



Quercetin enhances radiosensitivity in T47D breast cancer cells: impact on DNA damage, clonogenic survival, and antioxidant defenses

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Abstract

Introduction: Radiotherapy resistance remains a significant challenge in breast cancer treatment. Quercetin, a natural flavonoid, has emerged as a potential radiosensitizer. This study examined its effects on hormone receptor-positive T47D breast cancer cells.

Materials and methods: T47D cells were treated with quercetin (20, 40, 60 μ M) alone or combined with ionizing radiation (2, 3 Gy). DNA damage (micronucleus assay), clonogenic survival, and antioxidant enzyme activities (SOD, catalase) were evaluated.

Results: Radiation alone significantly increased micronucleus formation (4.3-9.5 fold vs control, $p < 0.0001$) and reduced clonogenic survival (44-62% reduction vs control, $p < 0.0001$), while decreasing SOD (16-24.5%) and catalase (18-22%) activities ($p < 0.0001$). Quercetin pretreatment enhanced these effects in a dose-dependent manner. The combination of 60 μ M quercetin with 3 Gy radiation resulted in: a 10% greater micronucleus formation than radiation alone ($p < 0.01$), further reduction in clonogenic survival to 17% of control values (83% reduction vs radiation alone, $p < 0.001$), and up to 48% greater suppression of antioxidant enzyme activity compared to radiation-only groups ($p < 0.01$).

Conclusion: Quercetin demonstrates significant radiosensitizing effects in T47D cells through the enhancement of DNA damage and oxidative stress. The substantial reduction in clonogenic survival suggests potential clinical relevance, warranting further investigation in advanced models.

Keywords: Radiosensitizer, Breast cancer, Micronucleus, Oxidative stress, Radiotherapy

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Introduction

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer-related death among women globally, accounting for approximately 2.3 million new cases and 685,000 deaths in 2020 alone (1). Radiotherapy plays a central role in the treatment of breast cancer, especially for local and regional disease control. However, the efficacy of radiotherapy is often limited by the intrinsic or acquired radioresistance of tumor cells, which poses a major challenge in achieving optimal therapeutic outcomes (2, 3). Therefore, there is a growing interest in identifying and developing radiosensitizing agents that can selectively enhance the sensitivity of cancer cells to ionizing radiation while minimizing damage to normal tissues.

Natural compounds, particularly flavonoids, have attracted attention due to their potential to modulate oxidative stress, DNA damage responses, and cell survival signaling pathways (4). Quercetin, a dietary flavonoid abundantly found in fruits and vegetables, has demonstrated multiple biological activities, including antioxidant, anti-inflammatory, pro-apoptotic, and anti-proliferative effects (5, 6). Importantly, recent studies suggest that quercetin may also act as a radiosensitizer by enhancing radiation-induced cytotoxicity in various cancer cell lines, such as prostate, lung, and cervical cancers (7-11).

In comparison with quercetin, other naturally derived radiosensitizers have also been investigated. For example, curcumin has been shown to sensitize breast cancer cells to radiation via ROS-mediated apoptosis and inhibition of STAT3 signaling (12, 13). Resveratrol enhances radiosensitivity through downregulation of Bcl-2 and upregulation of p53 and Bax (14, 15). Genistein, an isoflavone from soy, sensitizes breast and prostate cancer cells by modulating DNA repair and cell cycle checkpoints (16).

Our research group previously investigated the radiosensitizing effects of quercetin in the MCF-7 human breast cancer cell line and demonstrated that quercetin significantly enhanced radiation-induced DNA damage and reduced clonogenic survival in a

dose-dependent manner (17). Encouraged by those findings, the current study aimed to evaluate whether similar radiosensitizing effects could be observed in another hormone receptor-positive breast cancer cell line, T47D. This cell line is characterized by estrogen and progesterone receptor positivity and serves as a well-established model for studying hormone-responsive breast cancer.

In this study, we investigated the combined effect of quercetin and ionizing radiation on T47D cells. Specifically, we assessed DNA damage using the micronucleus assay, evaluated long-term cell survival via clonogenic assay, and measured changes in antioxidant enzyme activities (superoxide dismutase and catalase). This work not only builds upon our previous findings in MCF-7 cells but also provides additional insight into the radiosensitizing potential of quercetin in hormone receptor-positive breast cancer subtypes.

