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Radioprotective properties of eckol against ionizing radiation in mice

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Abstract **We have investigated the radioprotective efficacy of eckol, a component of brown seaweed *Ecklonia cava*, against the gamma ray-induced damage in vivo. Our results showed that eckol significantly decreased the mortality of lethally irradiated mice. The mechanisms of eckol's protection were found to include: an improvement in hematopoietic recovery, the repair of damaged DNA in immune cells and an enhancement of their proliferation, which had been severely suppressed by ionizing radiation. Thus, we propose eckol as a candidate for adjuvant therapy to alleviate radiation-induced injuries to cancer patients.**
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Keywords: Eckol; Ionizing radiation; Radioprotection; Mice

1. Introduction

Exposure to ionizing radiation induces the production of reactive oxygen species (ROS), which include superoxide, hydroxyl radicals, singlet oxygen, and hydrogen peroxide [1]. These free radicals react with critical cellular components, such as DNA, RNA, proteins, and membranes resulting in cell dysfunction and death [2]. Recently, the synthetic agents WR2721 (amifostine), OK-432, and ethiofos were investigated for their efficacy in protecting against radiation-induced tissue damage [3]. However, these agents have the potential cause serious side-effects including decreased cellular function, nausea, hypotension, and death [4,5]. Alternatively, natural plant extracts that can protect cells and tissues against ionizing radiation without obvious side-effects would be a considerable adjunct to successful radiotherapy.

Ecklonia cava, brown algae (Laminariaceae) abundant around Jeju Island in Korea, contains phlorotannin components with known biological activities [6,7]. Phlorotannin has anti-inflammatory effects [6] and protects cells from oxidative stress by scavenging intracellular ROS [7]. Phlorotannin, which is a phloroglucinol polymer found in marine algal polyphenols, has been identified in various Ecklonia species [8]. We previously reported that eckol inhibits oxidative cell damage by scavenging ROS and modulating a cellular signal pathway in lung fibroblast cells [8]. To extend these results, we tested eckol in an *E. cava* extract for the ability to protect mice from radiation-induced oxidative damage in vivo after exposure to a single dose of whole-body irradiation (WBI) in vivo.

2. Materials and methods

2.1. Preparation of eckol and irradiation of animals with ^{60}Co γ-ray

Eckol (Fig. 1) was obtained as described previously [8]. C57BL/6 mice (Orientbio, Sungnam, Korea) weighing 18–25 g each were used at 6–8 weeks of age for these experiments. These mice were housed in conventional animal facilities with the NIH-07-approved diet and water ad libitum at a constant temperature (23 ± 1 °C) according to the guidelines for the Care and Use of Laboratory Animals of the institutional ethics committee. Each mouse was placed individually in a close-fitting Perspex box (3 × 3 × 11 cm) and exposed to WBI with a ^{60}Co source irradiator (Theratron-780 Teletherapy Unit, Applied Radiological Science Institute, Cheju National University). Briefly, mice placed in the box were exposed to WBI with a dose rate of 1.5 Gy/min and source-surface distance of 150 cm, as previously reported [9,10].

2.2. Treatment of mice with eckol and survival studies

Eckol dissolved in phosphate-buffered saline (PBS, pH 7.4) was used at a dose of 10 mg/kg b.w. for intraperitoneal (i.p.) injection into the mice. The choice of this dose was inspired by the fact that, the survival rates were 86%, 86.6%, and 40%, respectively, when mice were treated with eckol at concentrations of 25, 10 or 5 mg/kg body weight (b.w.) after 9 Gy of irradiation whereas a survival rate of only 28.6% was observed in the irradiated control mice. Each mouse was injected twice, receiving the 10 mg/kg dose first at 18 h and then again at 2 h before irradiation. Additional non-irradiated and irradiated groups of mice were injected i.p. with PBS at the same volumes. The mice were randomly divided into the following four groups: (1) non-irradiated normal group; (2) irradiated control group; (3) eckol-treated group; (4) eckol plus irradiation-treated group. To determine whether eckol conferred a survival advantage after lethal WBI, the treated mice were observed daily for up to 30 days after irradiation. At 31 days post-WBI, the surviving mice were killed by cervical dislocation.

