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PREVENTION OF RADIATION INDUCED HEMATOLOGICAL ALTERATIONS IN MICE BY *ALSTONIA SCHOLARIS* EXTRACT

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ABSTRACT:

Backround: The present study has been carried out to evaluate the radio-protective effects of *Alstonia scholaris* extract (ASE) on peripheral blood of mice.

Materials & Methods: Male Swiss albino mice were selected from an inbred colony and assorted into 4 groups. Animals in Group I were administered with double distilled water (DDW), volume equal to ASE, by oral gavage to serve as vehicle treated control. Mice in Group II were administered orally ASE once daily at a dose of 100 mg/kg b. wt. / animal/day for 5 consecutive days. In Group III, animals were given DDW for 5 consecutive days then exposed to 2.5 Gy gamma radiation. Group IV mice were treated with ASE (as in Group-II), and were exposed to 2.5 Gy after half an hour of the last administration of ASE. Animals of each group were autopsied on 12 hrs, days 1, 3, 7, 15 & 30 post-treatment intervals for hematological as well as biochemical estimations in blood.

Results: Total erythrocyte count, hemoglobin level, and hematocrit percentage were decreased from vehicle control in both the groups. A significant increase in these parameters was observed in ASE administered irradiated group, in contrast to without ASE irradiated one, by restoring towards normal values at the end of the experiment. An increase in lipid peroxidation level above normal was evident in serum of irradiated mice, while a significant decrease in such values was noted in Alstonia pretreated group. In irradiated group, glutathione level was registered low in the blood, whereas a significant elevation was estimated in Alstonia pre-treated animals.

Conclusion: From the results, it is evident that ASE may be responsible for the protection of stem cells in bone marrow which subsequently resulted in higher hematological constituents in peripheral blood. The study concludes the prophylactic use of such plant extract against radiation-induced hematological alterations.

INTRODUCTION: Ionizing radiation transfuses deleterious effects in biological systems. The realization about adverse effects of radiation began immediately after the discovery of X-ray in the form of skin cancer. Parallely, the awareness about existence of radionucleides intensified the threat of radiation. Rapid advancement in technology also further added varied kind of radiation stresses. Ionizing radiations inflict damage to biological systems essentially through direct deposition of

energy into crucial bio-macromolecules or by radiolysis of milieu water and generation of reactive free radicals [1]. The latter includes formation of reactive oxygen species like super oxide radicals, hydrogen peroxide, singlet oxygen and most reactive hydroxyl radicals [2]. These reactive oxygen species in turn react with different bio-molecules viz., lipid, DNA, proteins and inflict oxidative damage in them.

Although efforts have been directed to mitigate radiation-induced normal tissue damages since the discovery of the deleterious effects of radiation [3], the expanding role of radiotherapy (RT) in cancer treatment along with the potential threat of nuclear or radiological terrorism creates new imperatives for developing safe and effective agents for prophylaxis and treatment of ionizing radiation-induced normal tissue damage [4, 5].

Despite putting into unlimited man hours and input of huge finance, the available radioprotectors are not efficient for safe and sufficient inhibition of radiation energy absorption by critical macromolecules and water existing in the cell. However, last one decade has been exhaustively utilized in screening of various plants having radioprotective properties [6, 7, 8, 9]. Considering toxicity as the major constraint with the use of synthetic compounds, numerous plants have been screened for radioprotective efficacy against the deleterious effects of ionizing radiation.

Alstonia scholaris, a tree belonging to family Apocyanaceae, is a popular remedy in India for the treatment of various types of disorders in both the Ayurvedic and folklore systems of medicine. It is commonly known as the devil's tree and it has been widely used in the traditional system of medicine, reported to be of immense use in the treatment of various ailments [10].

The decoction of Alstonia scholaris bark has been used as a folk medicine in coastal part of Karnataka (India) to treat cold and other ailments like fever every year only in the monsoon season. The bark of the plant is most extensively used part and is reported to have anticancer properties by the people of different cultures and civilizations like India, Admiralty Islands and Thailand [11, 12, 13]. The alcoholic extract of Alstonia scholaris has been recently reported to be antineoplastic and chemopreventive [14, 15].