Materials and methods

Chemicals and Reagents

Quercetin and Cytochalasin B were purchased from Sigma-Aldrich (St. Louis, USA). Superoxide dismutase (SOD) and catalase (CAT) activity assay kits (Nasdox™ and Nactaz™, respectively) were obtained from Navand Salamat Co. (Iran). Methanol, Giemsa stain, and glacial acetic acid were purchased from Merck (Germany). All other chemicals were of analytical grade.

Cell Line and Culture Conditions

The human breast cancer cell line T47D was obtained from the Iranian National Cell Bank (National Institute of Genetic and Biological Resources, Iran). The cell line was authenticated and characterized by the cell bank using standard morphological and molecular criteria. All experiments were conducted within six months of cell line revival to ensure genetic stability and authenticity. Cells were maintained in RPMI-1640 medium (Gibco, USA), supplemented with 10% fetal bovine serum (FBS; Gibco), 100 U/mL penicillin, and 100 µg/mL streptomycin, at 37°C in a humidified incubator with 5% CO₂. Cells were subcultured upon

reaching 80–90% confluence using 0.25% trypsin-EDTA (18).

Quercetin Treatment and Irradiation Protocol

Twenty-four hours after cell seeding, quercetin was added to the medium at final concentrations of 20, 40, or 60 μM . After 4 hours of incubation, cells were irradiated with 2 or 3 Gy of X-ray using a clinical linear accelerator (6 MV X-ray, Varian or equivalent system, USA) at a dose rate of 1.96 Gy/min and a source-to-sample distance (SSD) of 60 cm. Control groups received no radiation or drug treatment. After irradiation, cells were returned to the incubator under standard conditions (17).

Cytokinesis-Block Micronucleus (CBMN) Assay

Following irradiation, the quercetin-containing medium was replaced with fresh medium, and cells were incubated for 48 hours under standard conditions. Subsequently, cytochalasin B (6 $\mu\text{g/mL}$) was added to each well to block cytokinesis. After 28 hours of incubation with cytochalasin B, cells were harvested and fixed using a cold methanol–acetic acid solution (6:1), added dropwise. Fixed cells were used to prepare microscope slides, which were air-dried for 24 hours and stained with 10% Giemsa for 3 minutes. Slides were briefly rinsed with distilled water and left to dry at room temperature. Micronuclei were scored in 1000 binucleated cells per sample using light microscopy (19, 20).

Clonogenic Survival Assay

T47D cells were seeded at appropriate densities (500–2000 cells/well) in 6-well plates, depending on treatment condition. After overnight attachment, cells were treated with quercetin for 4 hours, followed by irradiation. Plates were incubated for 10–14 days to allow colony formation. Colonies were fixed with methanol-acetic acid (6:1), stained with 10% Giemsa, and counted manually. Colonies containing ≥ 50 cells were considered viable²¹. Plating efficiency (PE) and surviving fraction (SF) were calculated using the following formulas:

$$\text{PE} = (\text{Number of colonies} / \text{Number of cells plated}) \times 100\%$$

$$\text{SF} = (\text{Colonies counted}) / (\text{Cells plated} \times \text{PE of control group}).$$

Antioxidant Enzyme Activity Assays

To evaluate oxidative stress response, SOD and CAT activities were measured using commercial kits. Cells ($\geq 1 \times 10^6$) were lysed in kit-specific lysis buffers, homogenized on ice, and centrifuged at 12,000 rpm for 5 minutes (SOD) or 8,000 rpm for 10 minutes (CAT). The resulting supernatants were used for analysis. SOD activity was determined by measuring the inhibition of color formation at 405 nm, while CAT activity was assessed by measuring absorbance at 550 nm. All assays were performed in accordance with the manufacturer's protocols.

Statistical Analysis

All experiments were performed in triplicate. Data are presented as mean $\pm$ standard deviation (SD). Statistical significance was determined using one-way ANOVA followed by Tukey's post hoc test (GraphPad Prism 8.0). A p -value < 0.05 was considered statistically significant.

