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Hematological and gastrointestinal protection effects of ginger rhizome on whole-body exposure of gamma radiation in mice

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Highlights

- **This study showed that ginger extract has protective effects against radiation exposure.**
- **The study also showed the protective effects of ginger extract against the haematological and gastrointestinal systems.**
- **This study would open doors for future research in many fields.**

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ABSTRACT

Radiation can induce acute radiation sickness in different ways. In this study, we investigated the radio-protective efficacy of ginger extract (GE) against the gamma (γ) ray-induced damage on mice. The source of gamma radiation was cobalt 60 (Co-60). GE was administered to mice at a dose of 5 ml/kg intraperitoneally (IP) for 5 consecutive days before exposing them to 8 Gray (Gy) (unit of ionizing radiation dose) of Co-60-gamma-radiation. Mice treated with GE before irradiation (pretreated group) showed a significant decrease in the mortality of lethally irradiated mice. Moreover, spleen weight was significantly increased. Besides, the GE treatment facilitated the recovery of white blood cells (WBC), and hemoglobin (HGB) cell number. Altogether, the findings indicated that ginger has remarkable effects on mice against hematopoietic suppression and gastrointestinal damage caused by irradiation.

1. Introduction

Normally, a balance is found between the generation of reactive oxygen species (ROS) which compose of superoxide, hydroxyl radicals, and hydrogen peroxide (Ewing and Jones, 1987) and the antioxidant systems in the cell (Forman and Fisher, 1998, Ho *et al.*, 1998). Upon exposure of cells to ionizing radiation, ROS is overly produced which results in an imbalance between pro-oxidants and antioxidants (Dasgupta *et al.*, 1997). The free radicals react with critical cellular components, such as DNA, RNA, proteins, and membranes causing oxidative stress (Cerutti, 1985). This leads to cell dysfunction such as bone marrow suppression and depletion of blood cells in the peripheral blood and then death (Patt *et al.*, 1949).

The utilization of chemical agents to protect mammals against damage induced by irradiation has started in 1949 (Patt *et al.*, 1949). It has been stated that cysteine could protect rodents against sickness and mortality induced by radiation (Patt *et al.*, 1949). Several drugs of synthetic origin have now been used for this purpose. However, they may cause serious side-effects including decreased cellular function, nausea, hypotension, and death (Bogo *et al.*, 1985; Satoh *et al.*, 1982; Sweeney, 1979).

The use of medicinal plants has a long history in the treatment of various diseases. It has been found that herbs were safer and less toxic than synthetic compounds. However, since no ideational radio-protective composites are available, there was a growing interest in the pharmacological evaluation to regard herbs as an option to the synthetic compounds (Pietta *et al.*, 1998). Many studies have reported that plants have radio-protective effects such as decreasing mortality, anti-oxidative activity, improving hematopoietic function. (Jagetia *et al.*, 2003; Jagetia *et al.*, 2006; Jagetia *et al.*, 2004; Kumar and Kuttan, 2004; Ohnishi *et al.*, 1990; Samarth, 2004; Sancheti and Goyal, 2007).

The rhizome of *Zingiber officinale*, also named as ginger, is used as a spice and flavoring agent. Indians, Chinese, and Arabs have widely used rhizome of ginger in several medicinal preparations (Chemexcil, 1992; Grzanna *et al.*, 2005; Nadkarni, 1976; Tsai *et al.*, 2005). The rhizome of *Zingiber officinale* contains several compounds including phenols like gingerol, shogaol, zingerone, and paradol (Chemexcil, 1992; Rastogi and Mehrotra, 1998). Most of these compounds possess antioxidant property, free radical scavenging activities (Aeschbach *et al.*, 1994; Tanaka, 1994), which increase antioxidant enzymes (Kong *et al.*, 2000), and decrease lipid peroxidation (Ahmed *et al.*, 2000). Du and his colleagues stated that gingerol possessed the radio-protective effect on the immune system in mice pre-treated with gingerol (Du *et al.*, 2010). Several researchers have also shown that the rhizome of *Zingiber officinale* acted as a radio-protective agent (Jagetia *et al.*, 2003, Jagetia *et al.*, 2004). Ginger extract, even at high concentration (up to 100 mg/kg), did not show any side effects on blood glucose, blood coagulation, blood pressure, or heart in the rat (Weidner and Sigwart, 2000).