The common usage, wide acceptability in human beings, and diverse medicinal and antioxidative characteristics attributed to this plant stimulated us to obtain insight into possible radioprotective effect of *Alstonia scholaris* bark extract in mice exposed to whole-body lethal gamma irradiation.

MATERIALS AND METHODS:

Animals: Animal care and handling were performed according to the guidelines set by the World Health Organization (WHO), and the Indian National Science Academy (INSA). Male Swiss albino mice (*Mus musculus*), 6-8 weeks old and weighing 22 ± 2 g from an inbred colony, were used for the present study. These animals were maintained under controlled conditions of temperature and light (light: dark, 10 hours: 14 hours.). They were provided standard mouse feed (procured from Ashirwad Industries Chandigarh, India) and water *ad libitum*. Tetracycline water once a fortnight was given as preventive measures against infections. The Departmental Animal Ethical Committee approved the present study.

Irradiation: Cobalt teletherapy unit (ATC-C9) at the Cancer Treatment Centre, Radiotherapy Department, SMS Medical College & Hospital, Jaipur, was used for irradiation. Unanaesthetized animals were restrained in well ventilated perspex boxes and exposed to gamma radiation at the distance of 77.5 cm from the source to deliver the dose of 2.5 Gy.

Plant material & extract preparation: The bark of *Alstonia scholaris* (Sapthaparna) was collected after proper identification in herbarium of Botany Department (Voucher No. RUBL-19939). The plant bark was powdered in a mixture and the extract was prepared by refluxing with the double distilled water (DDW) for 36 hrs (12 hrs. × 3) at 40^0 C. The extract was cooled and concentrated by evaporating its liquid contents in incubator. The extract was stored at low temperature until further use. The required dose for treatment was prepared by dissolving the drug pellets in double distilled water and administered by oral gavage with a micropipette (100 µl/ animal) at a dose of 100 mg/ kg body wt./animal.

Experimental design: A total of 70 animals used for the experiment were assorted into 4 groups. Mice of Group 1 (Vehicle treated control, n=5) were orally administered double distilled water (DDW), volume equal to ASE. Animals belonging to Group II (ASE

treated, n=5) were given Alstonia extract daily at a dose of 100 mg/ kg b.wt/ animal for 5 consecutive day. Animals of Group III (irradiated control, n=30) were exposed to 2.5 Gy gamma rays alone 30 min. after DDW administration on day 5th. Group IV (ASE experimental, n=30) received ASE (100 mg/ kg b. wt. / animal) as in Group II. Half an hr after the last administration of ASE, such mice were exposed to above used radiation dose. A minimum of 5 animals from group III & IV were necropsied on 12 hrs. ,day 1, 3, 7, 15 and 30 post-treatment to evaluate hematological and biochemical parameters.

Hematological study: For the study, blood was collected from the orbital sinus of animals from each group in a vial containing 0.5 M EDTA. Total number of erythrocytes (RBC), hematocrit (Hct) and hemoglobin (Hb) percentage were determined by adopting standard procedures.

Biochemical determinants: Biochemical alterations were studied in animals of all the groups at one hour post-exposure to gamma radiation. The lipid peroxidation (LPO) level in the serum and liver was measured by the assay of thiobarbituric acid reactive substances (TBARS) according to the method of Ohkhawa *et al* (1979) [16]. The level of glutathione (GSH) was determined in blood and liver by methods of Beutler *et al* (1963) [17] and Moron *et al* (1979) [18] respectively.

