

Effects of Radiofrequency Radiation on Cell Viability and Cisplatin Response in Melanoma Cells

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ABSTRACT

With the widespread use of wireless communication technologies, exposure to radiofrequency (RF) electromagnetic fields has markedly increased. Considering that cancer patients are continuously exposed to RF sources in daily life, the potential interaction between RF exposure and chemotherapeutic agents remains insufficiently explored. This study aimed to evaluate the time-dependent effects of RF exposure, alone and in combination with low-dose cisplatin, on B16 melanoma cell viability. B16 melanoma cells were cultured in 96-well plates and divided into control, RF exposure (1, 6, and 24 h), cisplatin control, and cisplatin + RF groups. Cisplatin was administered at a low dose (0.5 μ M). RF exposure was performed at 3.5 GHz using a GTEM cell, with a calculated specific absorption rate (SAR) of approximately 1.04 W/kg. Cells were maintained under physiological conditions (37 °C, 5% CO₂). Cell viability was assessed using the MTT assay, and statistical analyses were performed using appropriate tests. RF exposure alone did not significantly affect cell viability at 1 and 6 h, whereas a significant reduction was observed at 24 h ($p < 0.01$). In cisplatin-treated cells, RF exposure for 1 and 6 h showed no significant effect. However, 24 h RF exposure significantly increased cell viability compared to the cisplatin control group ($p < 0.01$). RF exposure induces time-dependent biological effects in melanoma cells and may alter the cellular response to cisplatin. Prolonged RF exposure appears to attenuate cisplatin-induced cytotoxicity, suggesting a modulatory effect on chemotherapy response. Further studies are needed to clarify the mechanisms and clinical relevance of RF-chemotherapy interactions.

Keywords: Radiofrequency radiation, Melanoma, Cisplatin, Chemotherapy response, Cell viability

Introduction

The biological effects of radiofrequency (RF) electromagnetic fields on living systems have attracted increasing scientific attention, particularly with the rapid expansion of wireless communication technologies. As RF exposure has become an integral part of daily life, understanding its potential effects at the cellular and molecular levels has become increasingly important. Experimental and epidemiological studies suggest that RF electromagnetic fields may influence various biological processes, including cell proliferation, oxidative stress responses, and intracellular signaling pathways (1-5).

The introduction of fifth-generation (5G) communication systems has further increased public and scientific interest in RF-related biological effects. In particular, mid-band frequencies around 3–4 GHz, widely used in 5G

infrastructure, have raised questions regarding potential biological interactions (3, 6). Although RF exposure is generally considered non-ionizing, accumulating evidence indicates that it may act as a modulator of cellular processes rather than a direct cytotoxic agent. In the present study, a 3.5 GHz RF signal was used as a representative mid-band frequency; however, it does not fully replicate the complex modulation characteristics of real 5G signals. Studies have reported that RF exposure can influence oxidative stress, reactive oxygen species (ROS) production, and apoptosis-related pathways in different cell types, including cancer cells (7-10). However, these effects are often inconsistent and appear to depend on multiple parameters such as exposure duration, frequency, power density, and the biological model used (3, 11, 12). Therefore, further studies are required to clarify the biological relevance of

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Received: 08.04.2026, Accepted: 25.08.2026

RF exposure, particularly under conditions relevant to current communication technologies.

Melanoma is an aggressive malignant tumor characterized by high metastatic potential and resistance to conventional therapies. Despite advances in targeted and immunotherapies, chemotherapy remains an important component of treatment strategies (13, 14). Cisplatin is a widely used chemotherapeutic agent that exerts its cytotoxic effects primarily through DNA crosslinking, leading to apoptosis and inhibition of cell proliferation (15, 16). However, emerging evidence suggests that low-dose cisplatin may activate adaptive cellular responses, including stress signaling and survival pathways, which can contribute to chemoresistance (17, 18).

The combined application of physical stimuli and chemotherapeutic agents has been proposed as a strategy to modulate cellular responses and potentially enhance or attenuate drug efficacy. Previous studies have demonstrated that electromagnetic or physical interventions can alter drug sensitivity in cancer cells (19-22). However, it remains unclear whether RF electromagnetic fields, particularly at frequencies relevant to modern communication systems, can influence the cytotoxic effects of chemotherapeutic agents such as cisplatin.