Because of the properties that were attributed to the ginger rhizome, in the present study, the radio-protective effect of the hydroalcoholic extract of ginger (*Zingiber officinale*) was studied in

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mice after exposure to whole-body irradiation with different doses of Gy radiation to support previous studies.

1. Materials and Methods

1.1. Animals

Swiss albino mice weighing 25–30 grams (gm) from colony obtained from the animal house in the faculty of medicine, Benghazi University, Benghazi Libya. The albino mice were protected in considerable conditions of temperature (23+2QC), light (14 and 10 hours. of illumination and dimness, respectively), and humidity (50+5%).

1.2 Preparation of ginger extract and irradiation of animals

Ginger Rhizome was bought from the local market in Benghazi. Four hundred grams of Ginger were washed, dried, powdered, and extracted with 1000 ml of 30/70 of the hydroalcoholic solution, by the maceration method. The obtained extract was filtrated by vacuum and then evaporated into semi-solid form, by Vacuum Rotary Evaporator Apparatus (Onyeagba *et al.*, 2004). The residue was dissolved into distilled water (5 ml/Kg), just before administration. The lethal dose and the therapeutic dose, that used in these experiments, were chosen according to previous studies (Wu *et al.*, 1990).

Mice were irradiated by Co-60-gamma-radiation in the Radiotherapy Department, at Benghazi Radio-diagnosis and Radiotherapy Centre (BRRC). Un-anesthetized mice were placed in well ventilated elastic cages and irradiated in groups of 10 mice each. The whole body was exposed to Gamma radiation at 77.7 centimeters (cm) from the delivery source (source-skin distance (SSD)), the size of the field was 30x30 cm, at a radiation dose rate of 1.028 GY/min. The mice were irradiated with a total dose of 8 GY once. The lethal dose used in these experiments was stated according to previous studies (Padwal Desai *et al.*, 1987).

1.3 Treatment with ginger extract and survival studies

Forty mice were divided into four groups; each group consisted of 10 mice. Control and radiation groups were given distilled water at a dose of 5ml/kg for five consecutive days by intraperitoneal route (IP). Pretreated and ginger groups were given ginger extracts at a dose of 10 mg/kg for five consecutive days by IP route. One to two hours after injections, the mice in radiation and Pretreated groups were exposed to gamma radiation at dose 8 Gy. The numbers of mice surviving in all four groups were recorded for the next 30 days.

1.4 Spleen and body weights

The difference in body weight of each group was calculated by subtracting the survived mice's body weight from the weight of the same mice treated on the starting day. At the end of the experiment; both survived and died animals were sacrificed by cervical dislocation and their spleen were extracted and weighted for further analysis.

1.5 Hematological study

From each mouse, the blood was drained into a vial containing EDTA. Complete blood counts (CBC) were identified at five, ten, and thirty days for survival animals post-irradiation.

1.6 Demonstration of dose reduction factor (DRF)

Both pretreated and Radiation groups were subjected to three doses of whole-body gamma radiation (6, 8, and 10 Gy). The groups were observed for continuous thirty days. By the end of this period, the percentage of survived mice exposed to different radiation doses was applied to graph survival-dose response curves.

1.7 Statistical analysis

Application of Dunnet's test/Tukey's test next to an analysis of variance (ANOVA) was performed with Graph Pad Prism for our statistical analysis. When P values were < 0.05, they considered statistically significant. Regression analysis was done to obtain LD 50/30 values and to demonstrate the dose reduction factor (DRF).