2.3. Blood sample collection and quantitation of eckol

The time required to attain the maximum concentration (T_{max}) and terminal half life ($t_{1/2}$) was determined by collecting blood samples from mice into heparinized tubes at 0.5, 1, 2, 6, and 24 h after treatment with

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Abbreviations: CFU, colony-forming unit; FITC, fluorescein isothiocyanate; Gy, gray; FACS, fluorescence-activated cell sorting; ROS, reactive oxygen species; WBI, whole-body irradiation; Con A, concanavalin A

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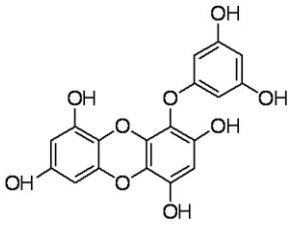

Fig. 1. The chemical structure of eckol.

eckol (10 mg/kg b.w.). The blood samples were centrifuged at $2000 \times g$ for 10 min. The resultant plasma was mixed with one-tenth volume of a preservative solution that contained 20% ascorbic acid and 0.05% Na_2EDTA in 0.4 M sodium phosphate buffer (pH 7.2). The level of eckol in the plasma was determined by HPLC with a Coulochem electrode array detector, as described previously [11]. The T_{max} and $t_{1/2}$ values were derived by visual inspection of the plasma concentration versus time profile. The T_{max} for eckol was 2 h, and the plasma concentration–time curves were fitted with $T_{1/2}$ of 17.8 h for the plasma samples of eckol-treated mice.

2.4. Endogenous colony-forming units (CFU)

An endogenous CFU assay was performed to confirm the effect of eckol (10 mg/kg b.w.) on the hematopoietic ability. The mice ($n = 3$ per group) were killed 10 days after exposure to 7 Gy of irradiation. The spleens were removed and scored with naked eyes for macroscopic colonies on the splenic surfaces [12]. The experiment was repeated three times with a minimum of three animals in each group.

2.5. Preparation of primary splenocytes

Spleens removed from test mice were the source of single-cell suspensions obtained using a cell strainer. The cells were lysed with ACK buffer, which contained 0.84% ammonium chloride, for 10 min at room temperature and washed with Dulbecco's phosphate-buffered saline (DPBS, Gibco-BRL). The splenocytes were suspended in RPMI-1640 medium (Gibco-BRL) that was supplemented with 10% fetal bovine serum (Gibco-BRL) and 100 U/ml penicillin–streptomycin (Gibco-BRL). Cell viability was determined by trypan blue dye exclusion (Sigma–Aldrich, St. Louis, MO, USA), and the purified cells (viability >90%) were used directly in the experiments.

2.6. Alkaline comet assay

An alkaline comet assay was used to determine the oxidative DNA damage induced in peripheral blood lymphocytes by 7 Gy of ionizing radiation. Peripheral blood lymphocytes were isolated from the whole blood by using Ficoll-Hypaque (Sigma–Aldrich). The basic alkaline technique was performed as described by Kang et al. [13]. The samples were observed under a fluorescence microscope and analyzed by using the Komet 5.5 program (Kinetic Imaging, Liverpool, UK). The percentage of fluorescence in the tail DNAs of 50 cells per slide was recorded. DNA damage inhibition activity (%) was calculated as: $[(A - B)/A] \times 100$.

2.7. ^{3}H-thymidine incorporation assay

To assess whether eckol stimulated the regeneration and proliferation of splenocytes damaged by irradiation, a thymidine incorporation assay was performed. The splenocytes were isolated 9 days after exposure to 7 Gy of irradiation and seeded at 4×10^5 cells/well in 96-well round-bottom microtiter plates (Nunc, Copenhagen, Denmark). After incubation in triplicate with 200 μl culture medium for 72 h at 37 °C in humidified air that contained 5% CO_2, 10 μl of Concanavalin A (Con A, Sigma) was added to the wells to give a final concentration of 5 μg/ml Con A. After incubation, triplicate wells for each experiment were pulsed for a final 18 h with 1 μCi of ^{3}H-methylthymidine (specific activity of 42 Ci/mmol; Amersham, Arlington Heights, IL, USA). An automatic cell harvester gathered the cells onto glass fiber filters. The amount of radioactivity incorporated into the DNA was determined in a liquid scintillation spectrometer (MicroBeta TriLux, Perkin–Elmer, Wallac, Germany).