Therefore, the aim of the present study was to evaluate the time-dependent effects of RF exposure on B16 melanoma cell viability and to investigate whether RF exposure modifies the cytotoxic response to low-dose cisplatin using the MTT assay.

Materials and Methods

Cell Culture: In this study, the murine melanoma cell line B16 was used. Cells were cultured in Dulbecco's Modified Eagle Medium (DMEM) supplemented with 10% fetal bovine serum (FBS) and 1% penicillin-streptomycin. All cell cultures were maintained in a humidified incubator at 37 °C with 5% CO₂. Cells were seeded into 96-well culture plates one day prior to the experiments and allowed to adhere for approximately 24 hours under standard conditions.

Experimental Groups: Cells were divided into the following experimental groups:

1. Control group
2. RF exposure groups (1 h, 6 h, and 24 h)
3. Cisplatin control group

4. Cisplatin + RF exposure groups (1 h, 6 h, and 24 h)

Cisplatin was administered at a concentration of 0.5 µM prior to RF exposure (23). This dose was intentionally selected to be well below cytotoxic concentrations reported for melanoma cells. Previous studies have indicated that the 24-hour IC₅₀ value of cisplatin in melanoma models is approximately 10 µM; therefore, the selected dose represents a sub-cytotoxic level (17).

RF Exposure and Specific Absorption Rate (SAR) Calculation: Cell cultures were exposed to RF-EMF at a frequency of 3.5 GHz using a Gigahertz Transverse Electromagnetic (GTEM) cell connected to an RF signal generator. The RF signal was generated using a Model 3500 PM10 RF generator (Everest, Adapazarı, Türkiye) and applied as a GSM-like pulsed signal with a pulse repetition frequency of 217 Hz and a pulse width of 0.576 ms. These exposure parameters were selected to reproduce a pulsed RF waveform commonly used in experimental bioelectromagnetic studies and were identical to those used in our previous investigations (3). This frequency lies within the mid-band spectrum commonly used in 5G communication systems; however, the applied RF signal does not fully replicate the complex modulation characteristics of real 5G signals.

Culture plates were placed in the test region of the GTEM chamber to provide a controlled and reproducible electromagnetic field environment. To maintain physiological conditions, the entire experimental setup was placed inside a standard cell culture incubator. During RF exposure, cells were maintained at 37 °C and 5% CO₂.

The electric field strength within the exposure environment was monitored using a calibrated NARDA EMR-300 electromagnetic field meter (Narda Safety Test Solutions, Pfullingen, Germany). Measurements were performed at the position of the culture plates, and field stability was verified throughout the exposure period.

SAR was calculated using the following equation (24):

$$SAR = \sigma E^2 / \rho$$

where σ (S/m) represents the electrical conductivity of the culture medium, E (V/m) represents the electric field strength within the exposure system, and ρ (kg/m³) represents the density of the medium. Dielectric properties of the culture medium were incorporated using values reported in the literature. SAR estimation was performed under steady-state conditions to

approximate RF energy absorption during exposure.

Cells were exposed to RF radiation for 1, 6, and 24 hours. Control cells were maintained under identical incubation conditions without RF exposure.

Cell Viability Assay: Cell viability was assessed using the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide] assay. Following RF exposure, MTT solution was added to each well, and cells were incubated for 2–4 hours to allow the formation of formazan crystals in metabolically active cells.

After incubation, the formazan crystals were dissolved in dimethyl sulfoxide (DMSO), and absorbance values were measured at 570 nm using a microplate reader. Cell viability (%) was calculated by normalizing absorbance values to those of the control group.

Statistical Analysis: All data were expressed as mean $\pm$ standard deviation (mean $\pm$ SD). Statistical analyses were performed using GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Differences between groups were evaluated using one-way analysis of variance (one-way ANOVA), followed by Tukey's multiple comparison test for post-hoc analysis.

In cases where data did not meet normality assumptions, the Kruskal–Wallis test was applied. p -value < 0.05 was considered statistically significant.