1.8 Results

1.8.1 Survival Study and body weight

It was observed that the difference between the initial and final mice weight was not significant in the control group as compared to the ginger group as shown in Fig. 1A. However, the same figure revealed a significant difference between the control and radiation groups. Although the animals in the pretreated group gained some weight, the difference was not significant as compared to animals in the radiation group (fig1A). In the current study, although there was a significant reduction in survivability in the pretreated group as compared to the control group, the survivability was higher in the Pretreated than in the radiation group (Fig. 1B).

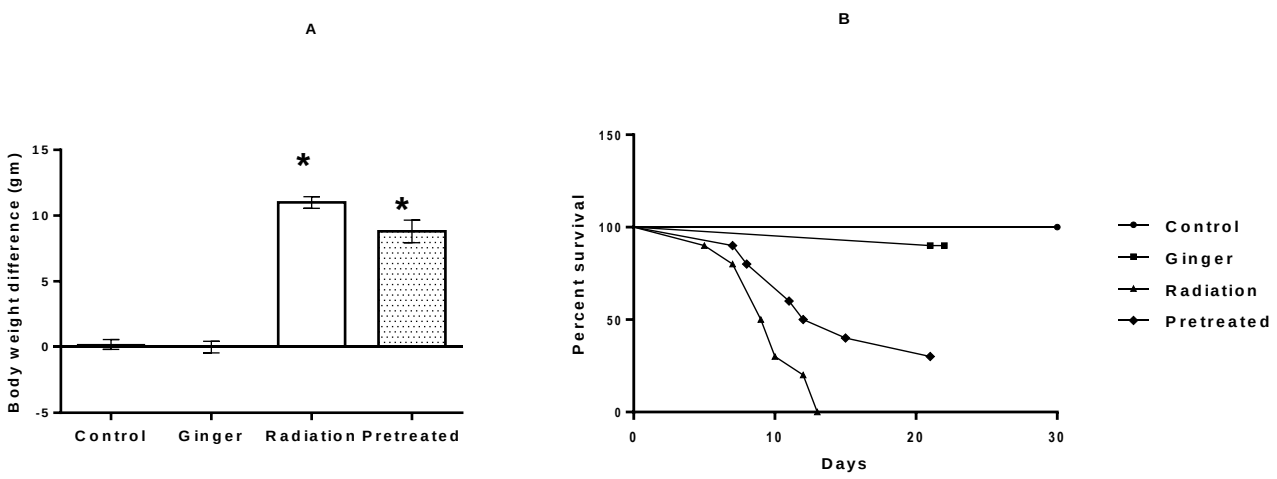

Fig. 1. The effect of ginger extract on (A) body weight difference and (B) survivability in mice exposed to 8 Gy radiation.
** indicates a significant difference as compared to the control group (p<0.001). Values are given as mean ± SD of six animals.*

1.8.2 Hematological study

In the current experiment, we assessed the protective activity of the ginger extract against hematopoietic tissue injuries induced by radiation by measuring spleen weight and analyzing hematological parameters. According to the results demonstrated in Fig 2A, there was a significant change in the weight of the spleen of mice in the control group as compared to the pretreated group. However, the shrinking in weight of the spleen of mice in the radiation group as compared to the pretreated group was also significant.

As shown in Fig. 2B, hemoglobin (HB) levels in the pretreated group were significantly dropped on day thirty after radiation exposure as compared to the control group. Whereas, the changes in HB levels on days five and ten were not significant. On the contrary, the change in HB levels on day ten was significantly decreased in radiation as compared to the control group. However, no animal in the radiation group could survive until day thirty. Thus, the comparison of HB levels was not done on that day (Fig. 2B). Furthermore, the same figure reveals that there was no significant change in HB levels on days five, and ten after exposure to gamma radiation in the pretreated group compared to the radiation group.