Statistical analysis: The results from all the groups at various necropsy intervals were expressed as mean ± standard error of the mean (SEM) to evaluate whether the mean of the sample drawn from experimental (ASE treated irradiated) deviated significantly from respective control (irradiated without ASE). Student's't' test was used by the method of Bourke *et al.*, (1985)[19]. The significance level was set at different levels as $p<0.05$, $p<0.01$ and $p<0.001$

RESULTS:

General: All hematological parameters (*i. e.* RBC, Hb, and Hct percent age) did not show any noticeable change from 12 hours. to day 30th after Sham irradiation (Group I). ASE treatment to Swiss albino mice (Group II) did not exhibit any significant alterations in these hematological parameters as compared to irradiated control animals. Animals subjected to 2.5 Gy gamma rays (Group III) exhibited mild signs and symptoms of radiation sickness. Food and water consumption was reduced and some appeared to be lethargic; however, no mortality was evident in any of the group. No adverse effects in terms of sickness were observed in animals treated with drug alone, and also these did not show significant change in body weight, urination, and defecation pattern.

Hematological: Following irradiation a slight decrease, as compared to the vehicle treated control, in erythrocytes count was observed from 12 hrs. (10.14 ± 0.04; $p \leq 0.01$) to day 3rd. Afterwards, the RBC count increased progressively and reached to normal range (99.43%) on the last autopsy interval i. e. day 30. In ASE pretreated irradiated animals, counts were significantly higher to irradiated control on 12 hrs. ($p \leq 0.01$), day 1 and 3 ($p \leq 0.05$) (**Fig. 1**).

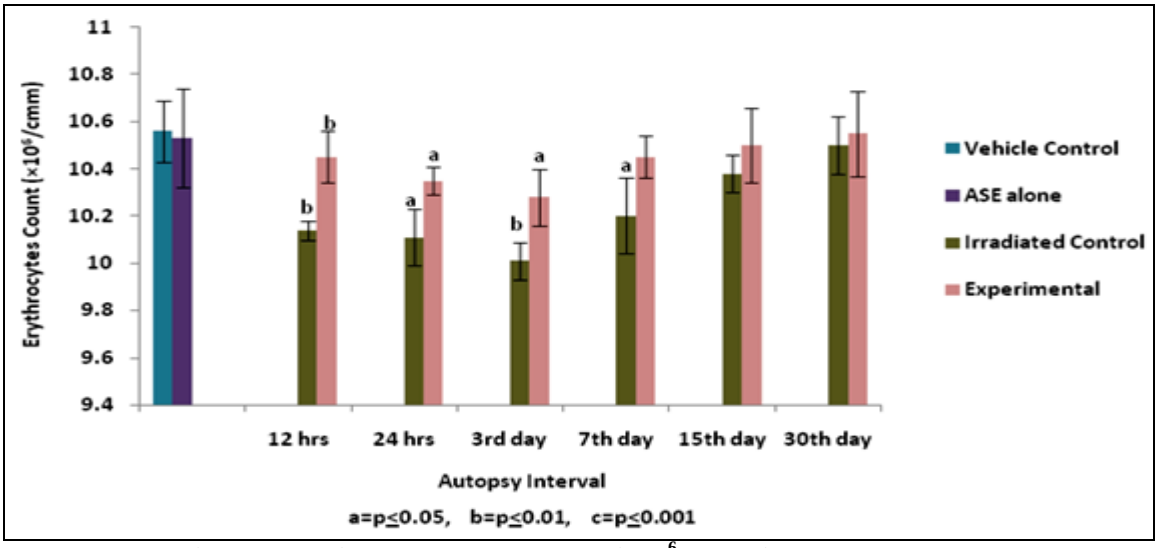

FIGURE 1: VARIATIONS (MEAN±S.E.) IN ERYTHROCYTE (X10^6 IN CM) IN THE PERIPHERAL BLOOD OF MICE AFTER EXPOSURE TO GY 2.5 GAMMA RADIATION WITH (EXPERIMENTAL) OR WITHOUT (CONTROL) *ALSTONIA SCHOLARIS* EXTRACT (ASE)

Similarly a significant fall in hemoglobin level also observed from 12 hrs. (12.52 ± 0.10) to day 3rd (11.88 ± 0.18) on irradiation. After day 3rd post-irradiation, the hemoglobin contents showed a rise till the last autopsy interval by restoring near normal (96.40%) value. In Experimental group, Like RBC, the hemoglobin content also declined till day 3rd (12.30 ± 0.08; $p \leq 0.05$) post-treatment, but the values were higher as compared to irradiated group. Following this autopsy interval, the hemoglobin level was found to be increased till the last autopsy interval i. e. day 30th (13.05 ± 0.20; 99.84%). Significantly ($p \leq 0.05$, $p \leq 0.01$) higher values than the respective control were observed from 12 hrs. to day 7 (**Fig. 2**).