Results

Cell Viability Results: The effects of RF exposure on B16 melanoma cell viability were evaluated using the MTT assay. In the groups exposed to RF alone, no statistically significant differences in cell viability were observed after 1 h or 6 h of exposure compared to the control group ($p > 0.05$). However, exposure to RF for 24 h resulted in a significant reduction in cell viability ($p < 0.01$) (Figure 1).

In cisplatin-treated cells, the impact of RF exposure on the chemotherapeutic response was also assessed. RF exposure for 1 h and 6 h did not significantly alter cell viability compared to the cisplatin control group ($p > 0.05$). In contrast, 24 h of RF exposure led to a significant increase in cell viability relative to the cisplatin control ($p < 0.01$) (Figure 1).

Specific Absorption Rate (SAR): During RF exposure, the electric field strength was measured using a calibrated NARDA EMR-300 probe

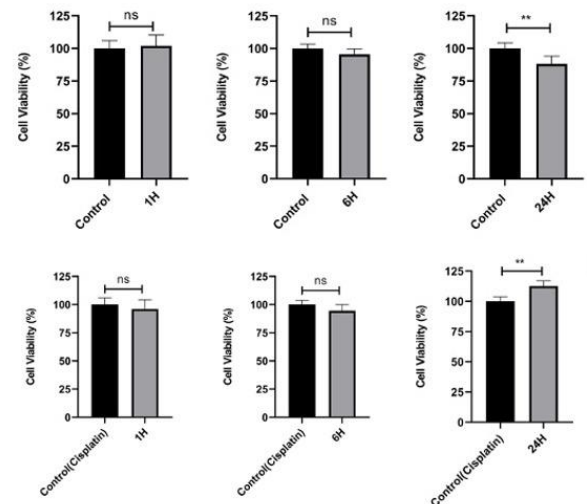


Fig. 1. Time-dependent effects of RF exposure alone and in combination with cisplatin on B16 melanoma cell viability assessed by the MTT assay. Cell viability was evaluated after 1, 6, and 24 hours of RF exposure. Data are presented as mean $\pm$ SD. $p < 0.01$; ns, not significant

(Narda Safety Test Solutions, Pfullingen, Germany), and the average electric field intensity was determined to be 29.5 V/m. The density of the culture medium was assumed to be 1000 kg/m³, and its electrical conductivity was assumed to be 1.2 S/m, based on reported dielectric properties of biological fluids in the radiofrequency range (25).

The calculated SAR value under the experimental conditions was approximately 1.04 W/kg, indicating a low-to-moderate level of RF energy absorption.

Figure 1. Time-dependent effects of RF exposure alone and in combination with cisplatin on B16 melanoma cell viability assessed by the MTT assay. Cell viability was evaluated after 1, 6, and 24 hours of RF exposure. Data are presented as mean $\pm$ SD. $p < 0.01$; ns, not significant.

Discussion

In the present study, the effects of 3.5 GHz RF exposure, corresponding to frequencies widely used in contemporary wireless communication systems, were evaluated on the viability of B16 melanoma cells, both alone and in combination with low-dose cisplatin. The findings of the present study demonstrate that RF exposure induces clear time-dependent biological effects. While short-term exposure (1 and 6 h) did not significantly affect cell viability, prolonged exposure (24 h) resulted in a significant reduction

in viability. In contrast, RF exposure in combination with cisplatin led to a significant increase in cell viability at 24 h, suggesting a modulatory effect on chemotherapy sensitivity and treatment response. The inclusion of the 24-hour exposure period was intended to evaluate whether prolonged RF exposure produces cumulative biological responses that may not become apparent after shorter exposure durations. The comparison of 1, 6, and 24 hours therefore allowed the assessment of time-dependent biological effects under controlled *in vitro* conditions rather than the simulation of a specific real-life exposure scenario.

The biological effects of RF electromagnetic fields reported in the literature are highly heterogeneous and appear to depend on exposure parameters and biological context. Previous studies have shown that RF exposure does not consistently induce direct cytotoxicity but may instead modulate cellular processes such as oxidative stress, signaling pathways, and gene expression (1-3, 10). In line with these findings, the absence of significant effects at early exposure times in our study supports the notion that RF acts primarily as a biological modulator rather than an immediate cytotoxic agent.