2.8. Flow cytometry

To define the specific cell population stimulated by eckol, the splenocytes were analyzed by fluorescence-activated cell sorting (FACS). Mice were killed 9 days after exposure to 7 Gy of WBI, and their spleens were removed. The splenocytes (1×10^6) were harvested, and non-specific staining was inhibited by treatment with an anti-mouse IgG (Caltag Laboratories, Burlingame, CA, USA) in PBS for 15 min at 4 °C. The cells were then stained for 15 min at 4 °C with FITC-labeled anti-CD3 (145-2C11) antibody, as a specific marker for pan T cells, and FITC-labeled anti-CD45R/B220 (RA3-6B2) antibody, as a specific marker for pan B cells. All the antibodies were purchased from BD Biosciences (San Jose, CA, USA). Viable cells (20 000 per mouse, as determined by the light scattering profiles) were analyzed by using the BD FACSCalibur™ (BD Biosciences). In the cytogram, we observed three main clusters related to the major cell types of the spleen: lymphocytes, monocytes, and polymorphonuclear granulocytes. All the results shown represent three separate experiments ($n = 3$).

2.9. Statistical and pharmacokinetic analyses

The results are reported as means ± S.E. or S.E.M. The results were analyzed by using the Student's t-test, and $P < 0.05$ or $P < 0.01$ was considered statistically significant. The plasma concentration–time data for the eckol T_{max} were analyzed using the PK Solution version 2.0 software package (Submit Research Service, Ashland, OH, USA).

3. Results

3.1. Eckol improves the survival rate of mice exposed to a lethal dose of irradiation

To test whether eckol could protect mice from radiation-induced damages, eckol was administered at doses of 10 mg/kg b.w. at 2 and 18 h before exposure to 8, 9, or 10 Gy of WBI. Only 28.6% (4/14) of the irradiated, untreated group survived for 30 days after exposure to 9 Gy of irradiation. However, 86.6% (13/15) of the mice that received eckol plus irradiation survived for 30 days, which represents a significantly diminished death rate (Table 1, $P < 0.05$). In regression analysis of the survival data, the $LD_{50/30}$ value was 8.0 Gy for the irradiated, untreated control group and 9.2 Gy for the eckol plus irradiation group, generating a dose reduction factor of 1.2 (Fig. 2). No deaths occurred in the non-irradiated group or the eckol-only treatment group during the 30 days. These results demonstrate that eckol confers marked radioprotection and subsequently prolongs the survival of lethally irradiated mice.

3.2. Eckol enhances hematopoietic recovery

To confirm the radioprotective effect of eckol on hematopoietic stem cells damaged by ionizing radiation, an endogenous CFU assay was performed. The number of endogenous CFUs is considered to be an indicator of hematopoiesis, which is a

Table 1
The radioprotective effects of eckol on lethally irradiated mice

Treatment	Survival rate (%)	Survival time (days) (means ± S.D.)
9 Gy IR ($n = 14$)	28.6 ± 13.5	19.0 ± 7.9
9 Gy IR plus eckol ($n = 15$)	86.6 ± 6.0	27.3 ± 7.2*

Mice were injected with i.p. with eckol (10 mg/kg b.w.) 2 and 18 h before being exposed to 9 Gy of WBI. The term 'n' represents the total number of mice in each group. The results shown are the means ± S.D. of three independent experiments. Differences in the 30-day survival rates were calculated with the Student's t-test.
*$P < 0.05$.

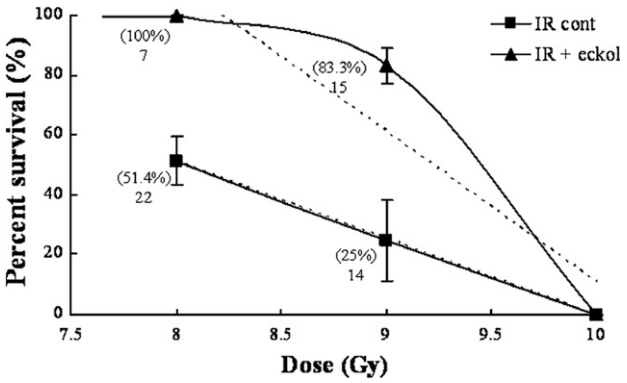

Fig. 2. The radioprotective effect of eckol on the survival of lethally irradiated mice. Mice were injected i.p. with eckol (10 mg/kg b.w.) 2 and 18 h before being exposed to 9 Gy of WBI. The results shown are the cumulative values from three independent experiments. The numbers inserted below the percentages indicate the numbers of mice per group.