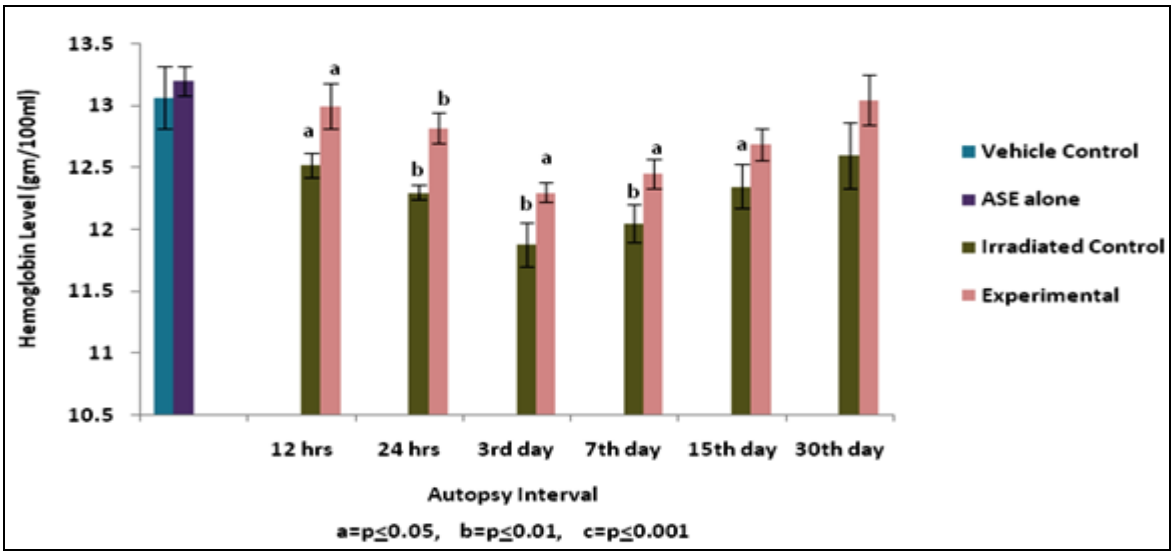

FIGURE 2: VARIATIONS (MEAN±S.E.) IN HAEMOGLOBIN LEVEL (GM/100ML) IN THE PERIPHERAL BLOOD OF MICE AFTER EXPOSURE TO GY 2.5 GAMMA RADIATION WITH (EXPERIMENTAL) OR WITHOUT (CONTROL) *ALSTONIA SCHOLARIS* EXTRACT (ASE)

The hematocrit value started diminishing significantly from 12 hrs (40.22 ± 0.21; $p \leq 0.001$) which attained its maximum decline on day 3 (38.32 ± 0.41) post-irradiation. From day 7th onwards, the values started to rise by attaining the almost normal level (98.24%) on day 30. In ASE pretreated irradiated mice, a gradual recovery in hematocrit percentage was observed at all the treatment intervals and a value close to normal was restored by day 30th (99.54%) post-exposure. The percentage were found to be significantly ($p \leq 0.05$, $p \leq 0.01$, $p \leq 0.001$) higher than the irradiated control group from 12 hrs. to day 7th (**Fig. 3**).

