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Exploring the Radiosensitizing Effects of Tolmetin in Radiotherapy for Human Clonal Cancer Cells

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ABSTRACT

Radiotherapy is a common treatment for cancer, though its effectiveness can be limited due to radiation resistance and damage to healthy tissues. Increasing the sensitivity of cancer cells to radiation while protecting normal cells is crucial for improving treatment outcomes. This study aimed to evaluate the radiosensitizing effects of tolmetin on human colon cancer cells (HT-29) during radiotherapy. HT-29 cells were divided into groups, with one receiving X-ray radiation and another receiving both X-rays and tolmetin at different concentrations. Micronucleus formation and the nuclear division index were used to assess genotoxicity and cytotoxicity, respectively. The results showed a significant increase in micronuclei in the radiation-only group compared to the control group. Groups treated with tolmetin at concentrations of 75 and 100 µM also showed an increase in micronuclei, with the highest increase observed at concentrations of 100 and 150 µM. However, tolmetin did not alter the nuclear division index at any of the concentrations tested. The findings indicate that tolmetin effectively sensitizes HT-29 colon cancer cells to radiation in a concentration-dependent manner, without inducing cytotoxicity.

Keywords: Radiotherapy, Cancer treatment, Radiosensitization, Human colon cancer, Tolmetin

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Introduction

Radiotherapy is widely used as a cancer treatment, either alone or in combination with chemotherapy. Ionizing radiation, a physical agent in radiotherapy, works by damaging the DNA of cancer cells, thus impairing their ability to divide and proliferate. Although radiation also harms healthy cells, the goal is to destroy as many cancer cells as possible while minimizing damage to surrounding normal tissues. Notably, cancer cells are less effective at repairing radiation-induced DNA damage than normal cells. Radiation resistance remains a major challenge in cancer therapy, and there is ongoing debate about the balance between its therapeutic benefits and potential physiological drawbacks. Various strategies aim to improve radiation therapy, such as protecting healthy tissues, reducing resistance in tumor tissues, and increasing the sensitivity of cancer cells to radiation [1, 2].

Ionizing radiation is known to cause structural damage to chromosomes [3, 4]. Micronuclei, which are fragments of chromosomes or whole chromosomes that fail to enter the daughter cell nucleus during cell division, serve as an indicator of radiation-induced genetic damage. The formation of micronuclei is commonly used as a biological marker to assess radiation exposure. Additionally, an increase in micronuclei formation has been observed after the administration of radiation sensitizers [1].

Genetic and chromosomal damage plays a crucial role in cancer development, a topic that has been extensively studied [5]. For example, various chromosomal abnormalities have been identified in solid tumors, including

colon cancer [6-8]. Colon cancer is the fourth leading cause of cancer-related death globally [9]. The link between inflammation and cancer is well-established, with non-steroidal anti-inflammatory drugs (NSAIDs) being a class of drugs that inhibit the cyclooxygenase (COX) enzyme [10]. Several studies have demonstrated that NSAIDs can inhibit tumor growth, and their use has been associated with a significant reduction in colon cancer mortality [11-13]. Some NSAID-derived compounds also exhibit pro-apoptotic effects and inhibit tumor growth [14-17].
Tolmetin, an NSAID, inhibits prostaglandin synthesis and has been studied for its potential role in cancer therapy. Research shows that tolmetin, like other NSAIDs, inhibits ß-catenin and enhances the cytotoxic effects of anticancer drugs [18, 19]. Due to this, tolmetin is recognized as a potential agent for developing new anticancer treatments [18]. Selective radiosensitizers are needed to enhance tumor control while limiting toxicity to normal tissues. Although several new agents have shown promise in preclinical studies, few have advanced to clinical trials [20].
Ionizing radiation generates significant oxidative stress, which can also harm normal tissues surrounding the tumor. Therefore, using a sensitizing agent that increases toxicity in cancer cells while minimizing damage to healthy tissues is desirable [21]. This study aims to explore the radiosensitizing effect of tolmetin in radiotherapy treatment on HT-29 colon cancer cells. To evaluate the genotoxicity of radiation and the drug, the micronucleus assay will be employed, while the nuclear division index (NDI) will be used to assess cytotoxicity [22, 23].

