Academic Sciences

International Journal of Current Pharmaceutical Research

ISSN- 0975-7066 Vol 5, Issue 4, 2013

Research Article

PROTECTIVE ROLE OF *EMBLICA OFFICINALIS* LINN. AGAINST RADIATION AND LEAD INDUCED HAEMATOLOGICAL CHANGES IN SWISS ALBINO MICE

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Received: 21September 2013, Revised and Accepted: 30 September 2013

ABSTRACT

The aim of present study was to evaluate the protective effect of *Emblica officinalis* against radiation and lead induced haematological changes in the Swiss albino mice. For the purpose 6-8 weeks old male mice from each of the experimental groups were exposed to 6.0 Gy of gamma rays with and without lead acetate treatment. The experimental animals were given *Emblica* seven days prior to irradiation or lead acetate treatment. The animals were autopsied after 1, 2, 4,7,14 and 28 days of post- treatment intervals by cervical dislocation. After sacrificing the animals the blood was collected by cardiac puncture in heparinized tubes for various haematological studies. The value of RBC, WBC, Haemoglobin and PCV were found to decrease up to day-14 in non drug treated groups (II, III and IV) there after they increased on day-28. The values decreased up to day-7 in *Emblica officinalis* groups (V, VI, and VII) thereafter increased up to day-28. After combined treatment of radiation and lead acetate synergistic effects were observed. The *Emblica* treated animals exhibited less severe damage as compared to non-drug treated animals at all the corresponding intervals. An early and fast recovery was noticed in *Emblica officinalis* pretreated animals. Thus, it appears that *Emblica* is potent enough to check lead and radiation induced haematological changes in the Swiss albino mice.

Keywords: Radiation, Lead, Blood, *Emblica* , Mice.

INTRODUCTION

Our universe has diverse kinds of radiation. These radiations have influence the formative processes of our earth's biological regime and enabled it to diversify its fauna and flora in various ways. When radiation fall upon any object on the earth's surface, they give away some or whole of their energy to the atoms of the materials through which they travel.

The problem of radiation hazard to living beings has risen due to an increasing use of nuclear energy in industrial, medical, engineering and scientific research. The inadvertent exposure of human to radiation alters the physiological and metabolic functioning of specific body organs by causing ionization and excitation of molecules, leading to the formation of free radicals. Free radicals are believed to play a role in more than sixty different health conditions including ageing process, cancer, radiation damage, atherosclerosis etc.[1]

Apart from ionizing radiation human beings are continuously exposed to a wide range of metallic pollutants, which are released in to the environment by the mining, smelting, discharging, and industrial, agriculture and domestic wastes burning fossil fuel and using pesticides.

Lead is absorbed by the gastrointestinal tract via food, beverage, soil and dust. Dietary factors, nutritional status, chemical form of the metal and patterns of food intake affect lead absorption. In humans, lead causes a wide range of biological effects depending upon the level and duration of exposure. It affects several organs and system including nervous renal, reproductive, hematological and immune system.[2-4]

After whole body exposure manifestations of injury to mammalian tissue are well reflected in peripheral blood. Changes in blood cell counts still considered the most sensitive biological evidence of excessive acute exposure to both external and internal irradiation. This is because of high sensitivity of blood and blood forming tissue to ionic radiation.

Emblica officinalis Gaertan (syn. *Phyllanthus Emblica* Linn.) family – Euphorbiaceae is being extensively used in traditional Indian system of medicine and is a constituent of several poly-herbal preparations. Brahma rasayan, which contains *Emblica* is reported to have an excellent radio protective activity in animal models as well as human volunteers undergoing radiotherapy.[5-6]

Emblica is an excellent antioxidant and free radical scavengers. It helps in protecting the skin from damaging effect of ultra violet radiation. *Emblica* was found to be hepatoprotective, anti-diabetic and reported to reduce to the ulcer of the stomach. The poly phenols such as ellagitannins, phyllembin, ellagic acid, trigalloylglucose, phyllantidin, nucleic acid, emblicannin and furosin are reporterd to be present in *Emblica.*[7-11]

MATERIALS AND METHODS

In the present investigation, protective effects of *Emblica officinalis* Linn. Against Lead and radiation induced haematological changes in Swiss albino mice have been studied.

