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Radiation and Peripheral Blood

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ABSTRACT: Ionizing Radiation Therapy or Radiotherapy is the use of Ionizing Radiation (IR) for the treatment of radio-sensitive malignancies. It is an indispensable treatment modality for cancer, alone or supported with surgery and or chemotherapy. It consists of electrons and gamma rays or as alternative radioisotope. Commonly used isotopes include Iodine¹²⁵, Iridium¹⁹², Strontium⁸⁹, Iodine¹³¹, Yttrium⁹⁰ and Cobalt⁶⁰. Normal tissue toxicity is a dose-limiting factor in radiation therapy. Therefore, a detailed understanding of the normal tissue response to radiation is necessary to predict the risk of normal tissue toxicity and to development strategies for tissue protection. One component of normal tissue that is continuously exposed during therapeutic irradiation is the circulating population of peripheral blood mononuclear cells (PBMC). PBMCs are highly sensitive to ionizing radiation (IR); however, little is known about how IR affects the PBMC response on a systemic level. It was the aim of this study to investigate whether IR was capable to induce changes in the composition and function of extracellular vesicles (EVs) secreted from PBMCs after radiation exposure to different doses. Therefore, whole blood samples from healthy donors were exposed to X-ray radiation in the clinically relevant doses of 0, 0.1, 2 or 6 Gy and PBMC-secreted EVs were isolated 72 h later. Proteome and miRNome analysis of EVs as well as functional studies were performed. Secreted EVs showed a dose-dependent increase in the number of significantly deregulated proteins and microRNAs. For both, proteome and microRNA data, principal component analysis showed a dose-dependent separation of control and exposed groups. Integrated pathway analysis of the radiation-regulated EV proteins and microRNAs consistently predicted an association of deregulated molecules with apoptosis, cell death and survival. Functional studies identified endothelial cells as an efficient EV recipient system, in which irradiation of recipient cells further increased the uptake. Furthermore an apoptosis suppressive effect of EVs from irradiated PBMCs in endothelial recipient cells was detected. In summary, this study demonstrates that IR modifies the communication between PBMCs and endothelial cells. EVs from irradiated PBMC donors were identified as transmitters of protective signals to irradiated endothelial cells. Thus, these data may lead to the discovery of biomarker candidates for radiation dosimetry and even more importantly, they suggest EVs as a novel systemic communication pathway between irradiated normal, non-cancer tissues.

KEYWORDS: radiation, peripheral blood, cancer, apoptosis, cell death, radioisotope, communication

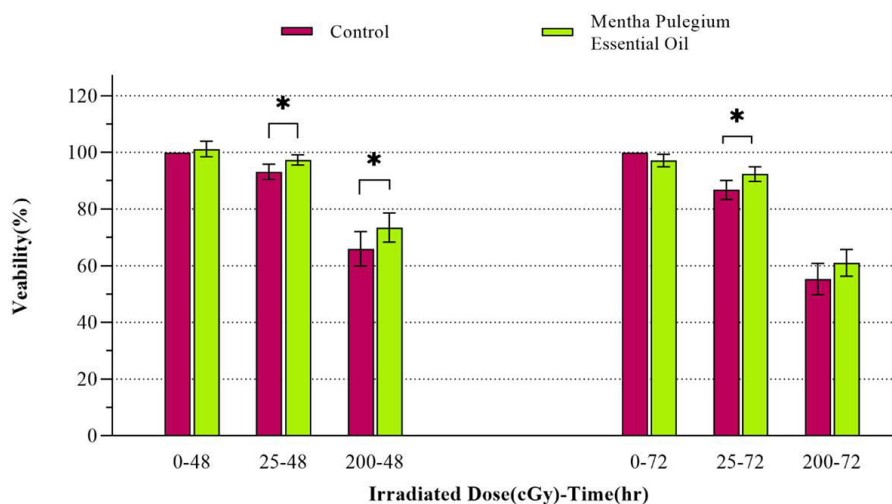
I. INTRODUCTION

Autologous hematopoietic stem cell transplantation (ASCT) after high-dose chemotherapy is used to treat relapsed malignant lymphomas. Radiation therapy (RT) is applied after ASCT. Comparison is done of the incidence of myelosuppression after RT with and without autologous peripheral blood stem cell transplantation (auto-PBSCT). Individual responses to radiotherapy are often observed whether or not regimes with identical treatments were applied. Patient-related factors, the therapeutic process, and therefore the intrinsic factors of individual radiosensitivity are considered to be causing the variability of side effects. A preliminary evaluation is done on cytogenetic biomarkers found in cancer patients. A high frequency of micronuclei in lymphocyte patients was seen after radiotherapy treatment but relatively not much higher compared to the range of micronuclei backgrounds in healthy people. The CBMN (Cytokinesis-Block Micronucleus assay) is the most effective assay for evaluation of the cytogenetic studies in cancer patients because it is more radiosensitive to study individual responses. By evaluating the effects of radiotherapy based on DNA damage, the severity of radiation exposure can be studied. This study can be useful for researchers and related stakeholders in the application of radiotherapy. The risk of exposure to ionizing radiation, as an important tool in the diagnosis and therapy, is high in medicine and can also cause serious side effects to living organisms; developed techniques have increased the number of X-ray examinations in the diagnosis and treatment of patients. Accordingly, public awareness of the harmful effects of ionizing radiation leads to further