In melanoma-related models, previous findings have also been inconsistent. For instance, RF exposure has been reported to increase melanogenesis through CREB activation and MITF upregulation (26), whereas earlier *in vivo* studies using B16 melanoma models showed no significant effects on tumor progression (27). Epidemiological data further support this variability, with no consistent association between RF exposure and melanoma incidence despite increased mobile device usage (28, 29). These discrepancies suggest that RF-induced biological effects are likely context-dependent and influenced by exposure duration, intensity, and cellular conditions.

The reduction in cell viability observed after 24 h of RF exposure alone in our study may be associated with the activation of cellular stress responses, including oxidative stress and alterations in intracellular signaling pathways. Previous studies have demonstrated that RF exposure can influence redox balance and stress-related signaling mechanisms (1, 3, 10). Therefore, the observed decrease in viability may reflect RF-induced metabolic stress or reduced proliferative capacity rather than direct cytotoxicity. However, since molecular endpoints were not evaluated, the exact mechanism remains to be elucidated.

A key finding of this study is the increase in cell viability observed in cisplatin-treated cells following prolonged RF exposure. Cisplatin exerts its cytotoxic effects primarily through DNA damage and the induction of apoptosis (30). However, it is well established that low-dose cisplatin exposure may activate adaptive stress responses, including autophagy and pro-survival signaling pathways (30). In this context, the observed increase in cell viability is likely explained by an RF-induced enhancement of these adaptive cellular mechanisms. Electromagnetic fields have been reported to influence membrane permeability, ion channel activity, and intracellular calcium signaling (22, 31), which may contribute to altered drug sensitivity and reduced cytotoxicity. From a clinical perspective, these findings suggest that RF exposure, which is common in daily life, may influence the response to chemotherapy in cancer patients. Therefore, potential interactions between environmental RF exposure and anticancer treatments should be considered, particularly in patients receiving cisplatin-based therapies.

Importantly, the RF exposure conditions used in this study correspond to frequencies within the mid-band spectrum of 5G communication systems. The RF signal was applied as a GSM-like pulsed waveform rather than a continuous wave; however, it does not fully replicate the complex modulation characteristics of real 5G communication signals. Several experimental studies have demonstrated that the biological effects of RF exposure depend not only on frequency and intensity but also on signal modulation and exposure duration (11). Therefore, the use of a GSM-like pulsed signal together with multiple exposure durations strengthens the biological relevance of the experimental design. Nevertheless, the findings provide relevant insight into potential biological effects associated with contemporary RF exposure scenarios.

Future studies should focus on elucidating the molecular pathways involved in RF-drug interactions, particularly through the evaluation of oxidative stress markers, apoptosis-related proteins, and autophagy pathways. Additionally, studies using multiple cell lines, three-dimensional culture systems, and *in vivo* models are required to validate the generalizability of these findings.

In conclusion, the present study demonstrates that RF exposure at 3.5 GHz induces time-dependent effects on B16 melanoma cell viability and can modulate the cellular response to low-dose

cisplatin. While prolonged RF exposure alone reduced cell viability, it attenuated cisplatin-induced cytotoxicity when applied in combination, suggesting a modulatory effect on chemotherapy sensitivity. This finding indicates a potential attenuation of chemotherapeutic efficacy under prolonged RF exposure conditions.

Although the underlying mechanisms were not directly investigated, the observed effects may be associated with the activation of cellular stress responses and adaptive survival pathways. Given that the exposure frequency used in this study falls within the range of contemporary wireless communication systems, these results provide relevant insight into the possible biological implications of RF exposure in cancer-related contexts. These findings may have potential clinical relevance, as cancer patients are continuously exposed to RF fields through modern communication technologies.

Further studies are required to elucidate the molecular mechanisms underlying RF–drug interactions and to determine their relevance across different biological models. A better understanding of these interactions may contribute to improved evaluation of environmental RF exposure in the context of cancer treatment and therapeutic outcomes.

Ethics Committee Approval: Ethical approval was not required for this study as it was conducted using an established cell line and did not involve human participants or animal subjects.

Conflict of Interest Statement: The authors declare that they have no conflicts of interest.

Financial Disclosure: The authors declare that this study received no financial support.

Author Contributions: All of the authors declare that they participated in designing, executing and analysing the paper.

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