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BOOK OF PROCEEDINGS

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The effects of a selected methoxy substituted chalcone in human melanoma cells irradiated with γ-rays

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Abstract: Given the well-established potential of chalcones in modulating the response of cancer cells to therapeutic interventions, coupled with the growing imperative to enhance their biological attributes, the objective of this study was to synthesize a methoxy-substituted chalcone (OCH3) and assess its capacity to amplify the inhibitory effects of radiation in melanoma cells known for their resistance to radiotherapy. The A375 melanoma cells were subjected to a clinically relevant dose of 2 Gy gamma irradiation. OCH3 was employed either as a standalone treatment or in conjunction with irradiation. The obtained results unveiled the substantial radiosensitizing potential of OCH3 within this specific cell line. Our subsequent investigations will be designed to investigate the underlying mechanisms that contribute to the radiosensitizing properties of OCH3. Moreover, we intend to evaluate the efficacy of OCH3 against other types of radioresistant cancer cells. The presented data not only illuminates the enhanced therapeutic possibilities offered by OCH3 but also highlights its potential as a valuable agent in addressing a wider array of challenging malignancies.

Keywords: methoxy substituted chalcone, melanoma, irradiation

1. Introduction

Effective anti-cancer treatments necessitate a comprehensive assessment through drug screening protocols to ensure their safety and efficacy [1]. Over recent years, there has been a significant focus on phytochemicals, including chalcones, owing to their cost-effectiveness, relatively low toxicity, and ability to target molecular pathways implicated in carcinogenesis [2]. Moreover, chalcones extend beyond their anti-tumor properties and have demonstrated a versatile range of beneficial effects. These encompass anti-

inflammatory, antioxidant, anti-microbial, antidiabetic, and neuroprotective potentials, as documented [3, 4], in addition to their established anti-tumor activities.

To increase the biological potency of chalcones, enhancing their chemical attributes continues to be a relevant approach [5]. The combination of medical therapies can heighten the effectiveness of treatments and is frequently necessary in real-world medical scenarios. Our prior research has shown promising inhibitory effects of recently developed methoxy-substituted chalcone in melanoma cells. In this work, our objective was to explore the potential of the synthesized chalcone to enhance the sensitivity to radiation therapy, thereby investigating its radiosensitizing potential.

2. Experimental

2.1 Synthesis of OCH3

The synthesis of metoxychalcone was achieved by ClaisenSchmidt condensation of 2 - hydroxyacetophenone with the 2-methoxybenzaldehyde (Figure 1). The reaction is a base-catalyzed aldol condensation that takes place at room temperature.

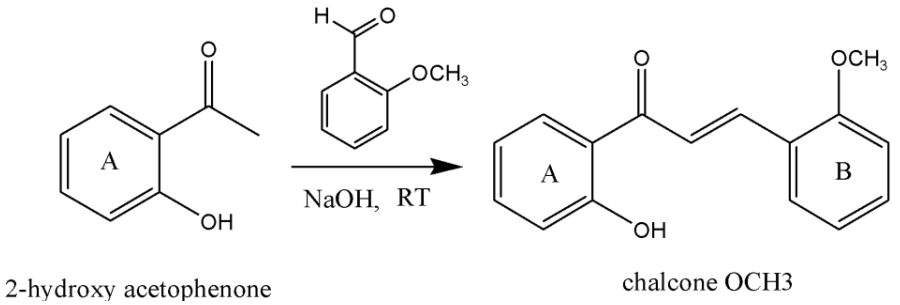

Figure 1. The synthesis of OCH3 metoxychalcone.

2.2 Cell cultivation, OCH3 treatment and irradiation conditions

The human A375 malignant melanoma cell line was obtained from the American Type Culture Collection (ATCC, Rockville, MD, USA). These cells were cultivated in RPMI 1640 medium, supplemented with 10% fetal bovine serum (FBS), penicillin/streptomycin, and L-glutamine. The cell cultures were maintained at a temperature of 37°C within a humidified atmosphere containing 5% CO_2 (Heraeus, Hanau, Germany). Prior to exposure to treatments, the cells were allowed to grow in the culture medium for a period of 24 hours. After incubation with OCH3 for an additional 24 h cells were exposed to irradiation with γ-rays. Stock solutions of the chalcone compound were appropriately diluted in the culture medium to achieve the desired final concentration. The concentration of dimethyl sulfoxide (DMSO) in the treated samples did not exceed 0.1% [6].