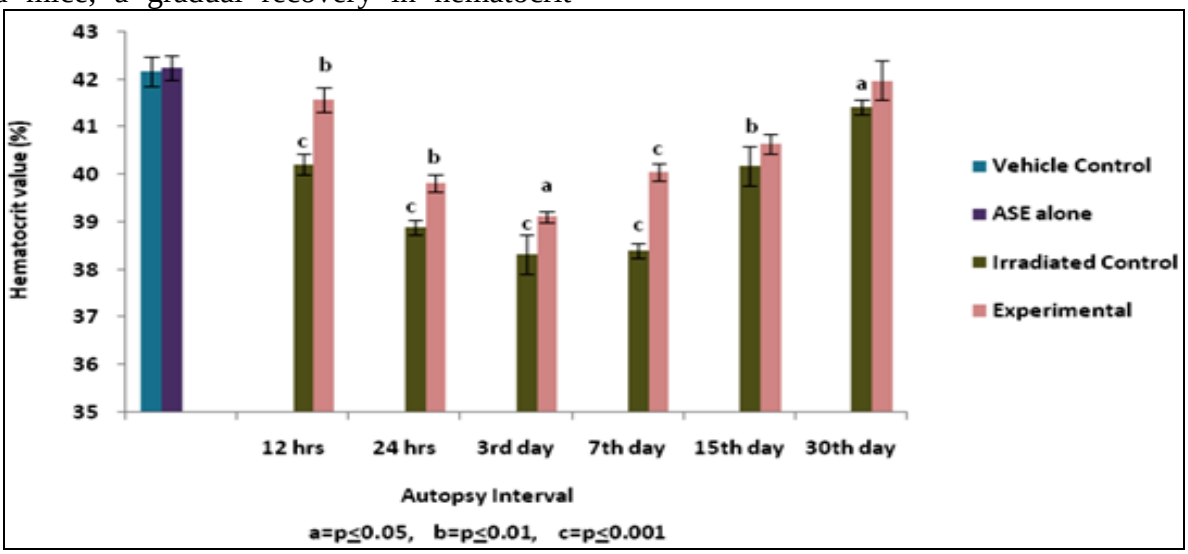

FIGURE 3: VARIATIONS (MEAN±S.E.) IN HEMATOCRIT (%) IN THE PERIPHERAL BLOOD OF MICE AFTER EXPOSURE TO GY 2.5 GAMMA RADIATION WITH (EXPERIMENTAL) OR WITHOUT (CONTROL) *ALSTONIA SCHOLARIS* EXTRACT (ASE)

Biochemical determinants: There was no significant difference in the levels of glutathione (GSH) and lipid peroxidation (LPO) in hepatic as well as blood/ serum content between vehicle treated control and ASE alone treated animals. A significant increase ($p < 0.001$) in blood and hepatic lipid peroxidation levels was noted in gamma irradiated animals (Group III) as compared to vehicle treated control. However, these levels declined significantly in the ASE pre-treated irradiated (Group IV) animals. (**Fig. 4**).

