ISSN NO. 2320-5407

Journal homepage: http://www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH

RESEARCH ARTICLE

HAEMOPROTECTIVE EFFECT OF *ALOE VERA* ON GAMMA IRRADIATED AND CADMIUM TREATED SWISS ALBINO MICE

Manisha Agarwal, Seema Singariya, Venkteshwar Songara, Aruna Chakrawarti and R.K. Purohit
Radiation Biology Laboratory, Department of Zoology, Govt.Dungar College, Bikaner, India. 334001

Manuscript Info

Manuscript History:

Received: 12 August 2013
Final Accepted: 23 August 2013
Published Online: September 2013

Key words:
Radiation, Cadmium,
Aloe vera, Mice, Blood.

Abstract

The aim of study was to evaluate the haemoprotective effect of *Aloe vera* on gamma irradiated and cadmium treated Swiss albino mice. For the purpose of experiment six to eight weeks old male Swiss albino mice were divided in to seven groups. Group I (sham irradiated), group II (treated with cadmium chloride solution 20 ppm), groupIII (irradiated with 7.0Gy gamma rays), groupIV (Both irradiated and treated with cadmium chloride solution), group V (Cadmium and *Aloe* treated), groupVI (radiation and *Aloe* treated), group VII (radiation, cadmium and *Aloe* treated). The animals were sacrificed at post treatment intervals of 1, 2, 4,7,14 and 28 days. After sacrificing the animals the blood was collected by cardiac puncture in heparinized tubes. The various haematological parameters assessed from day- 1 to day-28.After autopsy of experimental animals the results showed a significant decline ($P<0.02$, $P< 0.001$ respectively) in RBC count, WBC count, Hb, Haematocrit in peripheral blood up to day-14. Peak values in all the parameters were observed on day- 7 after irradiation. Thereafter the value increased on day-28 in non drug treated groups. Decrease in the values in all the parameters was lesser in *Aloe* treated groups. *Aloe vera* pre treated irradiated animals showed a significant early recovery in all the values as compared with non drug treated groups.

Introduction

One of the components of the modern technology is the use of radiation in the medicine for the diagnostic and therapeutic purposes, research, industries and construction site. Because of the wide spread use of radiation in diverse fields, it is important to concern the possible adverse biological effects of radiation.

Man has always been exposed to ionizing radiation from natural sources. The natural background exposure varies with the locations. No ill effects have been uniquely correlated. Either no deleterious effects are produced at these levels of exposures or their frequency is too low to be statistically observable. Direct source of information of radiation hazards in man is obviously based on follow-up of population groups exposed to certain levels of radiation. Harmful effects of ionizing radiation recorded from exposed radiologists during 1920s and 30s, minors exposed to air borne radio activity, workers in the radium industry, follow-up date of Japanese nuclear bomb survivors of Hiroshima and Nagashaki, the Marshallese accidents in 1954, and the victims of the limited number of accidents at nuclear installations including Chernobyl form the basis of data to develop various recommendations. From these various sources, the pattern of events that follows a total body exposure to a dose of ionizing radiation have been well documented. Mostly these information are from situations involving higher doses and dose rates (Ravichandran, 2012).

Cadmium (Cd) has been in industrial use for a long period of time. Its serious toxicity moved into scientific focus during the last century. Cadmium is regularly found in ores together with zinc, copper and lead. Therefore volcanic activity is one natural reason for a temporary increase in environmental cadmium concentrations. Cadmium is widely used in industrial processes, e.g.: as an anticorrosive agent, as a stabilizer in PVC products , as a color pigment , a neutron absorber in nuclear power plants and in the fabrication also show a big cadmium load . Although some cadmium- containing products can be recycled,

a large share of the general cadmium pollution is caused by dumping and incinerating cadmium-polluted waste. (Jarup L. 2003)

Metal induced toxicity is very well reported in the literature (Leonard *et al*., 2004; Flora *et al*., 2008) Cadmium is listed by the US environmental Protection Agency as one of 126 priority pollutants. The most dangerous characteristic of cadmium is that it accumulates throughout the lifetime. Cadmium accumulates mostly in the liver and kidney and has a long biological half –life time of 17 to 30 years in human (Shimada *et al*., 2008; Draz *et al*., 2009).

