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Reform of Hematopoietic, Apoptotic and Oxidative Disturbance Induced by Accumulated γ-irradiation in Rat's Bone Marrow via Curative Efficacy of Bradykinin Potentiating Factor Isolated from Bee Venom

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BEE venom contains a strong bradykinin-potentiating factor (BPF). In previous studies, BPF isolated from scorpion venom has been shown to be protective against hepato- and nephrotoxicity by reducing oxidative stress. Therefore, the authors aimed at evaluating the novel ability of BPF isolated from bee venom in treating oxidative and apoptotic defects induced by accumulated doses of γ-irradiation in rat's bone marrow (BM). Rats were exposed to 8 Gy of γ-irradiation as accumulated doses and subsequently treated with BPF (1μg/g i.p.) aiming at elucidating the possibility of BPF to reduce irradiation harmful effects. The data obtained showed that the irradiated animals suffered from marked changes of many important hematopoietic parameters including red blood cells, white blood cells, platelets, viable bone marrow count, and serum hematopoietic growth factors as well as oxidative stress markers and apoptotic index in BM tissue. Interestingly, BPF was able to rescue the deleterious effects of irradiation in rats and normalized the aforementioned parameters to the basal levels.

In conclusion: The considerable amelioration of hematic morbidity, oxidative stress and apoptosis in BM exhibited new accomplishment to the BPF isolated from bee venom against accumulated irradiation defects.

Keywords: Apoptosis, BPF, Bone marrow, Oxidative stress, γ-irradiation.

Introduction

Radiation has an important role in human life, it is utilized in several fields such as in medicine, industry and power generation (Galland-Girodet et al., 2014). One of the main purposes of radiobiology is to investigate an appropriate radio-protector to protect people under the risk of radiation exposure, including patients undergoing radiotherapy, radiation workers, and people involved in nuclear accidents (Zangeneh et al., 2015).

Ionizing radiation potentially induces hematopoietic cell loss, immunosuppression and serious damage to other organs such as the central nervous system, lung and kidney (Augustine et al., 2005; Hasan et al., 2020a). Irradiation in doses higher than 2 Gy, causes hematopoietic syndrome, described as rapid and massive cell death in stem and/or progenitor cells (Harfouche & Martin, 2010).

Bone marrow is the most sensitive organ in response to the cytotoxic effects of ionizing radiation. In this situation, unrepaired BM damage may lead to cell death or genomic instability. Therefore, the risk of death or hematopoietic malignancies threatens the exposed people (Cao

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et al., 2011). Irradiation-induced bone damage parallels adipocyte infiltration of the bone marrow (BM) resulting in compositional alterations of the microenvironment that may further affect bone quality and disease state (Costa & Reagan, 2019).

Animal venom contains small bioactive peptides that have biological and physiological significance in health and disease referred to as BPF. Bradykinin (BK) has been linked to a variety of physiological activities, including blood pressure regulation, contraction, and inflammatory reactions (Couture et al., 2001). BPF found in *Bothrops* venom was able to potentiate the biological actions of BK (Ferreira et al., 1998). It inhibits the action of the angiotensin-converting enzyme (ACE) which is responsible for the conversion of angiotensin I (Ang I) to angiotensin II (Ang II) (Murayama et al., 1997). It was discovered that there is a clear relationship between whole-body irradiation dosage and ACE activity (Korystova et al., 2018). Furthermore, BPF extracted from scorpions (*Buthus occitanus*) works as a growth factor *in vivo*, and accelerates burn wound repair (Salman, 1995; Guo et al., 1999). In addition, BK regulates animal cell proliferation (Roberts, 1989).

Polypeptides, enzymes, amines, lipids, and amino acids are among the biochemically or pharmacologically active compounds found in bee venom (BV) (Danneels et al., 2015). It has been used to treat a wide range of ailments and problems, including arthritis, rheumatism, back discomfort, malignant tumors, and skin disease (Tu et al., 2008; Jang et al., 2009).

The purpose of this research is to evaluate the effect of BPF isolated from Egyptian honeybee venom *Apis mellifera* on hindering of hematic disorders, oxidative stress and apoptotic improvement post-irradiation in BM.

Materials and Methods

Bee venom purification

Apis mellifera (Egyptian) venom was obtained from Honey Bee Keeping Department, Agriculture Research Center – Egypt.

Purification was performed according to Ferreira (1965). The resulting water-soluble powder BPF was tested for ileum contraction, then stored frozen.

