation of cellular antioxidant components, including SOD2 and GPx1, as a compensatory mechanism.

TAM is also associated with organ toxicity, which may be mitigated by antioxidants. For instance, Meng et al. reported TAM-induced cardiac damage mediated via the IL-6/p-STAT3/PGC-1α pathway.[18] Given the interplay between inflammation and oxidative stress, antioxidants may reduce such toxic effects.[19] However, co-administration of antioxidants could, in theory, attenuate the efficacy of TAM if part of its anticancer activity is ROS-mediated. The dual role of ROS in tumor progression and drug response underscores the importance of understanding the interaction between TAM-induced oxidative stress and cellular antioxidant defenses, such as SOD2 and GPx1.

Both SOD2 and GPx1 were upregulated following 24-hour TAM treatment, indicating that these enzymes respond to oxidative stress via cis- and trans-regulatory elements. This compensatory induction reflects the cells'

attempt to counteract TAM-induced ROS. Notably, six hours of treatment was insufficient to induce measurable gene upregulation, consistent with the known time course of eukaryotic gene transcription.[20]

Co-treatment with Vit C and Vit E attenuated TAM-induced enzyme expression, indicating that these antioxidants mitigated the oxidative signal responsible for gene induction. Interestingly, the combined administration of both vitamins did not yield a synergistic enhancement in enzyme expression but did produce a complementary increase in TAC. This suggests that the antioxidant mechanisms of Vit C and Vit E may operate through overlapping pathways, neutralizing ROS and thereby reducing the stimulus for antioxidant enzyme production.

Vit E exhibited superior protective efficacy, likely due to its lipophilic properties, which facilitate interactions with the lipophilic domains of cellular membranes and TAM itself, enabling direct neutralization of ROS at the site of generation. Vit C also demonstrated a protective trend but was generally less effective than Vit E in this model. These findings indicate that, in the context of TAM-induced oxidative stress, a single appropriately selected antioxidant -particularly Vit E- may be sufficient to counteract oxidative insult.

We acknowledge certain limitations in the present study. Measuring the enzymatic activities of SOD2 and GPx1 would strengthen our conclusions, and future studies should include these assessments. Additionally, we did not perform cell viability assays for all groups; in the H_2O_2-treated positive control, complete cell death was observed. These limitations highlight areas for further investigation.

Conclusions

In MCF-7 cells, TAM induces significant oxidative stress within 6 hours. A compensatory upregulation of antioxidant enzymes facilitates a partial recovery of total antioxidant capacity by 24 hours. While both Vitamins E and C effectively counteract TAM-induced oxidative stress (with Vit E showing greater efficacy), their lack of synergistic effect suggests that a single, potent antioxidant may be sufficient to mitigate these adverse effects. This insight could inform strategies for adjuvant antioxidant therapy in patients receiving TAM treatment.

Practical points in Biochemistry/Nutrition:

► Vitamin E co-administration may mitigate tamoxifen-induced oxidative stress in breast cancer therapy more effectively than Vitamin C, potentially improving treatment tolerability without diminishing therapeutic efficacy by restoring cellular antioxidant capacity.

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Competing interests

The authors declare that they have no competing interests.

Abbreviations

BC: Breast Cancer; triple-negative breast cancer: TNBC; cDNA: Complementary DNA; ER: Estrogen Receptor; FBS: Fetal Bovine Serum; FRAP: Ferric Reducing Antioxidant Power; GPx1: Glutathione Peroxidase 1; H_2O_2: Hydrogen Peroxide; mRNA: Messenger RNA; PR: Progesterone Receptor; qRT-PCR: Quantitative Real-Time Polymerase Chain Reaction; ROS: Reactive Oxygen Species; SOD2: Superoxide Dismutase 2; TAC: Total Antioxidant Capacity; TAM: Tamoxifen; TNBC: Triple-Negative Breast Cancer; TPTZ: 2,4,6-Tris(2-pyridyl)-s-triazine; Vit C: Vitamin C; Vit E: Vitamin E.

Authors' contributions

All authors read and approved the final manuscript. All authors take responsibility for the integrity of the data and the accuracy of the data analysis.

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Role of the funding source

None.

Availability of data and materials

The data used in this study are available from the corresponding author on request.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. Institutional Review Board approval (code: IR.KaUMS.REC.1396.119) was obtained (April 2023). The present study did not interfere with the process of diagnosis and treatment of patients and all participants signed an informed consent form.

Consent for publication

By submitting this document, the authors declare their consent for the final accepted version of the manuscript to be considered for publication.

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