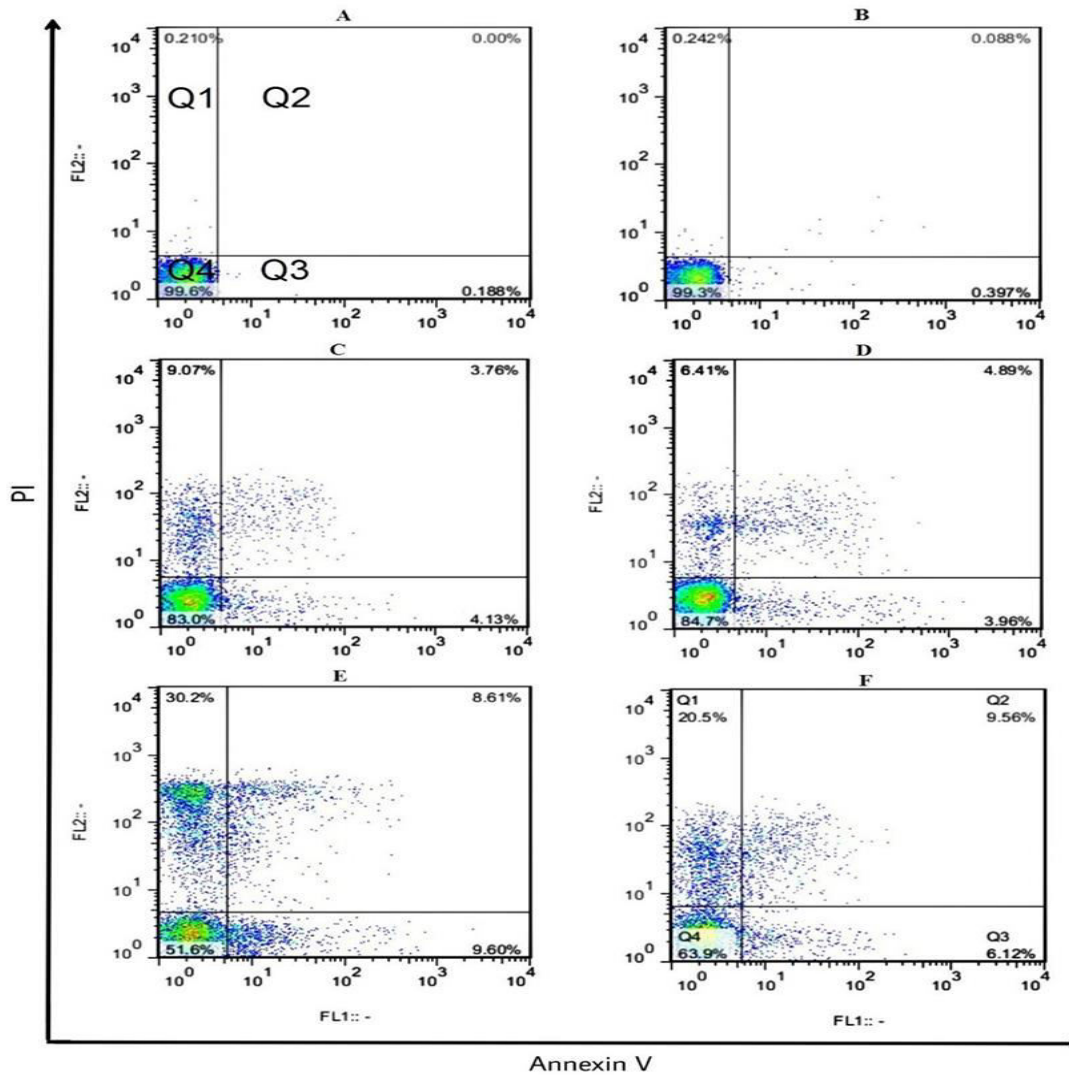
public concerns [1 , 2]. International Commission on Radiological Protection (ICRP) established a guideline for physicians and radiographers about the principles of radioprotection due to numerous changes, which are also confirmed by the ALARA principle (As Low As Reasonably Achievable), over the past three decades; minimizing the radiation exposure can be reasonably achievable [3 , 4]. Exposure to ionizing radiation can directly cause different types of Deoxyribonucleic acid (DNA) damage, such as a double-strand break, the most severe. Ionizing radiation can also cause damage by indirect effects, such as the production of reactive oxygen species (ROS). In dispersed ionizing radiation (low Linear Energy Transfer [LET]), such as X-ray and gamma rays, the damage due to reactive oxygen species is dominant compared to the direct damage to DNA [5]. X-ray and gamma rays are most used in medical diagnosis and treatment and play a major role in the effective annual dose due to natural and man-made radiation sources [6 , 7]. Generation of free radicals and ROS by the interaction of X-rays with the biological systems can lead to an imbalance between intracellular antioxidants; ROS results in oxidative stress damage to macromolecules, such as DNA, Ribonucleic Acid, and proteins [8].