Materials and Methods

Cell culture
Cells were grown in RPMI medium (Dacell), supplemented with 10% fetal bovine serum (Gibco), 200 µg/ml streptomycin, and 500 units/ml penicillin (Gibco). The culture conditions were set at 37 °C with 5% CO2 and 95% humidity. The culture medium was refreshed every three days to prevent changes in pH and acidity caused by cellular metabolism. When cells reached 80% confluence, they were detached using 0.25% trypsin (Gibco) and passaged for further cultivation.

Cell treatment
HT-29 cells were seeded at a density of 300,000 to 400,000 cells per well in 12-well plates. Different concentrations of tolmetin (75, 100, and 150 µM) were prepared for treatment. The cells were divided into eight groups: group 1 (control), group 2 (irradiation), group 3 (tolmetin 75 µM), group 4 (tolmetin 100 µM), group 5 (tolmetin 150 µM), group 6 (radiation + tolmetin 75 µM), group 7 (radiation + tolmetin 100 µM), and group 8 (radiation + tolmetin 150 µM). Tolmetin was applied to the cells three hours before irradiation. The appropriate concentration of tolmetin solution (100 µM) was added to the culture medium for the experimental groups.

Irradiation and treatment procedure
A linear accelerator from Shinva Company was used to deliver the radiation. The exposed groups received X-rays at a dose of 4 Gy, with a dose rate of 1.96 Gy/min, and a distance of 60 cm from the radiation source. Following the irradiation, the plates were placed back in the incubator at 37 °C with 5% CO2 and 95% humidity. After 48 hours, cytochalasin B (Sigma-Aldrich) was added at 6 µL/mL to halt cellular division and induce binucleation.

Micronucleus assay
28 hours after cytochalasin B treatment, the cells were collected and centrifuged at 5000 rpm for 7 minutes. The cell pellet was fixed with a mixture of acetic acid and methanol in a 1:6 ratio, followed by transferring the cells onto clean slides. After drying at room temperature for 24 hours, the slides were stained with 10% Giemsa. The number of micronuclei present in 500 binucleated cells was counted, and the average number of micronuclei in each group was calculated. The nuclear division index (NDI) was assessed by counting 500 cells per sample and categorizing them based on the number of nuclei (one-, two-, three-, or four-nucleated). The NDI was calculated using the formula described in Eq. 1.

$$NDI = \frac{(m1 + 2\,(m2) + 3\,(m3) + 4\,(m4))}{N} \quad (1)$$

In the equation above, m1, m2, m3, and m4 indicate the counts of cells with one, two, three, and four nuclei, respectively, while N refers to the total cell count [1].

Statistical approach

For this study, all quantitative results are presented as the mean ± standard deviation. To assess differences between the groups, a one-way ANOVA followed by Tukey's post hoc test was applied. The analysis was conducted using Prism version 9 software, with a significance level of 0.05.

Results and Discussion

Assessing the effect of tolmetin on radiation sensitivity in HT-29 cells using the micronucleus assay

To evaluate the radiosensitizing effect of tolmetin, HT-29 cells were treated with tolmetin concentrations of 75, 100, and 150 μM for 3 hours. The control and radiation-only groups (cells exposed solely to ionizing radiation) were cultured simultaneously. Subsequently, the radiation-exposed groups, including those treated with tolmetin, were irradiated with 4 Gy of X-rays. Cytochalasin B was added to stop the division of binucleated cells. After collection and staining, the micronucleus assay was performed on all groups. The results, based on three repetitions, are summarized in **Table 1**.

Table 1. Mean percentage of micronucleus and NDI produced in HT-29 cells.