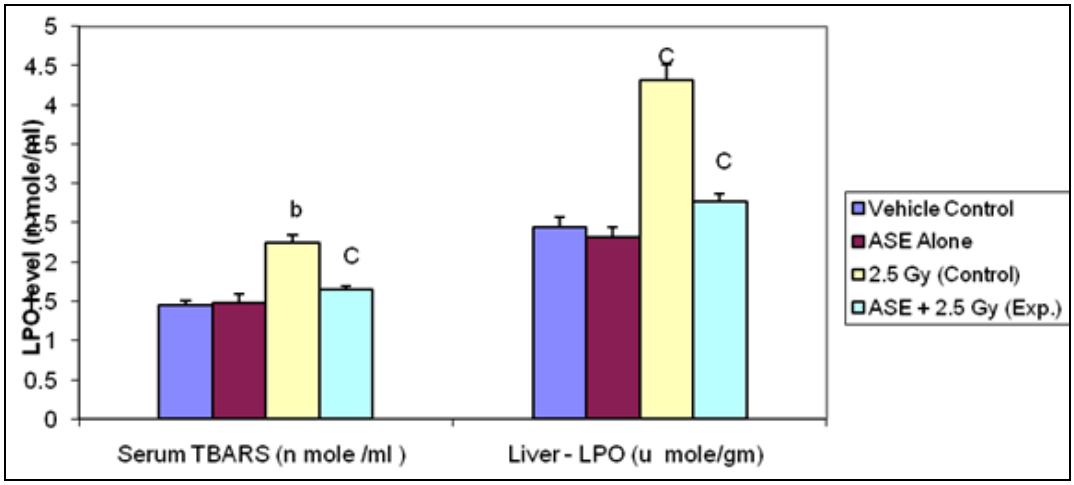

FIGURE 4: LIPID PEROXIDATION (LPO) LEVEL IN SERUM AND LIVER OF SWISS ALBINO MICE AFTER EXPOSURE TO GY 2.5 GAMMA RADIATION WITH (EXPERIMENTAL) OR WITHOUT (CONTROL) *ALSTONIA SCHOLARIS* EXTRACT (ASE)

Glutathione level was found to be decline in Irradiated control group as compared to vehicle treated control. A significant elevation in the values of hepatic and blood GSH was estimated in ASE pre-treated animals (**Fig. 5**).

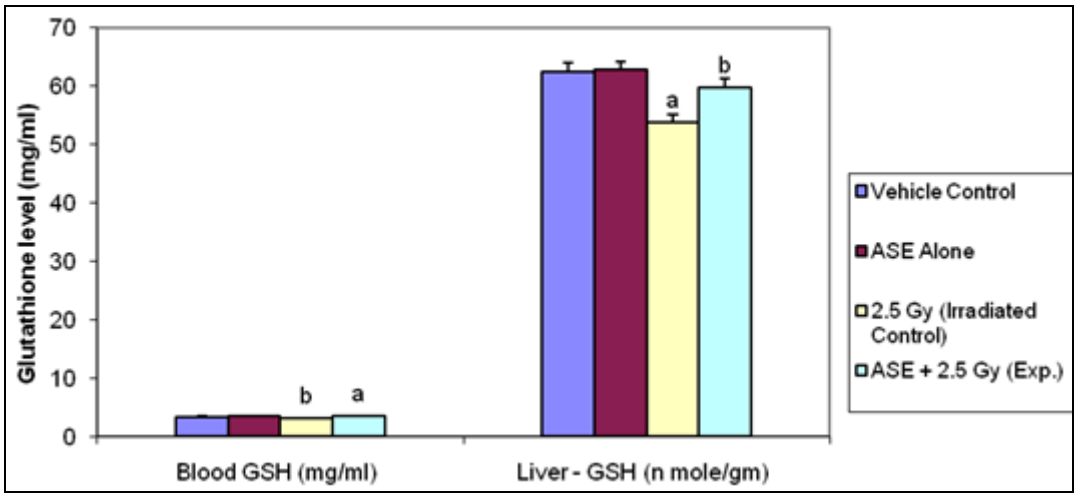

FIGURE 5: REDUCED GLUTATHIONE (GSH) LEVEL IN SERUM AND LIVER OF SWISS ALBINO MICE AFTER EXPOSURE TO GY 2.5 GAMMA RADIATION WITH (EXPERIMENTAL) OR WITHOUT (CONTROL) *ALSTONIA SCHOLARIS* EXTRACT

DISCUSSION: Exposure of mammals to ionizing radiation leads to the development of a complex dose dependent cascade of changes including injury to the lymphoid and haematopoietic system, which can result in septicaemia and death [20]. Agents capable of enhancing survival in the radiation dose inducing the haemopoietic syndrome have typically been associated with accelerated haemopoietic regeneration. An accelerated ability to regenerate new haemopoietic elements, especially those that are important in controlling microbial infections, such as granulocytes, allows the host to resist opportunistic infections better and, hence, enhances survival.

The present study revealed that after exposure to 2.5 Gy, 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 [21].

A similar depression was observed by Chaudhary et al [22] after exposure to gamma radiation.