critical survival factor [12]. For the eckol plus irradiation group and irradiation control group, the numbers of endogenous CFUs were 2.3 ± 0.5 and 3.5 ± 0.5, respectively ($P < 0.05$) (Fig. 3). Eckol given alone did not alter the results for the non-irradiated group (data not shown). Therefore, eckol increased the number of CFUs by about 50%, indicating the restoration of hematopoietic ability by the splenic progenitor cells.

3.3. Eckol reduces DNA damage in lymphocytes

Given that eckol is known to have ROS scavenging activity [8], we studied the influence of eckol on the DNA damage to peripheral blood lymphocytes caused by ionizing radiation using the alkaline comet assay [14]. We measured the post-irradiation DNA damage in the tails of eckol-treated (Fig. 4B) and untreated control (Fig. 4C) mice, as compared to the corresponding levels in non-irradiated normal mice (Fig. 4A). In Fig. 4D, the columns contain the percentage of tail DNA and the inhibition of activity for each group. Before irradiation, the percentage of tail DNA in the lymphocytes of mice was $8.0 \pm 4.1\%$. In contrast, after exposure to 7 Gy of WBI, their content of tail DNA increased to $42.5 \pm 8.7\%$. However, eckol treatment significantly decreased the percentage of tail DNA in lymphocytes damaged by irradiation to $14.7 \pm 5.6\%$ (Fig. 4, $P < 0.05$).

3.4. Eckol induces splenocyte proliferation and increases the populations of T and B cells

To define the precise cell population(s) stimulated by eckol, murine splenocytes were analyzed by flow cytometry. Three days after irradiation, the number of lymphocytes, monocytes, and granulocytes that had been damaged by exposure to 7 Gy of WBI increased by 14.9%, 90.4%, and 85.6%, respectively, in the eckol-treated mice, as compared to the untreated control groups (Fig. 5A). Next, the proliferation of splenocytes was assessed by measuring the incorporation of ^{3}H-thymidine 9 days after irradiation to verify the survival benefit conferred by eckol upon radiosensitive immune cells. As illustrated in Fig. 5B, eckol significantly increased the thymidine incorporation of splenocytes, i.e., by as much as twofold in 9 days, in comparison with the splenocytes of irradiated mice without eckol treatment ($P < 0.05$). The background proliferation was 411 ± 92 cpm. When measured as a positive control, Con A-induced proliferation was $31\,004 \pm 4292$ cpm. Additionally, the numbers of $CD3^+$ pan T cells and $CD45R/B220^+$ pan B cells increased in the eckol-treated groups, as compared to the untreated control groups after irradiation (Fig. 5C). In particular, the number of $CD3^+$ T cells increased from 32.9% to 47.5%, which indicated a 44.3% increase against the untreated controls (Fig. 5C, upper panel). Moreover, the $CD45R/B220^+$ pan B cell population expanded from 17.2% to 21.0% (27.6%) (Fig. 5C, lower panel). These results confirm that eckol enhanced immunoprotection by increasing the recovery rates of specific populations of immune cells.

4. Discussion

In the present study, we demonstrate that eckol effectively protects mice against potentially lethal irradiation and prolongs the survival of lethally irradiated animals. The survival time for lethally irradiated animals can be lengthened by various manipulations, such as inhibition of free radical generation or acceleration of their removal, enhancement of DNA repair, replenishment of dead hematopoietic cells, and stimulation of