Maintenance of Animals

For the study, adult healthy male Swiss albino mice (6-8 weeks old) were procured from Lala Lajpat Rai University of Veterinary and Animal Sciences, Hisar (India). The animals were kept in polypropylene cages. They were fed with standard mice feed and water was given *ad libitum*. The cages were cleaned daily. The temperature of the room was maintained between 22-27ºC. The Govt. Dungar College, Bikaner is registered under CPSCEA, Chennai (Registration no. 1066/ac/07/CPCSEA) and has its own Institutional Animal Ethics Committee (IAEC). The experiments mentioned in the research paper were conducted strictly under the supervision of IAEC of the college.

Lead

Lead salt in the form of Lead acetate was used for the present study. It was purchased from SDS chemicals, India.

Emblica (Amla)

Fresh fruits of the *E. officinalis* were cleaned, cut into small pieces, air dried, powered and extracted with double distilled water (DDW) by refluxing for 36 hrs. (12 hrs.x 3). The extract thus obtained was vacuum evaporated so as to make it in powder form. The extract was redissolved in DDW just before oral administration. An approximate 38% yield of the extract was obtained. The drug was given from seven days prior to Lead acetate treatment or irradiation.

Source and procedure of irradiation

Cobalt-60 gamma radiotherapy source (Theratron) of AECL make, obtained from Canada was used to expose the animals. This facility was provided by the Radiotherapy Department of Prince Bijay Singh

Memorial Hospital, Bikaner (Rajasthan). The animals were irradiated at the dose rate of 0.82 Gy/min. The dose was calculated at the mid point by multiplying dose rate and tissue air-ratio. The tissues of Swiss albino mice were assumed to be equivalent to human soft tissues.

Plan of experimentation

The animals were divided into following groups:

Group – I The animals of this group were Sham-irradiated and served as normal group.

Group – II The animals of this group were fed with Lead acetate (20 ppm) orally *ad libitum* up to the end of the experiment.

Group – III The animals of this group were exposed to 6.0 Gy of gamma rays from Co[60]source at the dose rate of 0.82 Gy/min.

Group – IV The animals of this group were orally fed with Lead acetate at the dose rate of 20 ppm and also exposed to 6.0 Gy of gamma radiation.

Group – V The animals of this group were orally fed with Lead acetate at the dose rate of 20 ppm and were also administered *Emblica* orally for seven days prior to Lead acetate treatment and continued up to the last autopsy interval.

Group – VI The animals of this group were exposed to 6.0 Gy of gamma radiation from Co[60] source. The *Emblica* was given seven days prior to irradiation and continued up to last autopsy interval.

Group – VII The animals of this group were orally fed Lead acetate at the dose of 20 ppm and also irradiated with 6.0 Gy of gamma radiation. The *Emblica* was given orally for seven days prior to irradiation and lead feeding till the last autopsy day of experiment.

Autopsy of the animals

Five animals from each group (II to VII) were autopsied by cervical dislocation at each post-treatment interval of 1, 2, 4,7,14 and 28 days. Five sham-irradiated animals (group-I) were also autopsied. Prior to autopsy the animals were weighed. Immediately after the autopsy the blood was collected by cardiac puncture in heparinized tubes for various haematological studies.

Haematological Parameters

The various haematological parameters estimated were as follows:

I Red blood corpuscles (R.B.C.)

II White blood corpuscles (W.B.C.)

III Haemoglobin (Hb)

IV Packed cell volume (PCV)

RESULTS

R.B.C (Red blood corpuscles)

The value of RBC showed a decreasing trend in the non drug treated groups II, III and IV in the present investigation. The value declined significantly ($p<0.02$) on day-1 and continued to decrease up to day -14. On day-28, the value increased significantly ($p<0.01$) but it was lower than that of the normal value. In the drug treated groups V, VI and VII also, the value declined from day-1 to day-7. On day-14, the value increased and continued so up to day-28. But decrease in the value was comparatively lesser as compared to the non-drug treated animals (fig.1).