However, a decrease in the value of Hb level was observed in the present study. Similar findings were proposed earlier by Sancheti and Goyal [23] who found noticeable depletion in hemoglobin concentration in Swiss albino mice exposed to 3 Gy gamma radiation. The decrease in content is an indication of the loss of progenitor cells to form new red blood cells. It can be related to either direct destruction of the RBCs or loss of RBCs in circulation due to hemorrhage or leakage through capillary walls, and loss of production of cells due to the direct cytopathic effects of radiation on the dividing cells of the hemopoietic system.

Similarly, the changes in hematocrit values in the current study were in line with the erythrocytic changes reflecting radiation-induced damage to the erythroid elements. A depression in the hematocrit value can be attributed to total cell depletion in peripheral blood aided by disturbances in steady state mechanisms in blood forming organs as well as an increase in plasma volume after irradiation. This is in agreement with the recent findings of various researchers [24, 23, 22 .

Alstonia scholaris extract (ASE) used in the present study, showed a significant increase in total number of erythrocytes, hemoglobin content and hematocrit values as compared to their respective controls at all the intervals. The maintenance of the higher number of such blood cells happen through the stimulation and production of bone marrow progenitor cells which are the main ways for protection from gamma irradiation [25]. A tendency of ASE to inhibit cell necrosis and inflammatory cell infiltration caused by H-Dgalactosamine in histopathological examination was observed by Lin *et al* [26] that supports the similar mechanism to an increase in the RBC counts after gamma radiation. Samarth [27] also reported the similar results by using *Mentha piperita* before gamma irradiation.

One of the basic mechanisms of radiation damage is generation of highly reactive oxygen species (ROS). The presence of polyunsaturated fatty acids (PUFA) in cell membrane makes it highly susceptible to oxidative attack leading to a chain reaction called as lipid peroxidation (LPO. The level of radiation-induced LPO increased considerably in 2.5 Gy irradiated animals whereas a decrease in the values was observed in ASE-treated group. Since lipid peroxidation is a good biomarker of damage which occurs due to radiation and so the inhibition of lipid peroxidation is suggestive of radioprotective action of the ASE supplementation prior to gamma irradiation. Prevention of lipid peroxidation by *Alstonia scholaris* extract via decrease in malondialdehyde level has been reported by Arulmozhi *et al* [28].

Antioxidants protect the cell against reactive oxygen/nitrogen species (ROS/RNS) by scavenging the free radicals in the cellular milieu. The increased levels of ROS/RNS generated during irradiation have been shown to be effectively scavenged by some antioxidants present in plants [29, 30]. Antioxidants delay the oxidation of biomolecules by inhibiting the initiation and propagation of oxidizing chain reactions thereby interfering with the initiation of apoptosis. Antioxidants can be phenolic compounds (tocopherols, flavonoids and phenolic acids), nitrogen compounds (alkaloids, amines, amino acids and chlorophyll derivatives) or carotenoids as well as vitamins including ascorbic acid [31]. A relation between the antioxidant property and radiation protection by plant flavonoids and phenols was suggested by Shimoi *et al* [32] and Emerit *et al* [33].

GSH is a versatile protector and executes its radioprotective function through free radical scavenging, restoration of damaged molecule by hydrogen donation, reduction of peroxides and maintenance of protein thiols in the reduced state. The present study demonstrates significant reduction in blood as well as liver GSH following radiation exposure may be due to enhanced utilisation of the antioxidant system to detoxify the free radicals generated by radiation. Oral administration of ASE during radiation exposure protects the endogenous GSH depletion. *Alstonia scholaris* contain flavonoids, alkaloids and triterpenoids [34] which may be responsible for the antioxidant activity of this plant in the present study.

CONCLUSION: The exact mechanism by which ASE protects against radiation is not clearly understood, but it appears that its anti-oxidant substances neutralize the toxic peroxides formed from water molecules after radiation exposure. It may increase the amount of excision repair in cells exposed to gamma rays.

ASE prevents direct cell killing against gamma radiation and thus maintains higher cell counts in blood. The compounds present in ASE may also protect hematopoietic precursor cells of bone marrow in mice against radiation injury, and hence attributes to an increased blood cells number in peripheral circulation.

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