In experiments involving irradiation, the cells were exposed to ^{60}Co γ-rays (CIRUS-Cis Biointernational) while positioned vertically at room temperature. These irradiation

procedures were carried out at the Vinca Institute of Nuclear Sciences in Belgrade, Serbia. Across all experiments, clinically relevant irradiation dose of 2 Gy was employed [7], with a dose rate of approximately 1 Gy per minute.

2.3 Survival of A375 melanoma cells after combined treatment with OCH3 and γ-irradiation

The procedure for clonogenic assay was performed according to the standard procedure [8]. The results have shown that OCH3 exhibited a notable inhibitory effect on the viability of A375 cells, observed 14 days following the treatment. The survival rate of A375 cells exposed to OCH3 was approximately 40% as compared to the untreated control (Figure 2A). Furthermore, the application of irradiation treatment also yielded a significant decrease in colony count, resulting in a cell survival rate of around 60%. This observation aligns with previously reported data that underscores the heightened radioresistance of these cells, as documented in studies [9,10].

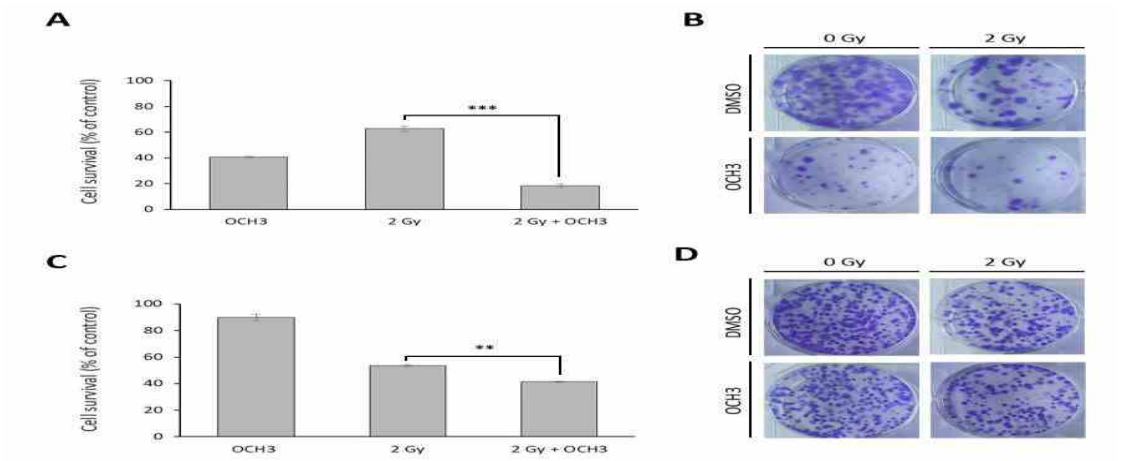

Figure 2. Effects of OCH3 and 2 Gy γ-irradiation on survival of A375 melanoma cells (A, B). Clonogenic survival was evaluated 14 days after the treatments. Statistical significance was determined by Student's t-test and expressed as: *p < 0.05; **p < 0.01; ***p < 0.001. (*- Statistical significance compared to irradiation).

The combination treatment of OCH3 and irradiation invoked an even more robust, statistically significant decrease in colony count, being less than 20% of the control value. The decline in cell survival was significant when compared to irradiation alone ($p < 0.001$) Moreover, there was a distinct diminution in the size of the colonies subsequent to treatment with both agents, as depicted in Figure 2B.

3. Conclusions

The findings from this preliminary study have illuminated the promising radiosensitizing capabilities of the recently developed methoxy-substituted chalcone within melanoma cells. Future experiments will aim to investigate the radiosensitizing potential of this compound across diverse types of cancer cells as well as the mechanisms underlying the observed radiosensitizing effects.

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