W.B.C (White blood corpuscles)

The value of WBC also exhibited a trend of decrease in all the groups. The value declined on day -1 in the non-drug treated groups II, III and IV. The value further declined on days 2 and 4 and continued to decline up to day-14 significantly ($p<0.001$). On day-28, the value increased but still the difference in value was significant ($p<0.001$) in comparison to the normal value. In the *Emblica* treated groups V, VI, and VII the value of WBC declined up to day- 7 then increased on day -14 and continued so up to day-28. In the *Emblica* treated groups the decrease in the value was comparatively lesser as compared to the non drug treated groups (fig.2).

Haemoglobin

The haemoglobin content reduced on day-1 in all the groups. This decline was continued up to day-14 in non-drug treated groups against day-7 in the drug treated groups. Thereafter, it increased up to day-28 without reaching to the normal (fig.3).

PCV (Packed Cell Volume)

The packed cell volume showed a decreasing trend in all the groups in the present investigation. The PCV decreased on day-1 and continued so up to day-14 in the non-drug treated groups II, III and IV against day- 7 in drug treated groups V, VI and VII. Thereafter a rise in the value was observed up to day-28 (fig.4).

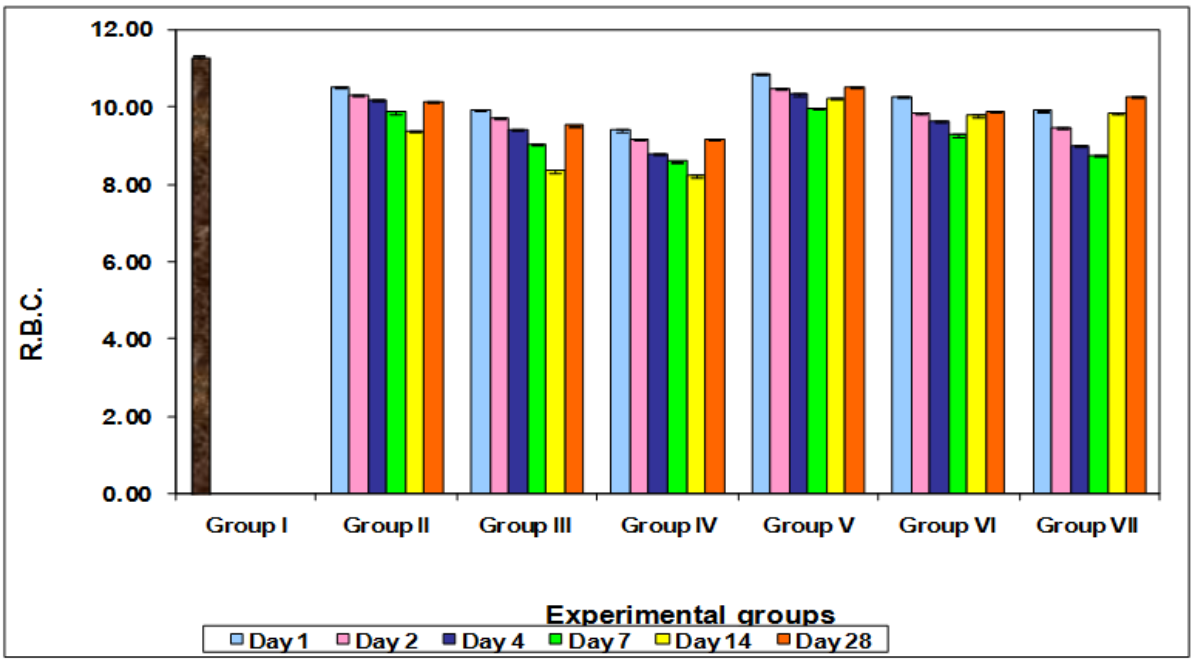

Fig. 1: Variation in the values of RBC (thousand/Cu.mm)