No.	Treated groups	Mean ± SD	
		Micronuclei in binucleated HT-29 cells	NDI in binucleated HT-29 cells
1	Control	0.11 ± 0.01	1.35 ± 0.10
2	Irradiated group	0.63 ± 0.03	1.01 ± 0.07
3	Tolmetin (75 μM)	0.13 ± 0.01	1.20 ± 0.19
4	Tolmetin (100 μM)	0.15 ± 0.01	1.06 ± 0.04
5	Tolmetin (150 μM)	0.12 ± 0.01	1.25 ± 0.08
6	Tolmetin (75 μM) + radiation	0.68 ± 0.02	0.99 ± 0.02
7	Tolmetin (100 μM) + radiation	0.91 ± 0.01	0.90 ± 0.04
8	Tolmetin (150 μM) + radiation	0.79 ± 0.01	1.01 ± 0.03

The average micronucleus index values across the eight experimental groups were as follows: 0.11 ± 0.01, 0.63 ± 0.03, 0.13 ± 0.01, 0.15 ± 0.01, 0.12 ± 0.01, 0.68 ± 0.02, 0.091 ± 0.01, and 0.79 ± 0.01. When examining the impact of tolmetin on micronucleus formation in HT-29 cells without radiation, significant differences were observed between the 75 and 100 μM tolmetin-treated groups and the control group ($P < 0.05$). Among the radiation-exposed groups, significant differences were noted when compared to the radiation-only group ($P < 0.05$), with the most pronounced effects observed at the 100 and 150 μM tolmetin concentrations. Additionally, a significant difference between the radiation group and the control was also noted ($P < 0.05$).

Evaluating tolmetin's cytotoxic effect on HT-29 cells using the nuclear division index

To assess the cytotoxic effects of tolmetin, HT-29 cells were treated with concentrations of 75, 100, and 150 μM for three hours. Control and radiation-only groups were maintained under the same conditions. After this treatment, each group was exposed to 4 Gy of X-ray radiation. To halt the proliferation of binucleated cells, cytoclaisin B was added. After cell collection and staining, the nuclear division index (NDI) was determined by counting cells with one, two, three, or four nuclei. The results of three separate trials are summarized in **Table 1**. The mean NDI values were 1.35 ± 0.10, 1.01 ± 0.07, 1.20 ± 0.19, 1.06 ± 0.04, 1.25 ± 0.08, 0.99 ± 0.02, 0.90 ± 0.04, and 1.01 ± 0.03, respectively. The effect of tolmetin on the NDI of HT-29 cells in the absence of radiation is illustrated in **Figure 1**.

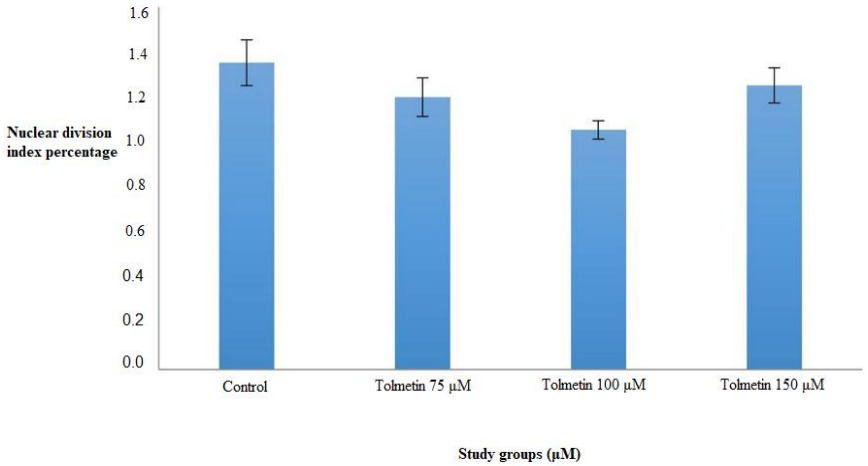

Figure 1. Cytotoxic effect of tolmetin (at concentrations of 75, 100, and 150 µM) on HT-29 cells, evaluated by the nuclear division index (NDI) in groups not exposed to radiation.

The results showed that there was no notable difference in the average nuclear division index between the tolmetin-treated groups and the control group. In the radiation-exposed groups **(Figure 2)**, the NDI did not show any significant variation between the tolmetin-treated and radiation-only groups. The only significant difference observed was between the radiation group and the control group ($P < 0.05$).