Radiation facility

Irradiation was performed at the NCRRT, Cairo, Egypt using a Gamma Cell – 40 (^{137}Cesium) biological irradiator. Rats were irradiated at a dose rate of 0.42 Gy/ min. to induce curable damage (Elbakrawy et al., 2019).

Experimental animals

Male Wistar albino rats (100-110g) were obtained from the NCRRT, Cairo, Egypt and kept under normal conditions, fed on rat diet and tap water.

Design of the experiment and treatment protocol

Forty rats were randomly assigned to four groups: Group I (control group; C) rats were intraperitoneally (i.p.) administered 0.9% saline; Group II (bradykinin potentiating factor treated; BPF for four weeks) rats were given BPF at a dosage of 1µg/g i.p. biweekly (Nassar et al., 1990); Group III (irradiated; IRR) rats were given 0.9% saline before being exposed to total body irradiation (TBI) using four fractions of γ-rays (2Gy each fraction up to the cumulative dose of 8Gy over four weeks; these rats served as the positive control group).; Group IV (irradiated and treated with BPF; IRR+BPF) rats were given BPF at a dosage of 1µg/g i.p. biweekly for four weeks, beginning one hour after irradiation, concurrently with exposure to γ-irradiation (4 fractions; 2Gy per fraction up to the cumulative dose of 8Gy over 4 weeks).

Each week, the irradiation procedures were carried out at a predetermined time interval (1st day along the experimental course, to maintain optimum experimental conditions).

Throughout the period of the trial, all animals were carefully observed. Rats were sacrificed under mild anesthesia at the end of the experiment and blood was collected. Femur bones were dissected out and cleaned then the bone marrow tissue was blown out.

Haematological analysis

Red blood cells (RBCs), white blood cells (WBCs) counts were determined according Dacie & Lewis (1991) and platelets count was determined according England et al. (1984).

Assessment of viable BM cell count percentage

A uniform cell suspension of BM was prepared by dilution in saline solution. BM

film was prepared on a microscope slide and stained using trypan blue, where only dead cells absorbed the dye, all the cells were counted on a haemocytometer. The percentage of viable cells was determined by the following formula:

[Viable cell number/ Total cell number] x 100, (Esser et al., 2001).

Assessment of hematopoietic growth factors

Erythropoietin (EPO) (Cat. No. CSB-E07323r), Granulocyte Colony Stimulating Factor (G-CSF) (Cat. No. CSB-E04564m), and Interleukin-11 (IL-11) (Cat. No. CSB-E07358r) levels were measured using ELISA kits (CUSABIO, Houston, USA) according to the manufacturer's instructions.

Assessment of oxidative stress

Reduced glutathione (GSH) was measured by the method of Beutler (1963), malondialdehyde (MDA) was determined according to Yoshioka et al. (1979), Advanced oxidation protein products (AOPP) were determined according to Witko-Sarsat et al. (1996), Total nitrate/nitrite [NOx)] was measured as the stable end product, according to the method of Miranda et al. (2001) and glutathione peroxidase (GPx) was measured by the method of Chiu et al. (1976).

Assessment of apoptosis

The levels of B cell leukemia/lymphoma-2 (BCL2) (Cat. No. MBS452319), Bcl-2 Associated X Protein (PAX) (Cat. No. MBS730995) and caspase-3 (Cat. No. MBS261814) were assessed using ELISA kits (MyBioSource, San Diego, USA) according to the manufacturer's instructions.

Analysis of data

Data were expressed as mean ± S.E.M. All statistical analyses were performed using Statistical Package for Social Science (SPSS) version 21.0 for windows and results were compared using One-way ANOVA followed by Tukey-Kramer post-hoc test. Differences were considered statistically significant when P values < 0.05.

Results

Exposure of animals to accumulated gamma irradiation (8Gy) induced a significant ($P< 0.05$) drop of RBCs, WBCs and platelets counts as well as BM viability in comparison with the control. A significant improvement was observed in all the aforementioned parameters upon the treatment of the irradiated rats with BPF as compared to the irradiated group (Fig.1).