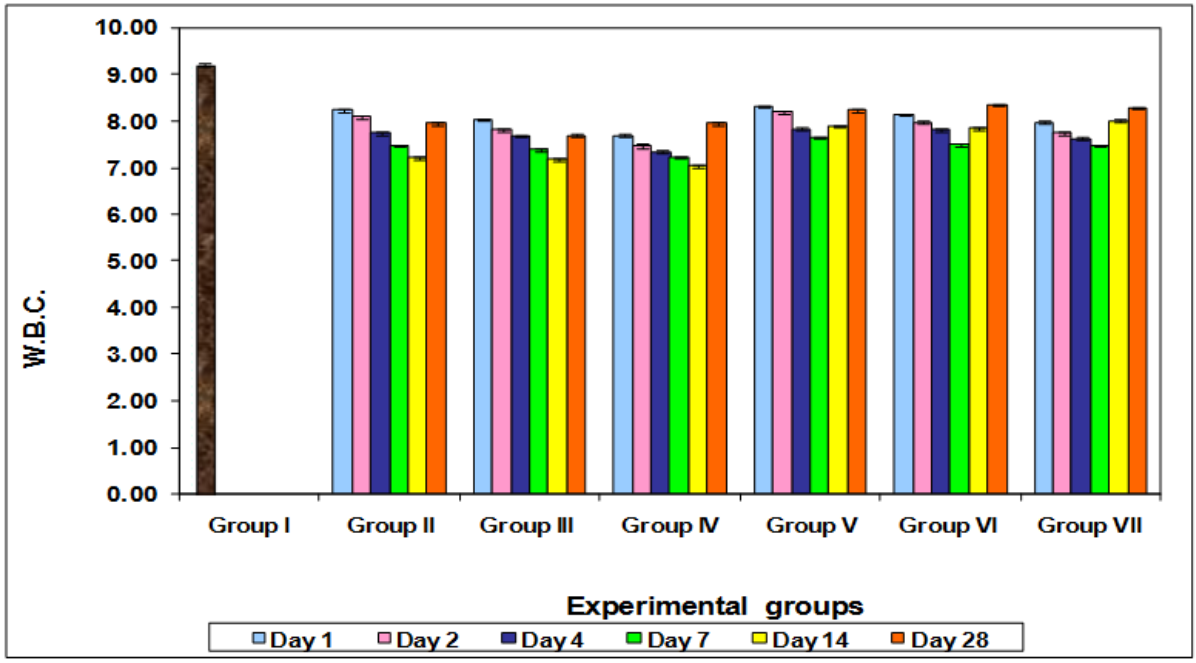

Fig. 2: Variations in the values of W.B.C. (thousand/Cu.mm)