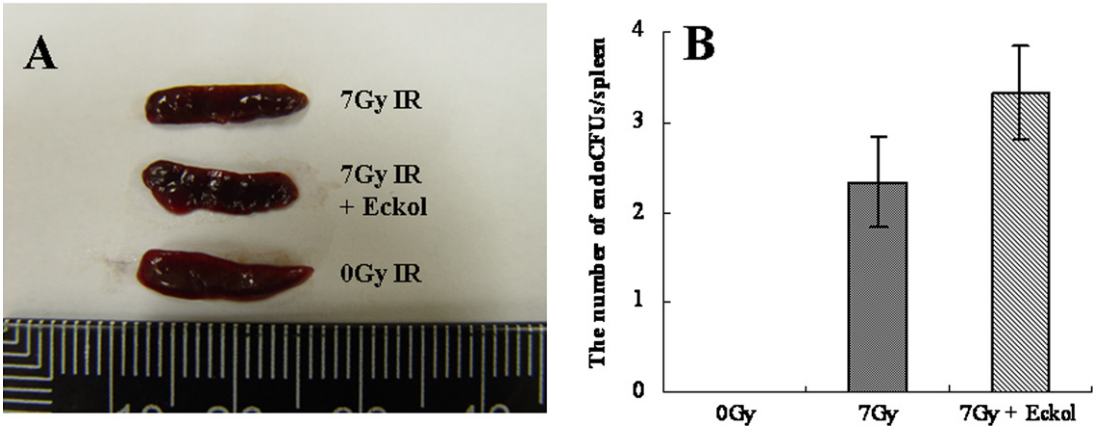

Fig. 3. The effect of eckol on endogenous spleen colonies of 7 Gy-irradiated mice. (A) Photograph of spleens from non-irradiated, irradiated, and eckol-treated plus irradiated mice. (B) CFU counts on the splenic surfaces 10 days after exposure to 7 Gy of WBI. Eckol (10 mg/kg b.w.) was injected i.p. 2 and 18 h before irradiation. The data represent the mean ± S.E.M.