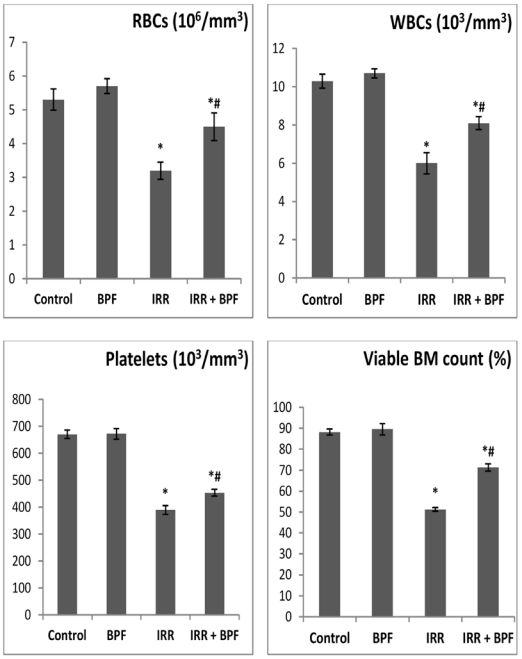


Fig. 1. Effect of BPF isolated from bee venom on cellular count of RBCs, WBCs, platelets and viable BM in irradiated rats [Each value indicates the mean±SEM. *: Significantly different from the control group at P<0.05, #: Significantly different from the IRR group at P< 0.05 using one-way ANOVA with Tukey–Kramer as a post-hoc test. C: Control, IRR: Irradiated rats, BPF: Bradykinin potentiating factor, RBCs: Red blood cells, WBCs: White blood cells, BM: Bone marrow]

As for the control group, gamma irradiation induced a significant decrease in serum EPO and G-CSF, IL-11 values ($P< 0.05$). BPF administration ameliorated the irradiation effect and induced a significant increase in EPO and G-CSF, IL-11 levels as compared to the irradiated group (Fig. 2).

Results presented in Fig. 3 demonstrated a significant decrease in GSH and GPx levels ($P< 0.05$) and a significant increase ($P< 0.05$) in MDA, AOPP and NO levels after accumulated exposure to four fractions of 2Gy gamma radiation in BM tissue as compared to the control group. Administration of BPF to the irradiated rats counteracted the irradiation effects.

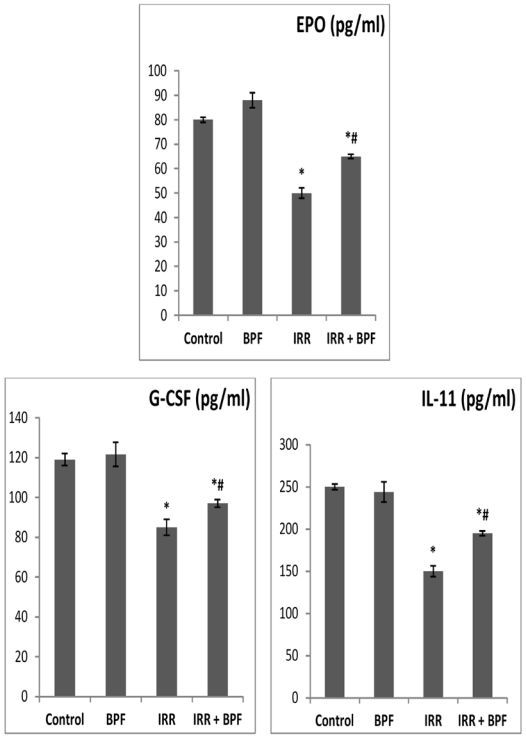
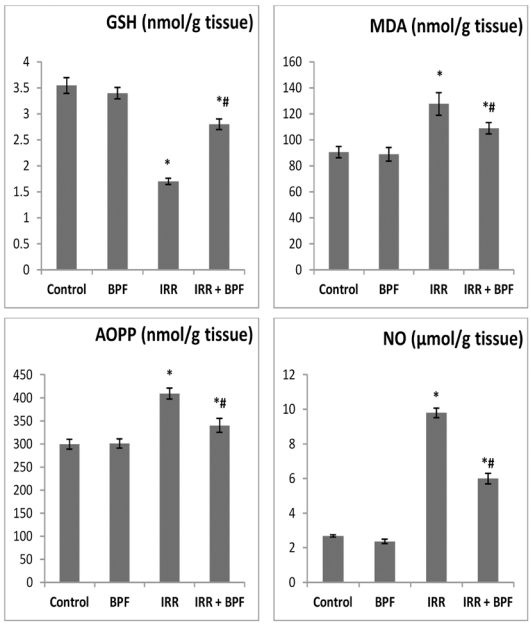


Fig. 2. Effect of BPF isolated from bee venom on serum EPO, G-CSF, and IL-11 in irradiated rats [Each value indicates the mean±SEM. *: Significantly different from the control group at P<0.05, #: Significantly different from the IRR group at P< 0.05 using one-way ANOVA with Tukey–Kramer as a post-hoc test. C: Control, IRR: Irradiated rats, BPF: Bradykinin potentiating factor, EPO: Erythropoietin, G-CSF: Granulocyte Colony Stimulating Factor, IL-11: Interleukin-11]