Results

Quercetin Potentiates Radiation-Induced DNA Damage in T47D Cells

The induction of micronuclei (MN) was evaluated to assess DNA damage across different treatment groups. As shown in Figure 1, in the control group, the mean MN frequency was 0.048 ± 0.017 . Treatment with quercetin alone at concentrations of 20, 40, and 60 μM resulted in slight, non-significant increases in MN formation (0.100 ± 0.013 , 0.115 ± 0.013 , and 0.118 ± 0.009 , respectively; $p > 0.05$ vs. control), indicating that quercetin alone did not induce significant genotoxicity.

Exposure to 2 Gy ionizing radiation significantly elevated MN frequency to 0.360 ± 0.035 ($p < 0.001$ vs. control). When combined with quercetin, a further increase in MN formation was observed in a dose-dependent manner. However, a statistically significant enhancement was noted only at the highest concentration of 60 μM (0.453 ± 0.034 , $p < 0.01$ vs.

2 Gy alone), while the 20 and 40 μM groups (0.376 ± 0.041 and 0.400 ± 0.041 , respectively) did not differ significantly from radiation alone ($p > 0.05$).

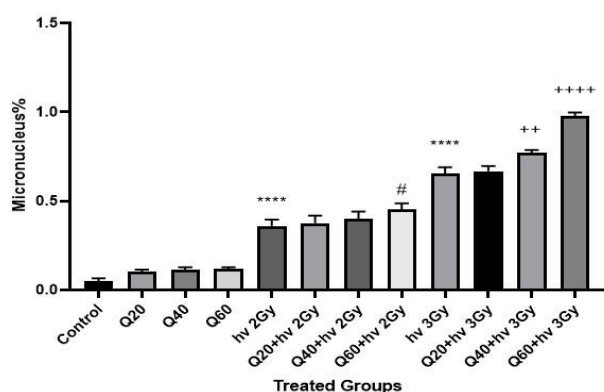


Figure 1. Frequency of micronuclei (%) in T47D breast cancer cells treated with different concentrations of quercetin (20, 40, and 60 μM), ionizing radiation (2 Gy and 3 Gy), and their combinations. Cells were harvested 28 hours after the addition of cytochalasin B. A significant increase in micronucleus frequency was observed in irradiated groups compared to control. Combined treatments further increased micronucleus formation compared to their respective irradiation-only groups. Data are presented as mean $\pm$ SD from three independent experiments. **** $p < 0.0001$ vs. control; # $p < 0.05$ vs. 2 Gy alone; ++ $p < 0.01$, ++++ $p < 0.0001$.

Similarly, 3 Gy radiation alone resulted in a marked increase in MN frequency (0.655 ± 0.035 , $p < 0.001$ vs. control). Co-treatment with quercetin further enhanced, with statistically significant elevations observed at 40 μM (0.769 ± 0.017) and 60 μM (0.975 ± 0.021) concentrations ($p < 0.001$ vs. 3 Gy alone). In contrast, the 20 μM dose (0.668 ± 0.029) did not produce a significant difference compared to radiation alone ($p > 0.05$).

These results suggest that quercetin potentiates radiation-induced DNA damage in T47D breast cancer cells, with significant radiosensitizing effects evident at higher concentrations, particularly when combined with 3 Gy irradiation.

Quercetin Enhances the Inhibitory Effect of Radiation on Colony Formation

Figure 2 illustrates the effects of different treatments on colony formation. Quercetin treatment alone resulted in

a moderate, dose-dependent reduction in colony formation compared to the control group ($91.97\% \pm 4.20$ for 20 μM , $73.26\% \pm 4.12$ for 40 μM , and $70.24\% \pm 1.78$ for 60 μM). However, these reductions were not statistically significant ($p > 0.05$). In contrast, exposure to ionizing radiation alone significantly suppressed clonogenic survival, with 2 Gy and 3 Gy treatments reducing survival to $55.64\% \pm 4.42$ and $37.03\% \pm 3.02$ of control values, respectively ($p < 0.0001$ for both).