II. DISCUSSION



The Colorimetric assay for assessing cell metabolic activity (MTT assay)-Mean survival percentage of irradiated Peripheral blood mononuclear cells (PBMCs) at radiation doses of 0, 25, and 200 cGy in the presence and absence of Mentha Pulegium Essential Oil (MP-EO) at 48 and 72 hours of incubation periods, * $P \leq 0.05$.

The radioprotective effect of a natural antioxidant on protecting radiation staff in radiation centers and patients exposed to radiation for therapeutic and diagnostic purposes. Dispersed X-ray is widely used, especially in medical diagnosis and treatment, and plays a major role in the effective annual dose from natural and man-made radiation sources [7]. The main mechanism of the interaction of these radiations with the biological system is through the generation of free radicals and ROSes [5 , 16]. Attenuation or neutralization of the deleterious effects of ROS is possible by compounds called antioxidants. In recent years, increasing awareness of the toxic nature of some synthetic compounds has led to greater efforts to identify antioxidants of plant origin and low toxicity [17 - 19]. Mentha-pulegium has powerful antioxidant properties as a result of possessing a variety of natural compounds, such as flavonoids and phenols [12 , 20].



The flow cytometry analysis after 72 hours of incubation at a concentration of 170 µg/ml Mentha Pulegium Essential Oil (MP-EO) at different radiation doses using a 6 MV X-ray linear accelerator. A: control group (no treatment) at zero radiation dose, B: treatment group (treated with MP-EO) at zero radiation dose, C: control group at 25 cGy radiation dose, D: treatment group at 25 cGy radiation dose, E: Control group at 200 cGy radiation dose, F: Treatment group at 200 cGy radiation dose.[8.9]

III. RESULTS

Flow cytometry indicated that apoptosis and necrosis are increased following irradiation of cells, which is consistent with other studies conducted in radioprotection fields. The results of flow cytometry showed that in the treatment group of MP-EO, in both radiation doses of 25 and 200 cGy and both incubation periods of 48h and 72h, apoptosis and necrosis rates of PBMCs were significantly reduced compared to the control group that was greater for apoptosis during the 48-hour incubation period ($P \leq 0.05$).[10,11]



Necrosis is usually considered as the final fate of cells, so it can be expected at a 72-hour incubation period, a group of apoptotic cells is categorized into delayed apoptotic and necrotic cells. Unlike apoptosis, necrosis is an uncontrolled cell death due to stress and external damage, leading to the rupture of cell membranes and the shedding of organelles as well as cell contents.

The investigation of radioprotectors in various in-vitro studies is influenced by several factors, such as the type of radiation, radiation dose, cell line, mechanism, and the quantity examined. The lack of a unified system in this area leads to difficult comparison and evaluation of a radioprotectant. However, studies have been conducted on radioprotective effect of natural or chemical compounds on PBMCs by measuring apoptosis. The difference in radiation dose and other parameters, or the lack of the same quantities leads to difficult comparisons. Further, Fardid et al. examined the radioprotection effect of hesperidin on peripheral blood lymphocytes in rats at 2 and 8 cGy doses by analyzing apoptosis and necrosis, without any significant reduction in apoptosis and necrosis in a dose of 2 cGy. In a study conducted on cell survival by Menkovic et al. the radioprotective effect of Mangiferin extract was shown on peripheral blood lymphocytes in low doses. [12,13]

Based on our results in both radiation doses and incubation periods, the percentage of necrosis in treatment groups of MP-EO was significantly decreased compared with the control group. Reducing the percentage of radiation-induced apoptosis and necrosis of PBMCs in the presence of MP-EO shows the radio-protective role of this essential oil against low LET ionizing radiation.

IV. CONCLUSION

MP-EO as a natural antioxidant shows a remarkable radioprotective effect on irradiated PBMCs with X-ray that is shown more by reducing the apoptosis and necrosis of the cells, possibly thereby scavenging free radicals. [14,15]

Due to the natural compound, low toxicity, and cost-effectiveness of Mentha-pulegium essential oil, after complementary studies, it could be daily used as a radioprotector by radiation staff and patients exposed to radiation. Further studies are suggested for improving its kinetics to increase the efficiency of Mentha-pulegium essential oil. [16,17,18]

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