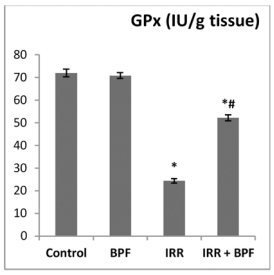


Fig. 3. Effect of BPF isolated from bee venom on bone marrow GSH, MDA, AOPP, NO and GPx in irradiated rats [Each value indicates the mean±SEM. *: Significantly different from the control group at P<0.05, #: Significantly different from the IRR group at P< 0.05 using one-way ANOVA with Tukey–Kramer as a post-hoc test. C: Control, IRR: Irradiated rats, BPF: Bradykinin potentiating factor, GSH: Reduced glutathione, MDA: Malondialdehyde, AOPP: Advanced oxidation protein products, NO: Total nitrate/ nitrite, GPx: Glutathione peroxidase]

A significant decline was shown in bone marrow BCL2 level, with significant elevation in BAX and caspase-3 levels in the irradiated rats as compared to the control. BCL2, BAX and caspase-3 exhibited a significant improvement in the irradiated group treated with BPF (Fig. 4).

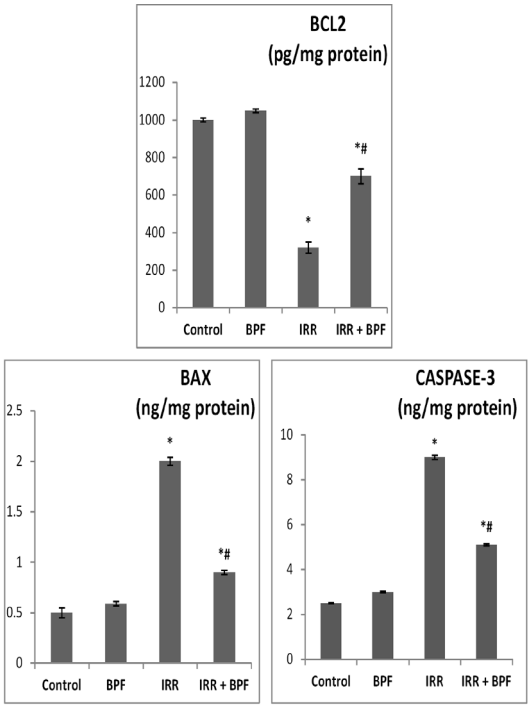


Fig. 4. Effect of BPF isolated from bee venom on bone marrow BCL2, BAX and caspase-3 in irradiated rats [Each value indicates the mean±SEM. *: Significantly different from the

control group at P<0.05, #: Significantly different from the IRR group at P< 0.05 using one-way ANOVA with Tukey–Kramer as a post-hoc test. C: Control, IRR: Irradiated rats, BPF: Bradykinin potentiating factor, BAX: Bcl-2 Associated X Protein, BCL2: B cell leukemia/lymphoma-2]

Discussion

Ionizing radiation induced cellular alterations mediated by the generation of free radicals and related reactive oxygen species (Maurya et al., 2007).

Hematological values showed a considerable drop by accumulated gamma irradiation (8Gy) in the present investigation. This decrease in RBC, WBC, platelets, and viable BM cells is most likely due to impaired cell division and obliteration of blood-forming organs (Nunia et al., 2007). Ashry et al. (2013), Klimenko & Iukhimuk (1993) reported that the deficiency in hemopoiesis and erythrocyte hemolysis was linked to increased cell membrane permeability, which resulted in the destruction of mature erythrocytes in response to gamma-radiolysis.

In the present outcomes, BPF administration showed a significant elevation of hematological indices which might be attributed to the accelerated restoration of remaining functional hematopoietic cells that are believed to be the major factor in survival post-irradiation (Meng et al., 2013). Widel et al. (2003) adduced that survival following irradiation is caused by the regeneration of the bone marrow and hemostatic systems.

Cytokines, hormone-like proteins, produced by stimulated cells and tissues, were found to protect against hematopoietic failure caused by ionizing radiation. Preclinical and clinical studies demonstrated that a broad range of cytokines can serve to accelerate bone marrow restoration following myeloablative cytotoxic drugs or radiation (Miller & Neta, 1993). Many of these cytokines such as granulocyte colony-stimulating factor (G-CSF), granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage colony-stimulating factor (M-CSF), Interleukin-6 (IL-6), IL- 11, erythropoietin (EPO), thrombopoietin (TPO), or stem cell factors (SCF) affect primarily proliferation and differentiation of hematopoietic cells (Neta, 1997).