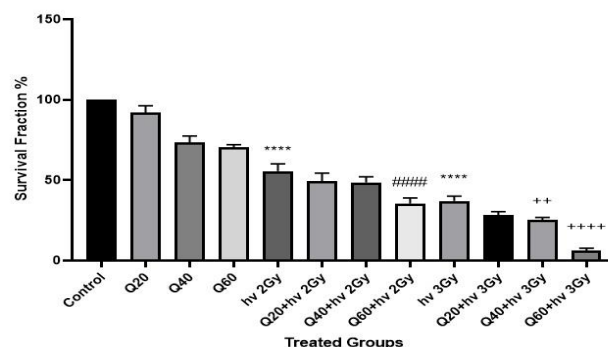


Figure 2. The effect of quercetin and ionizing radiation on clonogenic survival of T47D breast cancer cells. Cells were treated with different concentrations of quercetin (20, 40, and 60 μM) alone or in combination with 2 Gy and 3 Gy X-ray irradiation. A significant reduction in survival fraction was observed in irradiated groups compared to control, and a further reduction was observed in combined treatment groups compared to their respective irradiation-only groups. Data are presented as mean $\pm$ SEM from three independent experiments. **** $p < 0.0001$ vs. Control; ##### $p < 0.0001$ vs. 2 Gy alone; ++ $p < 0.01$, ++++ $p < 0.0001$ vs. 3 Gy alone.

Pre-treatment with quercetin enhanced the cytotoxic effects of radiation in a dose-dependent manner. In the 2 Gy radiation groups, survival decreased further to $49.40\% \pm 5.02$ (20 μM), $48.61\% \pm 3.48$ (40 μM), and $35.54\% \pm 3.40$ (60 μM), though a statistically significant difference compared to radiation alone was observed only at the highest concentration (60 μM , $p < 0.01$). The enhancement was more pronounced in the 3 Gy groups, where survival dropped to $28.10\% \pm 2.33$, $25.24\% \pm 1.58$, and $6.27\% \pm 1.39$ for 20, 40, and 60 μM quercetin, respectively. Importantly, both 40 μM and 60 μM quercetin significantly potentiated the effects of 3 Gy radiation compared to radiation alone ($p < 0.001$ and $p < 0.0001$, respectively).

Quercetin Potentiates Radiation-Induced Reduction in Catalase Activity

As shown in Figure 3, quercetin treatment alone resulted in a dose-dependent reduction in catalase activity, although the differences compared to the control group were not statistically significant (1.82 ± 0.06 for 20 μM , 1.66 ± 0.07 for 40 μM , and 1.64 ± 0.03 for 60 μM ; $p > 0.05$). Exposure to 2 Gy ionizing radiation alone significantly decreased catalase activity to 1.57 ± 0.02 , representing a 13.8% reduction compared to the control group ($p < 0.0001$). When quercetin was combined with 2 Gy radiation, a further reduction in catalase activity was observed, with values of 1.50 ± 0.01 (20 μM), 1.32 ± 0.01 (40 μM), and 1.29 ± 0.03 (60 μM). The decrease in catalase activity at 60 μM quercetin was statistically significant compared to the radiation-only group, with a 17.9% reduction ($p < 0.05$). In the 3 Gy radiation groups, the catalase activity was further reduced to 1.49 ± 0.02 for 20 μM , 1.41 ± 0.02 for 40 μM , and 1.22 ± 0.02 for 60 μM quercetin. The reductions at 40 μM and 60 μM quercetin were statistically significant, with a 12.7% reduction at 40 μM ($p < 0.01$) and a 22.4% reduction at 60 μM ($p < 0.0001$) compared to the radiation-only group.

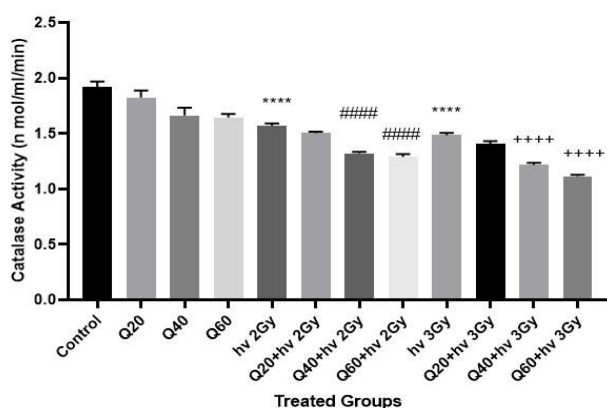


Figure 3. Effect of quercetin and ionizing radiation on catalase activity in T47D breast cancer cells. Cells were treated with different concentrations of quercetin (20, 40, and 60 μM) alone or in combination with 2 Gy and 3 Gy X-ray irradiation. A significant decrease in catalase activity was observed in irradiated and combined treatment groups. Co-treatment with quercetin and irradiation led to further reductions in catalase activity compared to their respective radiation-only groups. Data are presented as mean $\pm$ SEM

from three independent experiments. **** $p < 0.0001$ vs. Control; ##### $p < 0.0001$ vs. 2 Gy alone; ++++ $p < 0.0001$ vs. 3 Gy alone.