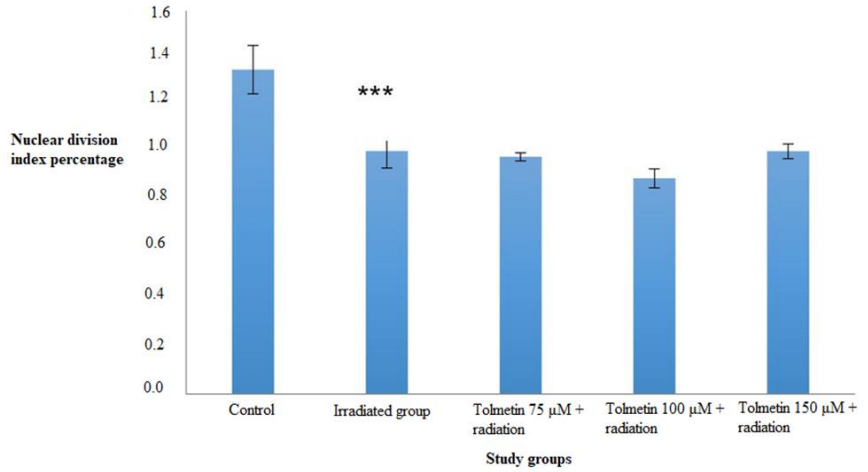

Figure 2. Cytotoxic effect of tolmetin (at concentrations of 75, 100, and 150 µM) on HT-29 cells, assessed by the nuclear division index (NDI) in groups not exposed to radiation; *** indicates a significant difference compared to the control group ($P < 0.001$).

Radiation therapy, in combination with chemotherapy, is a central approach in treating various cancers. The objective of radiation therapy is to direct the maximum radiation dose to the tumor while minimizing harm to the surrounding healthy tissues. This aims to destroy or reduce the size of cancerous masses without damaging the healthy cells. A major hurdle in radiotherapy is the ability of cancer cells to resist the effects of ionizing radiation. These cells often activate signaling pathways that protect them from radiation-induced cell death [24]. As a result, there is ongoing research into compounds that could sensitize tumor cells to radiation, potentially allowing for higher radiation doses with minimal side effects, toxicity, and low cost.

In recent years, there has been an increasing focus on the radiation-sensitizing effects of non-steroidal anti-inflammatory drugs (NSAIDs). For instance, a 2018 study by Hosseinimehr *et al*. [1] investigated the effect of mefenamic acid in combination with ionizing radiation on the HT-29 cancer cell line. The study found that the cells exposed to both mefenamic acid and radiation showed a significantly higher number of micronuclei than those that were not treated with mefenamic acid. In another study, Ahmad *et al*. [25] assessed the effects of naproxen on oxidative stress, genotoxicity, and hepatotoxicity in male Wistar rats. Their findings indicated that

naproxen caused a notable increase in DNA damage, indicated by an increase in micronucleus formation. The drug also led to oxidative stress and disrupted biochemical balance, causing significant damage to cell integrity and liver function, making naproxen a potential genotoxic agent [25].

Additionally, tolmetin has been studied for its potential to enhance the effectiveness of other treatments like cyclophosphamide in killing cancer cells. One study showed that tolmetin enhanced the cytotoxicity of cyclophosphamide without causing significant toxicity to CFU-GM bone marrow cells [26]. Pouyafar *et al.* [27] also explored the cytotoxic effects of resveratrol and sulindac on the HT-29 cell line, revealing that both compounds reduced the survival rate of the cancer cells.

In 2015, researchers developed new tolmetin derivatives and evaluated their effects on the HT-29 cell line. The MTT assay showed that these derivatives exhibited anticancer activity through the activation of caspase-8 and caspase-9, key components of the apoptosis pathway [28]. Furthermore, a study in 2019 investigated the effects of 5-aminolevulinic acid on the HT-29 cancer cell line, both in vitro and in vivo. The results indicated that cells treated with 5-aminolevulinic acid and exposed to multiple doses of radiation had a significantly lower survival rate. Additionally, the size of xenografted cancer tumors was considerably smaller in animals treated with both radiotherapy and 5-aminolevulinic acid compared to those receiving only radiotherapy [29]. These findings highlight the promising role of radiation-sensitizing compounds in improving the outcomes of radiotherapy.