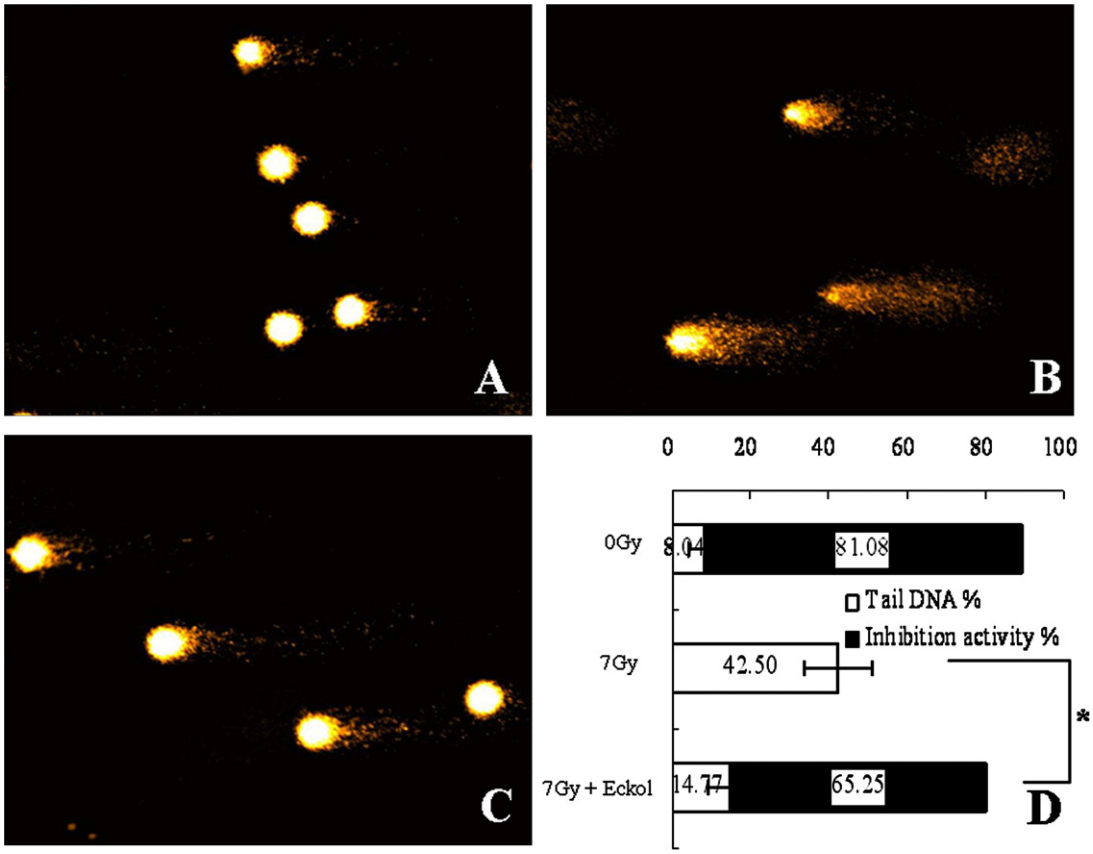

Fig. 4. The effect of eckol on DNA damage induced by irradiation of peripheral blood lymphocytes, as assessed with the alkaline comet assay. Mice were exposed to: (A) 0 Gy of irradiation; (B) 7 Gy of irradiation; (C) 7 Gy of irradiation plus eckol treatment (10 mg/kg b.w., i.p.); (D) percentage of fluorescence in the tail DNAs and inhibition activity of each group ($^{*}P< 0.05$).

immune cell formation or activity [15]. However, no other reports to date have described the protective effect of eckol against radiation-induced tissue damage or the underlying mechanism of that effect in vivo.

Radiation-induced oxidative damage to DNA encompasses several types of base damage and single- or double-strand breaks [16]. Using the comet assay, we observed that eckol treatment significantly decreased the percentage of tail DNA fluorescence in the peripheral blood lymphocytes of irradiated mice, which indicates that eckol protected cells against radiation-induced damage. This decrease in DNA breakage seen in our eckol-treated, irradiated mice underlines the cytoprotective efficacy of this compound in vivo, which may be attributed to its ROS scavenging activity [8]. These functions of eckol are likely to be factors in the prolonged survival of the lethally irradiated animals documented here.

Hematopoietic stem cells are highly sensitive to ionizing radiation as well as chemotherapeutic drugs administered to cancer patients. In fact, myelosuppression and hematopoietic dysfunction are the most common clinical complications of these treatments [17]. Therefore, an important adjunct to their use is to promote the recovery of hematopoiesis [18]. In our experiments, mice treated with eckol recovered from WBI as established by their increased numbers of splenic CFUs in comparison with the irradiated controls that did not receive eckol. The enhancement of endogenous CFUs in mice that received eckol before undergoing irradiation indicates that eckol protects and/or stimulates the proliferation of hematopoietic stem cells. This important mechanism of eckol-mediated survival described here appears to have a strong potential for clinical application.

Furthermore, eckol stimulated the proliferation of splenocytes that had been reduced in number by irradiation and facilitated the repopulation of specific immune cell types, including $CD3^{+}$ (all mature T cells) and $CD45R/B220^{+}$ (pan B cells) cells. These results indicate that eckol protects against radiation-induced damage by stimulating the proliferation and maturation (differentiation) of immune cells. This stimulatory effect of eckol on the differentiation and maturation of T and B cells may promote the synthesis of cytokines and antibodies. Radiation-induced destruction of the lymphoid and hematopoietic systems causes bone marrow suppression and depletion of peripheral blood lymphocytes, leading to a loss of immune function. Subsequently, the exposed individuals become susceptible to opportunistic pathogens, some of which cause mortality [19]. Therefore, the immunostimulatory potential of eckol is an important component of its radioprotective efficacy.

In summary, our current results demonstrate that eckol reduces the mortality rate of mice exposed to a lethal dose of WBI by accelerating hematopoietic recovery. Furthermore, in radiosensitive immune cells, eckol enhances the repair functions suppressed by ionizing radiation. Taken together, these attributes contribute to prolonged survival after an exposure to a potentially lethal dose of radiation. We propose that eckol