Superoxide Dismutase Activity is Further Suppressed by Combination Treatment

The SOD activity was evaluated across different treatment groups (Figure 4). In comparison to the control group (1.454 ± 0.0187), quercetin treatment alone did not induce a significant change in SOD activity, with values of 1.4287 ± 0.024 (20 μM), 1.3827 ± 0.0127 (40 μM), and 1.395 ± 0.0036 (60 μM), suggesting no dose-dependent effect ($p > 0.05$).

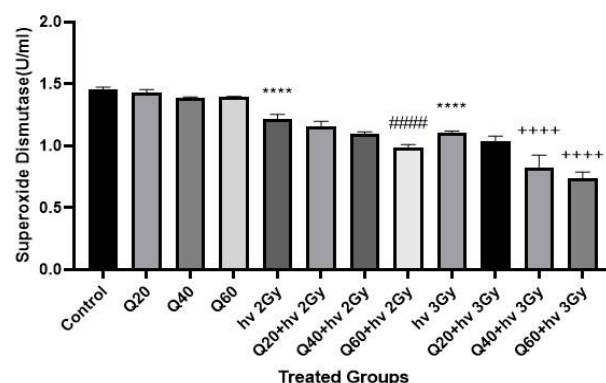


Figure 4. Effect of quercetin and ionizing radiation on Superoxide dismutase activity in T47D breast cancer cells. Cells were treated with different concentrations of quercetin (20, 40, and 60 μM) alone or in combination with 2 Gy and 3 Gy X-ray irradiation. A significant decrease in Superoxide dismutase activity was observed in irradiated and combined treatment groups. Co-treatment with quercetin and irradiation led to further reductions in catalase activity compared to their respective radiation-only groups. Data are presented as mean $\pm$ SEM from three independent experiments. **** $p < 0.0001$ vs. Control; ##### $p < 0.0001$ vs. 2 Gy alone; ++++ $p < 0.0001$ vs. 3 Gy alone.

However, a notable reduction in SOD activity was observed following ionizing radiation. In the 2 Gy radiation group, SOD activity significantly decreased to 1.214 ± 0.0386 , a reduction of approximately 16.6% compared to the control group ($p < 0.05$). This decrease

was further exacerbated in the 3 Gy radiation group, where the SOD activity dropped to 0.823 ± 0.1005 , showing a more significant reduction of approximately 43.5% compared to the control ($p < 0.0001$).

When quercetin was combined with radiation, a dose-dependent enhancement of the radiosensitizing effect was observed. For the 2 Gy radiation group, pre-treatment with quercetin reduced SOD activity to 1.1543 ± 0.0439 (20 μM), 1.096 ± 0.0156 (40 μM), and 0.984 ± 0.0255 (60 μM), with the greatest reduction observed at 60 μM (32.7% decrease, $p < 0.01$ compared to radiation alone). Similarly, in the 3 Gy radiation group, quercetin at 20, 40, and 60 μM further decreased SOD activity to 1.1087 ± 0.0099 , 1.0363 ± 0.0425 , and 0.736 ± 0.0521 , respectively, with the most pronounced effect at 60 μM (approximately 48.2% reduction, $p < 0.0001$ compared to radiation alone).

Discussion

Radiotherapy is a major modality for the treatment of breast cancer and many other solid tumors. Despite its widespread use, the therapeutic success of radiation is often hampered by the radioresistance of cancer cells and the unavoidable damage to surrounding normal tissues (22). Therefore, strategies to selectively enhance tumor cell radiosensitivity while minimizing off-target effects have garnered significant interest in recent years (23-25). One such strategy involves the use of radiosensitizers—agents that increase the susceptibility of tumor cells to radiation-induced damage.