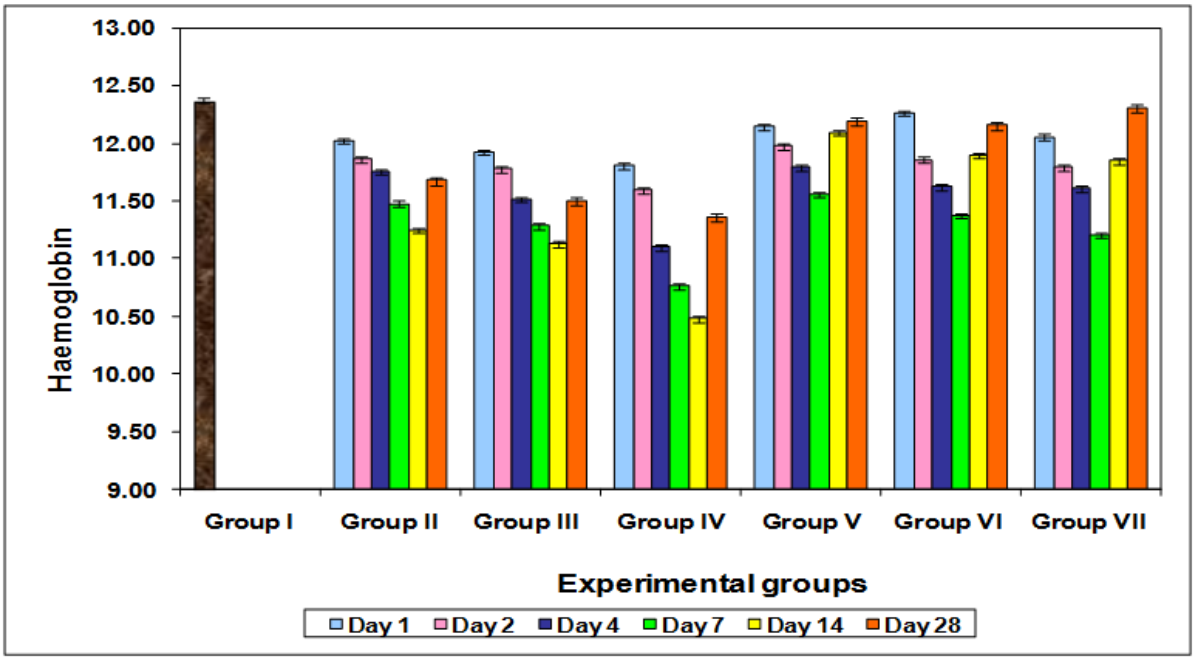

Fig. 3: Variations in the Haemoglobin content (gms/100ml.of blood)

DISCUSSION

Radiation exposure causes damage to biological systems and these damages are mediated by the generation of free radicals and reactive oxygen species targeting vital cellular components such as DNA and membranes. DNA repair systems and the endogenous cellular biochemical defense mechanisms against reactive oxygen species and antioxidants enzymes like reduced Glutathione (GSH), Super oxide dismutase, Glutathione peroxidase, catalase etc. fall upon exposures to higher as well as chronic radiation doses leading to alterations in cell functions, cell death or mutations. Radioprotectors prevent these alterations and protect cells and tissues from the deleterious effects of radiations. Radioprotectors are of great importance due to their possible and potential application during planned radiation exposures such as radiotherapy, diagnostic scannings, clean up operations in nuclear accidents, space expeditions etc. and unplanned radiations exposures such as accidents in nuclear industry, nuclear terrorism, natural background radiation etc. Many of the available synthetic radioprotectors are toxic to mammalian system at doses required to be effective as radioprotector. The blood is most sensitive vital cellular component to the Lead and ionzing radiation. The present work pertains to studies on protective effect of *Emblica* against radiation and Lead induced haematological changes in the Swiss albino mice.

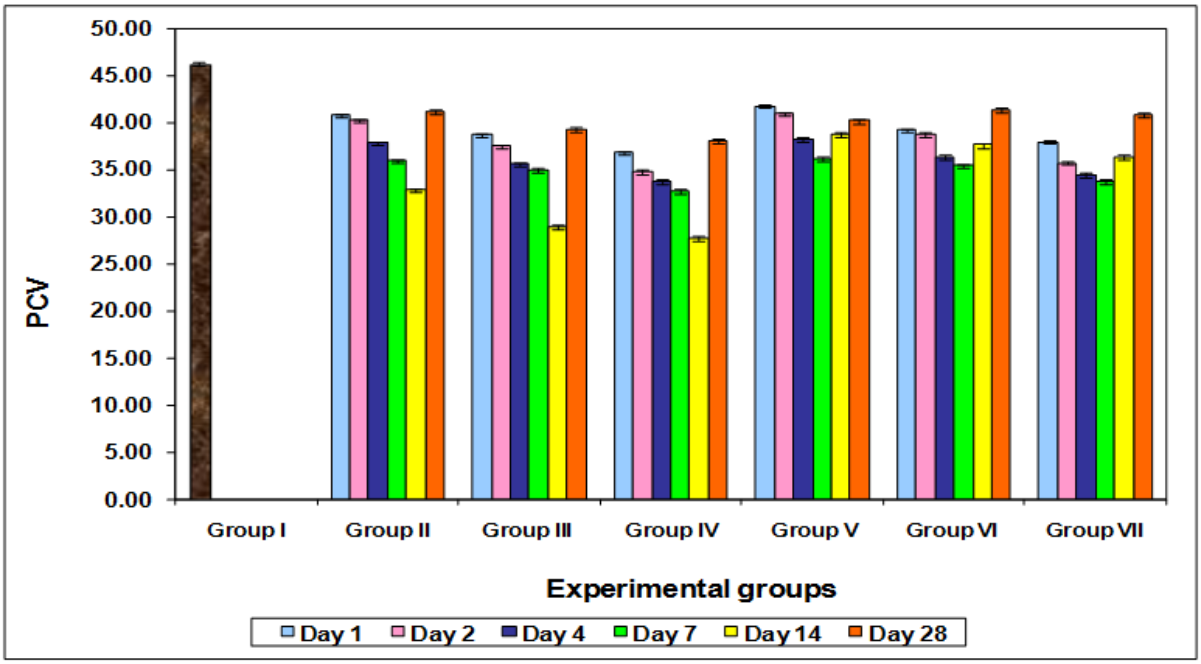

Fig. 4: Variations in the values of PCV (%)