The development of radio protective agents has been the subject of intense research in view of their potential for use within a radiation environment; however, no ideal, safe synthetic radio protectors are available to date, so the search for alternative sources, including plants, has been ongoing for several decades (Scarterrzzimi & Speroni, 2000; Lam & Ng, 2002; Song *et al.,* 2003; Arora *et al.,* 2005). As the utility of medicinal plants suffers from the fact that several of them lack scientific evidences,there is a need to provide scientific back up to justify their potential in treatment of various disorders including radiation damage to living beings (Ammon & Wahal,1991). In view of above perception the present study was examining haemo protective effect of *Aloe vera* on gamma irradiated and cadmium treated Swiss albino mice.

Aloe vera is known to contain well over 100 separate ingredient or constituents , between those found in the leaf and those found in the mucilaginous gel inside the leaf .It is also known that some of the ingredients found in the leaf such as Aloin or Emodins are recognized as having laxative and anti-microbial properties. *Aloe vera* provided ample protection to the blood of mice against radiation induced biochemical changes because Aloe is rich in Vitamin A (β-carotene), C and E, glutathione peroxidase, as well as isozymes of superoxide dismutase and various minerals such as zinc and selenium.

Cells and tissues are equipped with endogenous enzymes e.g. superoxide dismutase (SOD), glutathione peroxidase (GPx), catalase, reduced glutathione (GSH), glutathione S transferase (GST) capable of neutralising free-radical induced cellular damage (Parihar *et al.*,2007). GSH performs multifunctional activities to attenuate radiotoxicity by scavenging of free radicals, maintaining thiol-disulphide balance, synthesis of DNA precursors, synthesis of porphyrin and maintaining the cellular levels (Parihar *et al.,* 2007). However, once the level of reactive oxygen species increases above tolerable limits, the endogenous system fails to protect the cells from the hazardous effects of free radicals.

Exposure to high amounts of ionizing radiation results in damage to the haematopoietic, gastrointestinal and central nervous systems depending on radiation dose (Hosseinimehr *et al.,* 2006). The haematopoietic system is among the most radiosensitive in the body as it has a highest cell turnover (Zhou and Mi, 2005). The primary cause of mortality during the early phases of radiation-induced haematopoietic syndrome is sepsis, resulting from opportunistic infection, due to reduced neutrophils and increased entry of bacteria across the denuded gastrointestinal mucosa. The sitiuation is further complicated by thrombocytopenia and defects in adaptive immune system (Dainiak, 2002).

Blood is the most accessible sample one can obtain for analysis. It consists of 45% cells and 55% plasma. Red blood cells (RBC) constitute 99% of its cellular components. They mainly govern the blood behavior either rheologically (Pal, 2003) or electrically (Cheldze, 2002). RBC is a biconcave enucleated cell containing haemaglobin molecules. Several types of analysis can be performed to investigate the effect of radiation on blood.

Therefore in the present investigation, protective effects of *Aloe vera* against cadmium and radiation induced hematological changes in Swiss albino mice have been studied.

Material and Methods

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, India (Registration no. 1066/ac/07/CPCSEA) and has its own Institutional Animal Ethics Committee (IAEC). The animals used for the present investigation were sacrificed strictly under the supervision of IAEC of the college.

Cadmium

Cadmium salt in the form of cadmium chloride (SDS Chemicals, India) was prepared by dissolving 20 mg of cadmium chloride in 1000 ml of the glass distilled water, thus giving a concentration of 20ppm and then administered orally in drinking water.

***Aloe vera* extract**

Fresh leaves of the *Aloe vera* were cleaned, cut into small pieces, air dried, powdered 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 per cent yield of the extract was obtained. The drug was given from seven days prior to Cadmium chloride 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 0.69 Gy/min. The dose was calculated at the midpoint 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 (Sham-irradiated animals - normal) The animals of this group were Sham- irradiated and served as normal group.

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

Group – III The animals of this group were exposed to 7.0 Gy of gamma rays from Co^{60} source at the dose rate of 0.69 Gy/min.

Group – IV The animals of this group were orally fed with Cadmium chloride at the dose rate of 20 ppm and also exposed to 7.0 Gy of gamma radiation.

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

Group – VI The animals of this group were exposed to 7.0 Gy of gamma radiation from Co^{60} source. The *Aloe vera* was given seven days prior to irradiation and continued up to last autopsy interval.

Group –VII The animals of this group were orally fed Cadmium chloride at the dose of 20 ppm and also irradiated with 7.0 Gy of gamma radiation. The *Aloe vera* was given orally for seven days prior to irradiation and Cadmium feeding till the last autopsy day of experiment.

Autopsy of the animals

Five animals from each group (II to VII)were sacrificed 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.) (Plum, 1936)

II White blood corpuscles (W.B.C.) (Dacie and Lewis, 1974)

III Haemoglobin (Hb) (Drabkin and Austin, 1932)

IV Packed cell volume (PCV) (Wintrobe, 1967)

Results

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 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).