Fig. 2C shows a significant change in the white blood cells (WBC) count on days five and ten in the radiation group as compared to the control group. The WBC count in the pretreated group also decreased significantly on days five, ten, and thirty after exposure to gamma radiation. Although there was an increase in the count of WBC on day thirty in the pretreated group, the value could not reach the normal level (Fig. 2C). The WBC count was also elevated on days five in the pretreated group as compared to the radiated group. However, the elevation was not significant.

Platelet counts on day five, and ten after radiation in pretreated and radiation groups decreased significantly as compared to the control group (Fig. 2D). Besides, the platelet counts reached a normal level on day thirty in the pretreated group. Therefore, the change of the platelet level was not significant as compared to the control group (Fig. 2D).

1.8.3 Dose reduction factor

When exposed to different doses of gamma radiation, pre-treatment of GE ameliorated the survival percentage of rodents. GE pretreatment impeded mortality completely at 6 Gy. However, at 8 Gy, no animal deceased before day 7 and 50 % of the dying occurred from day 7 to day 14. Thirty percent of animals survival was observed after 30 days of observation (Fig. 3). In addition, at a dose of 10 Gy, the death of the animal stared at day 4, and all animals died within 14 days post-radiation (Fig. 3). The LD50/30 of the irradiation group and the pretreated (*ginger* and radiation) group of animals was determined by regression analysis. In our study, GE pretreatment provided a dose reduction factor (DRF) of 1.14 (Fig. 3).

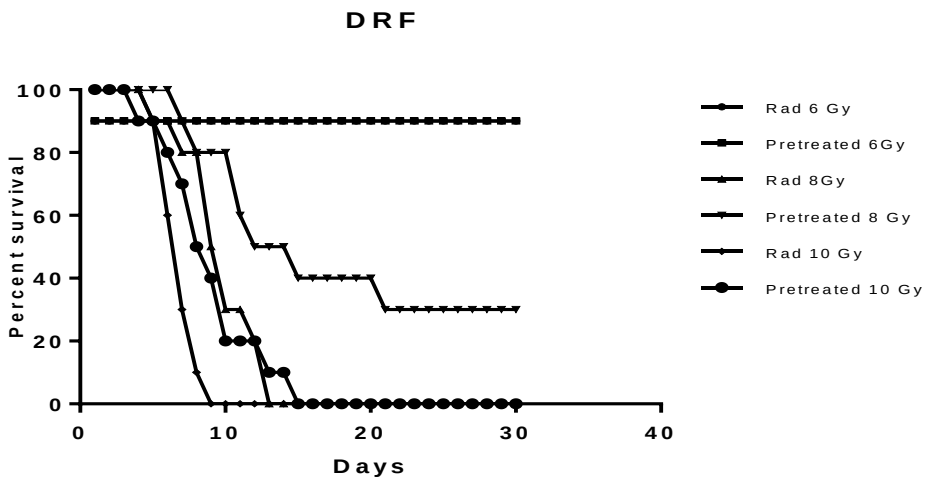

Fig. 3. Measurement of DRF after administration of GE on mice exposed to different doses of radiations

2 Discussion

Radiation could damage all the systems of the body. Destruction of the hematopoietic system is considered as a major cause of mortality after exposure to acute radiation (Casarett, 1968). The gastrointestinal damage may also contribute to mortality post-irradiation (Casarett, 1968). A significant loss of weight, vomiting, and diarrhea were reported as an important symptoms of gastrointestinal syndrome post-irradiation (Griffiths *et al.*, 1999). In addition, hemopoietic syndrome can be induced even by low doses of irradiation and is manifested by hemopoietic stem cell depletion and ultimately by the depletion of mature hemopoietic cells (Jagetia *et al.*, 2003). The organ weight is also an important indicator of the developmental levels and functions of the organ. The spleen is the largest immune organ and another important hematopoietic organ. Radiation could decrease spleen's size, weight, and the survival rate of splenocytes (Du *et al.*, 2010).