Changes in blood cell count are still considered (although imperfect indices) the most reliable biological evidences for acute exposure to both external and internal irradiation. This is understandable because of high sensitivity of blood forming tissues to ionic radiation and manifestations of injury to the blood even in the absence of demonstrable histopathological changes in blood forming or lymphatic tissues.[12]

At a higher dose of 9.0Gy, the erythrocyte count fell more sharply up to day -7, but recovered thereafter. It was suggested that the radiation-induced depletion of hematopoietic stem cells may be an important factor contributing to the decline in the erythrocytic population. The acute decline in the total RBC count may be attributed to the leakage on account of hemorrhage caused by radiation induced lesions in blood vessels.[13-14]

After exposure of 3.0Gy the erythrocyte count exhibited a fall that can be attributed to inhibition of new cells entering into blood, loss through haemmorhage and / or radiation-induced injury. A similar depression was observed in haemoglobin level without returning to normal till last day of experiment. The present investigation suggests that the haemoglobin concentration follows a pattern similar to that of RBC in general.[15] Similar result was observed in present study.

C57BL/6 mice (n=75) were exposed to 0, 0.5, 1.5 and 3.0 Gy gamma rays at 1 cGy/min (low-dose rate, LDR) and 80 cGy/min (high-dose rate, HDR) and euthanized 4 days later. Decreasing leucocyte and lymphocyte numbers occurred with increasing dose in blood and spleen at both dose rates. Overall, these data indicate that the observed changes were highly dependent on the dose, but not on dose rate and that cell in the spleen are more affected by dose rate than those in blood. The results also suggested that the response of lymphocytes in different body compartments may be variable.[16]

It is well known fact that radiation exposure reduces the number and functional activity of circulating lymphocytes and changes the distribution and ratio of their sub population. It has been stated that the rapid decline in the lymphocytes number is due to the direct destruction of such cells in peripheral blood.[17-18]

After exposure to 3.0Gy of gamma radiation the initial rapid fall in leucocytes count was mainly due to a fast decline of lymphocytes in peripheral blood that are the most radiosensitive as revealed by differential leucocyte count in the study. It is also in favor of earlier findings which reported depression in the number of leucocytes of gamma irradiated mice.[19] Present study also revealed these findings.

Lead impairs the rate of incorporation of iron into mature and immature RBC in cases of human lead poisoning. Lead effects the hematopoietic system and reduce the hemoglobin synthesis, but this occurs only with high levels of exposure. It might be due to decrease in heme and globin synthesis or erythrocyte formation and function. Erythrocyte survival also decreases by lead due to inhibition of membrane bound Na^+-K^+- ATPase.[20-21]

From blood factors studied, the number of RBC, the average MCV and percentage of platelets in the treated groups was significantly increased under the influence of the electromagnetic waves. On the other hand Hb level, percentage of lymphocytes and WBCs decreased. Increase in the number of RBCs may be due to the stimulating effect of waves on cell division of stem cells of bone marrow. Increase in cell volume may also be due to immature cells increase or reticulocytes on the other hand increasing. A review on effects of electromagnetic waves on human peripheral blood lymphocytes reveals that these waves do not affect micronucleus frequency and cell cycle.[22-23]

The lead is cumulative poison and unlike acute poison, lead poisoning occur slowly, One of the study on effects of the lead toxicity on hematological system, show that lead effects this system by inhibiting heme and hemoglobin synthesis and induced anaemia (decrease in RBC, WBC count, PCV value and Hb concentration) in mice . It is well known that the presence of lead in the organism decreases the level of iron in the blood causes the decrease in Hb concentration. According to some reports inhibition of ALAD a cytosolic sulfydryl enzyme and ferrochelatase by lead resulted in depressed heme synthesis that ultimate led to anaemia. It has been explained that ALAD inactivation may lead to the accumulation of delta- aminoleuvulinic acid that can cause overproduction of ROS, which could lead to lead induced oxidative damage in the cell and result in anemia.[24-29]

After exposure to 2.0 Gy and 4.0 Gy of gamma radiation alteration was noticed in some haematological parameters like haemoglobin level, haematocrit value in male Swiss albino mice. Haemaglobin and haematocrit value decrease till day-14. [30] Similar changes were noticed in present study.