In the current study, we examined the radiosensitizing effects of tolmetin on HT-29 cancer cells. Our results indicated that, in HT-29 cells not exposed to ionizing radiation, tolmetin treatment led to an increase in the number of micronuclei. However, significant radiation-sensitizing effects were only observed at tolmetin concentrations of 75 and 100 μM ($P < 0.05$). When the cells were exposed to ionizing radiation, the micronucleus test revealed that the radiation-only group showed a significant difference compared to the control group ($P < 0.05$). Moreover, all tolmetin-treated groups showed significant differences compared to the radiation-only group ($P < 0.05$), suggesting that tolmetin effectively enhanced the radiosensitizing effects in tumor cells. The highest number of micronuclei was observed in the 100 μM tolmetin group, which indicates that this concentration was the most effective for inducing radiosensitization **(Figure 3)**.

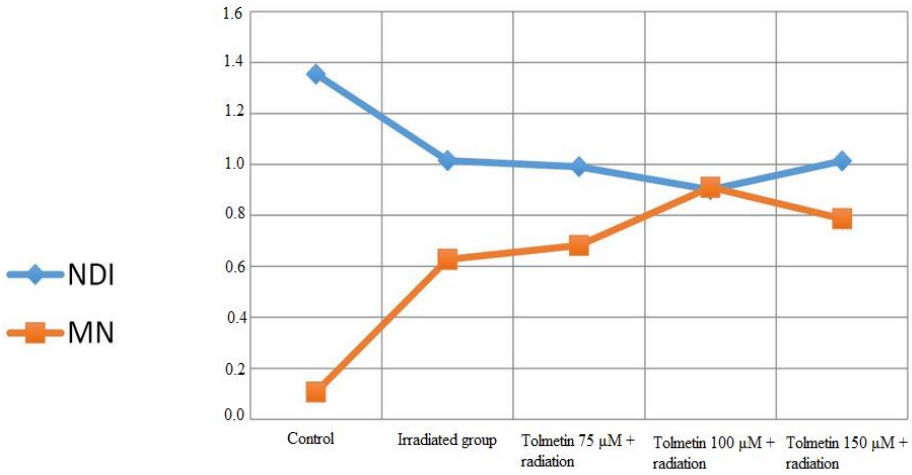

Figure 3. Comparison of the average percentage of the nuclear division index (NDI) and the average percentage of micronuclei in HT-29 cells across the radiation-only group and the groups receiving both radiation and tolmetin at concentrations of 75, 100, and 150 μM.

In the evaluation of tolmetin's cytotoxic effects on HT-29 cancer cells that were not exposed to ionizing radiation, a small reduction in the nuclear division index (NDI) was noted, though it was not statistically significant. The study also assessed tolmetin's impact on cytotoxicity in HT-29 cells subjected to ionizing radiation, with the NDI serving as the measurement. The findings revealed that tolmetin did not induce significant cytotoxicity at the concentrations tested.

The results suggest that tolmetin demonstrated radiosensitizing effects on tumor cells at the concentrations studied, without showing any cytotoxicity. The known mechanisms through which anti-inflammatory drugs like tolmetin enhance radiation sensitivity include inhibiting the cyclooxygenase-2 enzyme, which reduces prostaglandin production, subsequently increasing apoptosis and inhibiting angiogenesis and tumor growth.

Additionally, the arrest of the cell cycle in the G1-S phase is thought to play a key role in this sensitization, though the exact mechanism remains unclear. While the precise way in which NSAIDs act as radiation sensitizers is not fully understood, it is generally accepted that they alter the radiation response curve. As this is the first study to explore tolmetin's radiosensitizing effects on radiation-induced damage in HT-29 cells, future studies should focus on inflammatory markers in these cells and consider in vivo investigations using colon cancer mouse models.

Conclusion

This study aimed to evaluate the radiosensitizing potential of Tolmetin in radiotherapy for HT-29 human colon cancer cells. The results showed a significant increase in micronuclei in the radiation-exposed group compared to the control. Tolmetin at 75 and 100 μM also caused an increase in micronuclei relative to the control group. A significant rise in micronuclei was observed in all tolmetin-treated groups that received radiation, with the most noticeable effect at concentrations of 100 and 150 μM. However, tolmetin did not influence the NDI at the concentrations tested. Overall, the study indicates that Tolmetin has a concentration-dependent radiosensitizing effect on HT-29 human colon cancer cells without showing cytotoxicity at the tested concentrations.

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Ethics Statement: None

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