Although the sensitivity of the bone marrow stem cells to radiation is more than the sensitivity of intestinal crypt cells, the early mortality in post irradiated animals occurs as a result of gastrointestinal disturbance. While, the death from hemopoietic suppression happens from days 11 to 30 (Bond *et al.*, 1965). This may be attributed to a longer transient time that the peripheral blood cells possess than the intestinal cells (Bond *et al.*, 1965, Uma Devi and Ganasoundari, 1995). Additionally, the epithelial cells of the gastrointestinal system should be completely regenerated and restored after 7 days post-irradiation. Therefore, mortality in mice living more than this period cannot be caused by damage to the gastrointestinal epithelium (Potten, 1990). It is also stated that the gastrointestinal mortality is attributed to large doses of ionizing radiation (Dan *et al.*, 2010). This has been observed in the present study, which is consistent with the results of the previous studies. We found that 50% and 100 % of mice received 8 and 10 Gy of gamma radiation, respectively died before day 10 of the experiment. It was also noticed that the maximum suppression of hemopoietic stem cell post 8 Gy of gamma radiation was during the day 10. This may suggest that early death was due to gastric damage, especially it was accompanied by significant weight reduction and the late mortality was due to the destruction of the hematopoietic system.

Ginger is a dietary ingredient that possesses several properties (Chemexcil, 1992, Nadkarni, 1976; Warrier *et al.*, 1996). The present study aimed to evaluate the radioprotective activity of ginger in mice whole-body to various doses of gamma radiation. After

many radiation doses, the increase in the survival rate of mice treated with GE indicates the efficacy of ginger in lowering of deaths from both the GI and bone marrow syndromes. The radio-protective effect of GE was demonstrated by determining the LD50/30 (DRF=1.14).

In the present observation, GE pre-treatment prevented irradiated mice from death before the first 7 days. This might indicate that ZOE protects against radiation-induced gastrointestinal damage; thereby a survival improvement of mice is noticed. It has also been observed that most of the animal death occurred after day 7 when they were exposed to 8 or 10 Gy gamma radiations. This mortality, as reported by Potten, can be attributed to hematopoietic syndrome (Potten, 1990). It has been found that irradiated and GE pre-treatment animals showed only 70 % mortality in comparison to 100% mortality in the irradiated animals. These results indicate that GE pre-treatment has provided some protection against hematopoietic death.

It was reported that "a significant deficit in the hematological constituents of peripheral blood in animals of the irradiation radiation group was observed" (Deng *et al*., 2005). In the present study, the number of blood cells in 8 Gy radiation plus ginger treated groups was higher than the radiation groups. It is also noticed in the current study that spleen weight is significantly improved by the administration of ginger in irradiated mice. Therefore, it is suggested that ginger can protect the hematopoietic systems against free radical generated by ionizing radiation and boost the reconstruction of hematopoietic and immune function and consequently reduce deaths in these mice (Heda and Bhatia, 1986).

The reduction of the GI symptoms such as nausea, vomiting, gastrointestinal hemorrhage, in addition to gaining of body weight of mice by using of ginger may be due to the protection of the intestinal epithelium (Gong *et al*., 1989, Meyer *et al*., 1995). Since it was reported that the active ingredients of ginger inhibit gastric ulcerations that chemically induced in rats (Al-Yahya *et al*., 1989, Wu *et al*., 1990, Yamahara *et al*., 1992, Yamahara *et al*., 1988, Yoshikawa *et al*., 1992), therefore, they allow a perfect absorption of nutrients and result in increased survival rate during the first week.

In summary, our study provided evidence that ginger hydroalcoholic extract protects animals against radiation-induced sickness and acute damage to gastrointestinal and hematological organs and death. This study suggested that ginger is a promising candidate for a radio-protective agent. Further studies are needed to investigate the exact mechanism of action of this agent in clinical practice.

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