Rats were injected with cadmium (Cd) intraperitoneally doses were 0, 1.0.or 2.5 mg Cd kg^{-1} body wt. Twenty four hour after the last Cd injection (day-30) , each rat received an acute whole- body gamma radiation dose of 0, 3.62, or 5.43 Gray (Gy) at a dose rate of 33.04 Gy min^{-1}. Significant decreases were observed in the percentage of lymphocytes, heamoglobin, total number of red blood cells (RBC's) and hematocrit. In general, Cd acted as a debilitator which enchanced the overall effect of ionizing radiation when applied as the second insult.[31]

Cell damage resulting from exposure to ionizing radiation and cadmium chloride may be due to disruption of cellular organization, so that the enzymes come in contact with their substrates. Lysosomes contain many powerful hydrolytic enzymes such as cathepsin, phosphatases and nucleases, which upon release cause great damage. It has been suggested that irradiation induces physical and functional changes in the lysosomal membranes, permitting the release of these hydrolytic enzymes and indirectly causing destruction.[32]

The aqueous extract of the fruits of *Terminalia chebula , Emblica officinalis* and *Terminalia belerica* and their equiproportional mixture Triphala were evaluated for their *in vitro* antioxidant activity. Gamma- Radiation induced strand break formation in plasmid DNA (pBR322) was effectively inhibited by Triphala and its constituents. *Terminalia chebula* has greater radical scavenging activity while *Emblica officnalis* shows greater efficiency in lipid peroxidation and plasmid DNA assay. Their mixture, Triphala, is expected to be more efficient due to the combined activity of the individual components.[33]

Cyclophosphamide is one of the most famous alkylating anticancer drugs in spite of its toxic side effects including hematotoxicity and mutagenicity. *Emblica officinalis* or its medicinal preparations may prove to be benificial as a component of combination therapy in cancer patients under cyclophosphamide treatment.[34]

Ionizing radiation typically induces death by septicemia primarily due to damage to the hematopoietic system. System, a key component of immune system. Immunomodulators such as 5-androstenediol. (5-AED), meloxicam), AS101, CBLB502 (truncayed fleagellin of Salmonella enteric servovar Dublin, a proprietary drug or Cleveland BioLabs, INC.), and TS have all been shown to be effective radiation countermeasures.[35-38]

Radio Protective Mechanism of *Emblica*

The exact mechanism by which *Emblica* prevents the animals from radiation induced damage is not known and secondly, it may not have a single mechanism of artificial natural chemo protector. It seems that *Emblica* may protect by different mechanisms because of their various physiological and biochemical properties which are as follows:

1. It has been shown that the exogenous application of *Emblica* increases glutathione levels in the tissues and maintains -SH groups and increases protein synthesis on the other hand.

2. The protection offered by *Emblica* has been explained by scavenging or oxidizing free-radicals Thus it can be concluded that *Emblica* may inhibit the Lipid per oxidation by:

(i) Inhibiting the of free radicals,

(ii) Destroying the free radicals already formed,

(iii) Exudation the repair mechanism of damaged cell membrane faster.

Though *Emblica officinalis* has various medicinal applications, but it is the need of hour to explore its medicinal values at molecular level with help of various biotechnological tools and techniques. Further studies should be conducted to elucidate the molecular mechanism of interaction of various plant based drugs with human body in radioprotection.

ACKNOWLEDGEMENTS

Authors gratefully acknowledge Head, Department of Zoology and the Principal, Govt. Dungar College, Bikaner (India) for providing necessary facilities in the department. Authors are also thankful to the Radiotherapy Department, Acharya Tulsi Cancer Hospital and Research Centre, PBM Hospital Bikaner (India).

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