Growth factors play a role in hematopoiesis not only by causing differentiation of stem cells toward a particular cell type, but also by inducing the proliferation of the cells (ie, increasing their numbers) and by favoring maturation of the cells (Hauke & Tarantolo, 2000). G-CSF increases the number of neutrophils capable of fighting bacteria (Nemunaitis, 1997). EPO stimulates stem cells toward the production of RBCs and is used in treating patients with anemia. IL-11 stimulates megakaryocytic progenitor stem cells and increases platelet production to prevent severe thrombocytopenia and to reduce the need for platelet transfusions after standard chemotherapy (Hauke & Tarantolo, 2000).

The cytokines' supporting impact on bone marrow cells in the restoration of hematopoietic organs might explain the accelerated recovery observed with BPF therapy. The cytoprotective ability of bradykinin (BK) particularly in oxidatively stressed cells is evident from the ability of angiotensin-converting enzyme inhibitor (ACEI) to attenuate cellular injury (Linz & Schölkens, 1992).

Bradykinin potentiating peptides (BPPs) usually show two different activities, potentiation of BK and inhibition of ACE, so decreasing Ang II production (Ferreira et al., 1999). BK-induced cAMP has a major stimulatory effect on erythropoietic proliferation (Nakai et al., 1998).

Both radiation and Ang II act *via* reactive oxygen species (ROS) generation (Robbins et al., 2002). The present results showed a decrease in GSH content and GPx activity ($P< 0.05$) with a significant increase ($P< 0.05$) in MDA, AOPP and NO levels in BM tissues by γ-irradiation. Srinivasan et al. (2007) reported that the decrease in GSH was due to its utilization by the enhanced production of ROS. Whereas, Parihar et al. (2006) attributed the increase in tissue MDA to the susceptibility of lipids to free radical attacks, irradiation-induced oxidative damage to proteins is reflected by an increase in the level of AOPP (Eskiocak et al., 2007). ROS production may result in the activation of the renin-angiotensin system (RAS). Ang II enhanced AOPP serum accumulation (Thomas et al., 2005). Ashry et al. (2012), Hasan et al. (2017) suggested that AOPP accumulation that coexisted with decreased GSH and elevated MDA support the occurrence of oxidative stress. Because of the negative effects of peroxynitrite on antioxidant systems, the interaction between oxygen and

nitrogen species has received a lot of attention (Yousefipour et al., 2010).

BPF is an ACEI and possesses potent antioxidant activity, which can scavenge oxygen free radicals and inhibit lipid peroxidation (Chen et al., 2008, Hasan et al., 2020b). Interacting of BPF with accumulated irradiation resulted in the improvement of the antioxidant power of BM as compared to the irradiated group.

It is worthy to mention that apoptosis, as a physiological contrast of mitosis, arises during the early post-irradiation period as a response to the blockade of mitotic activity and causes its abortive effect on bone marrow cellularity (El-Missiry et al., 2007; Vlasov & Kvacheva, 1998).

Apoptosis is a highly regulated form of cell death with characteristic morphological and molecular features (Eriksson & Stigbrand, 2010). In coordination with cell proliferation and differentiation, apoptosis contributes to the maintenance of hematopoietic homeostasis by regulating the size of hematopoietic lineages. Dysregulation of apoptosis in hematopoietic cells can result in many pathological conditions (Wickremasinghe & Hoffbrand, 1999). It has been suggested that the induction of apoptosis in BM cells may be primarily responsible for the induction of acute radiation syndrome in the hematopoietic system after total body irradiation (TBI) (Domen et al., 1998).

To investigate the possible role of radiation-induced apoptosis, the authors examined the BCL-2, BAX and caspase-3 levels in the BM of the irradiated rats and found that 8Gy accumulated irradiation dose induces a marked deterioration in the former parameters when compared with the corresponding normal values. Radiation results in immediate interphase apoptosis, occurring within hours after exposure (Sia et al., 2020).

BPF administration to the irradiated rats restored the levels of the apoptotic parameters BCL-2, BAX, and caspase-3 toward the normal values. In the same concern, Sancho–Bru et al. (2007) suggested that BK exerts hepatoprotective effects by increasing their resistance to apoptosis.

Conclusion

Hematopoietic defects in the BM may be prevented by BPF that can likely improve oxidative stress and have anti-apoptotic efficacy regarding accumulated doses of γ-irradiation. The present work highlights novel properties of the BPF isolated from bee venom.

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