Natural compounds, particularly polyphenols such as quercetin, have been widely explored as potential radiosensitizers due to their antioxidant, anti-inflammatory, and pro-apoptotic properties (26). However, their dual role as both antioxidants and pro-oxidants depending on concentration and context introduces complexity to their therapeutic application (27). In this study, we investigated the radiosensitizing potential of quercetin in T47D human breast cancer cells using a combination of cytogenetic (micronucleus assay), functional (clonogenic assay), and biochemical (SOD and catalase activity) analyses.

Our results showed that quercetin alone, at concentrations of 20, 40, and 60 μM , did not significantly increase genotoxicity or impair clonogenic survival compared to the untreated control group. However, when combined with ionizing radiation, especially at higher doses (40 and 60 μM), quercetin significantly enhanced radiation-induced cytogenetic damage and cell death. In the micronucleus assay, the frequency of micronuclei increased significantly in groups receiving 60 μM quercetin with 2 Gy radiation and both 40 and 60 μM with 3 Gy radiation, compared to their respective radiation-only groups. These results are consistent with studies in MCF-7 and HepG2 cells, where quercetin was reported to increase radiosensitivity via DNA damage and apoptotic mechanisms (28).

The clonogenic assay confirmed these findings at a functional level. Quercetin alone caused a dose-dependent reduction in colony formation, though this reduction was not statistically significant. In contrast, when combined with radiation, especially 3 Gy, a marked decrease in clonogenic survival was observed. The most notable effect was seen with 60 μM quercetin plus 3 Gy, reducing survival to only 6.27%, compared to 37.03% with radiation alone—an over 80% reduction.

Furthermore, the biochemical assays revealed that co-treatment with quercetin and radiation significantly reduced the activities of two key antioxidant enzymes, superoxide dismutase (SOD) and catalase. These reductions were dose-dependent and more prominent in the combination treatment groups. For instance, SOD activity declined by approximately 43% in the 3 Gy + 60 μM group compared to the control. This supports the hypothesis that quercetin enhances radiosensitivity in part by impairing cellular antioxidant defenses, leading to accumulation of oxidative damage. Similar findings were reported by Russo et al (6) and Chen et al (9), who emphasized the role of redox imbalance in quercetin-mediated radiosensitization.

This study contributes to the growing body of evidence suggesting that quercetin may be a promising adjunct to radiotherapy in breast cancer treatment. Compared to prior studies using other cell lines (e.g., MCF-7, HepG2), our results in T47D cells highlight both

consistency in the radiosensitizing effect and the importance of cell-type-specific responses. The integrated analysis of DNA damage, survival capacity, and oxidative stress markers provides a comprehensive understanding of quercetin's mode of action.

despite the promising in vitro findings of this study, several limitations should be acknowledged. First, although our data support the radiosensitizing effects of quercetin in T47D cells, the study was limited to in vitro conditions and may not fully replicate the tumor microenvironment in vivo. Second, mechanistic insights such as the role of apoptosis pathways, cell cycle arrest, or signaling cascades (e.g., PI3K/Akt or MAPK) were not directly assessed and remain to be explored. Importantly, this study is part of a broader research project evaluating the radiosensitizing potential of quercetin across multiple breast cancer subtypes. Our previous published work on MCF-7 cells (17) showed similar radiosensitizing effects, and additional experiments on the triple-negative MDA-MB-231 cell line have been completed but are yet to be published. Collectively, these findings suggest that quercetin may exert radiosensitizing activity across different molecular subtypes of breast cancer. The bioavailability of quercetin in vivo is limited due to poor absorption and rapid metabolism (27). Additionally, its dual antioxidant/pro-oxidant behavior (29,30) necessitates precise control over dose and timing to avoid radioprotective effects in tumor cells. Overall, the current study adds to the growing body of evidence supporting the potential role of quercetin as an adjuvant in radiotherapy for breast cancer. Future studies should aim to address these limitations through improved delivery systems (e.g., nanoparticles), in vivo validation, and assessment in more complex tumor models.

Author contribution

MH Conceptualization, editing, review, and supervision.

YP Written and Laboratory tests.

HS Radiation therapy

Conflicts of interest

There are no conflicts of interest.

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