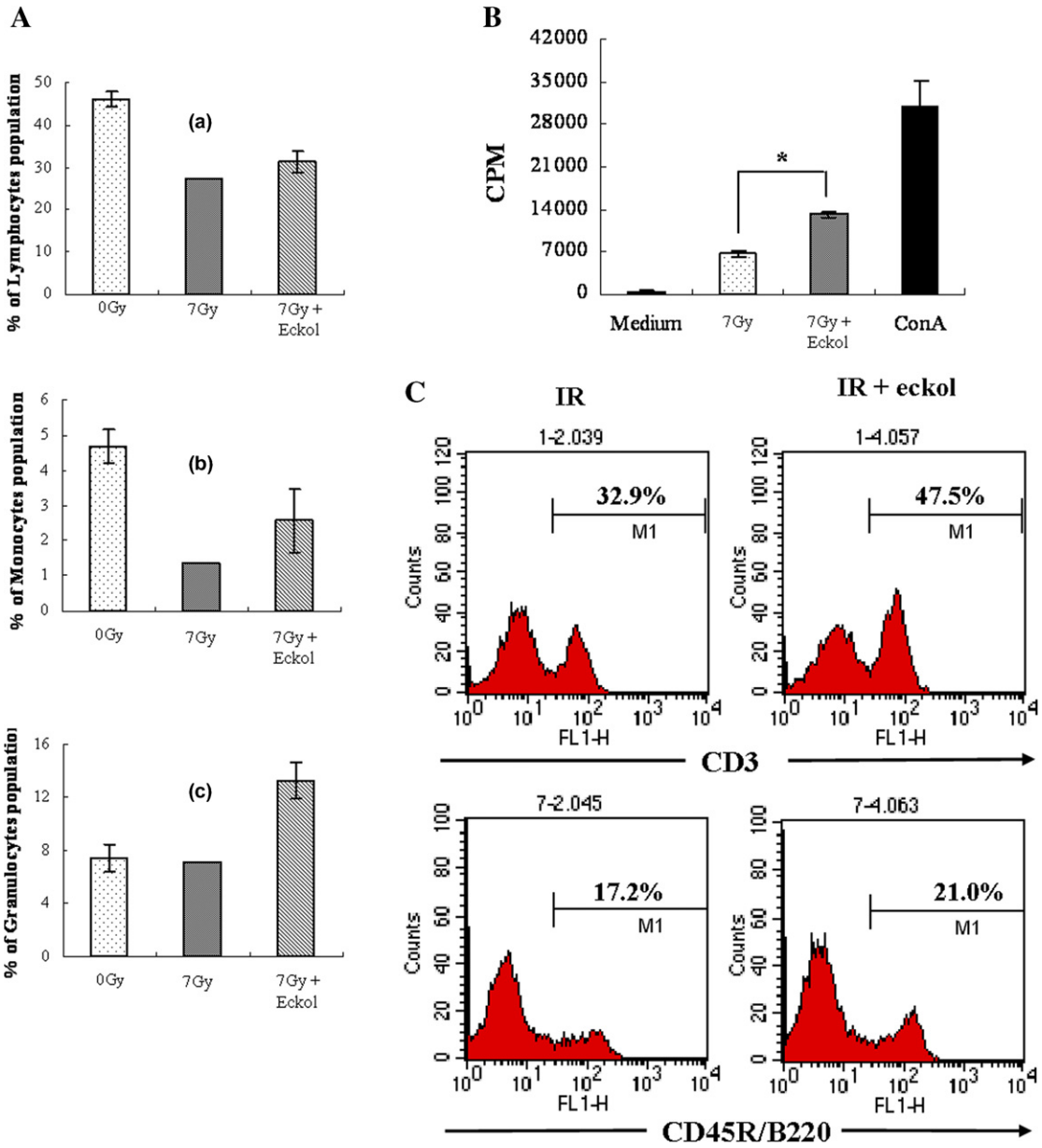

Fig. 5. Eckol contributes to the restoration of immune cell populations suppressed by ionizing radiation. Splenocytes were separated 9 days after the mice received 7 Gy of irradiation. Eckol was administered i.p. 2 and 18 h before irradiation. (A) The columns indicate lymphocytes (a), monocytes (b), and granulocytes (c). Each data-point represents the mean ± S.E.M. ($^{*}P < 0.05$, $^{**}P < 0.01$). (B) The values for proliferative responses are the mean ± S.E.M. of cpm ($^{*}P < 0.05$). (C) Phenotypic analysis of proliferating lymphocytes after eckol treatment. The expression level of each cell type was measured by FACS using anti-CD3 and CD45R/B220 monoclonal antibodies.

is a candidate for adjuvant therapy to alleviate radiation-induced damage to cancer patients.

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