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 declined 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 *Aloe vera* treated groups V, VI, and VII the value of WBC declined from day-1 to 7 then increased on day -14 and continued so up to day-28. In the *Aloe vera* treated groups the decrease in the value was comparatively lesser as compared to the non drug treated groups (Fig.2).

In the present work, 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).

The packed cell volume showed a decreasing trend in all the groups. 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 the value increased up to day-28 (Fig.4).

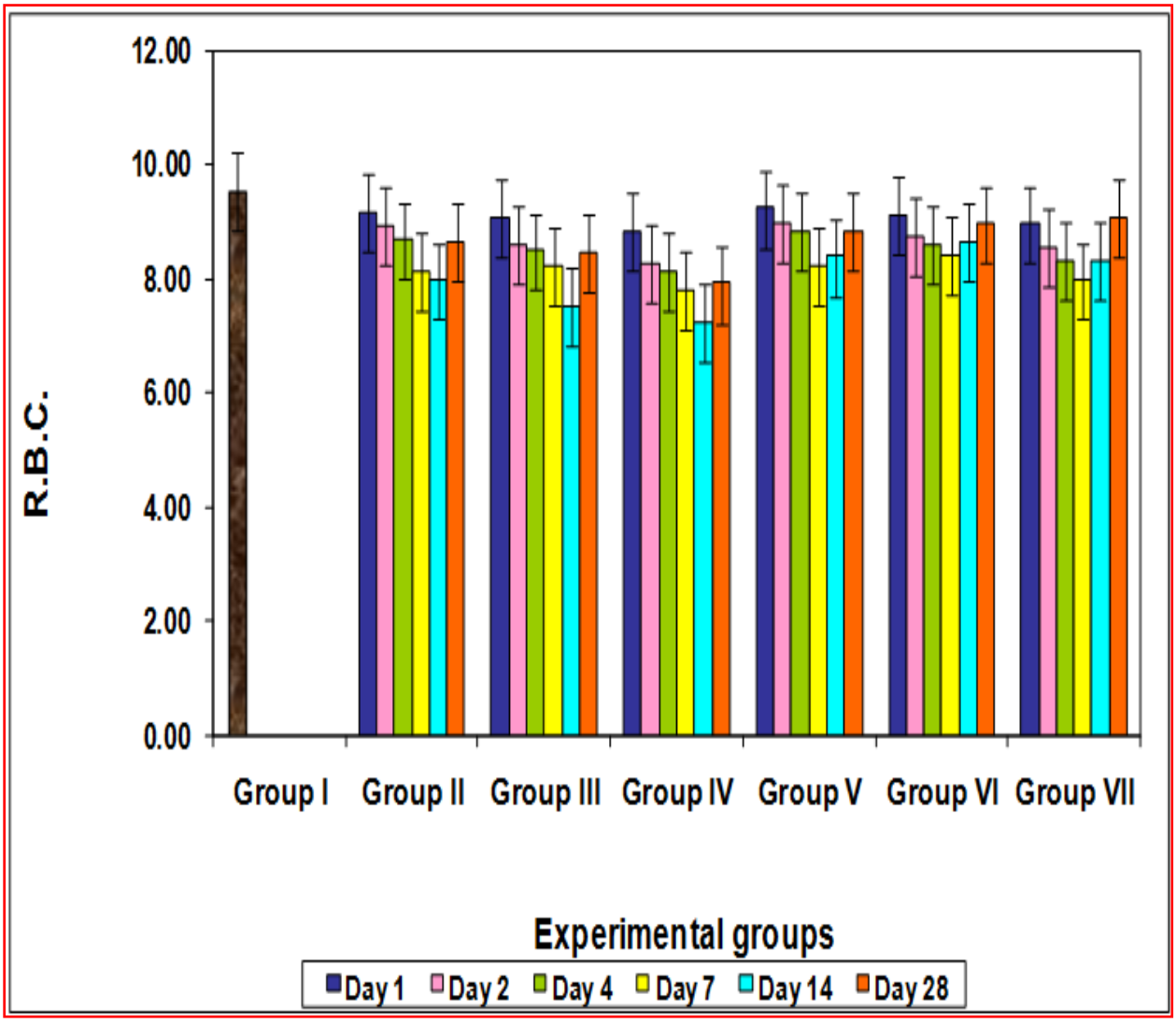

Fig.-1: Variations in the R.B.C. (thousand /cu.mm) of mice in various groups

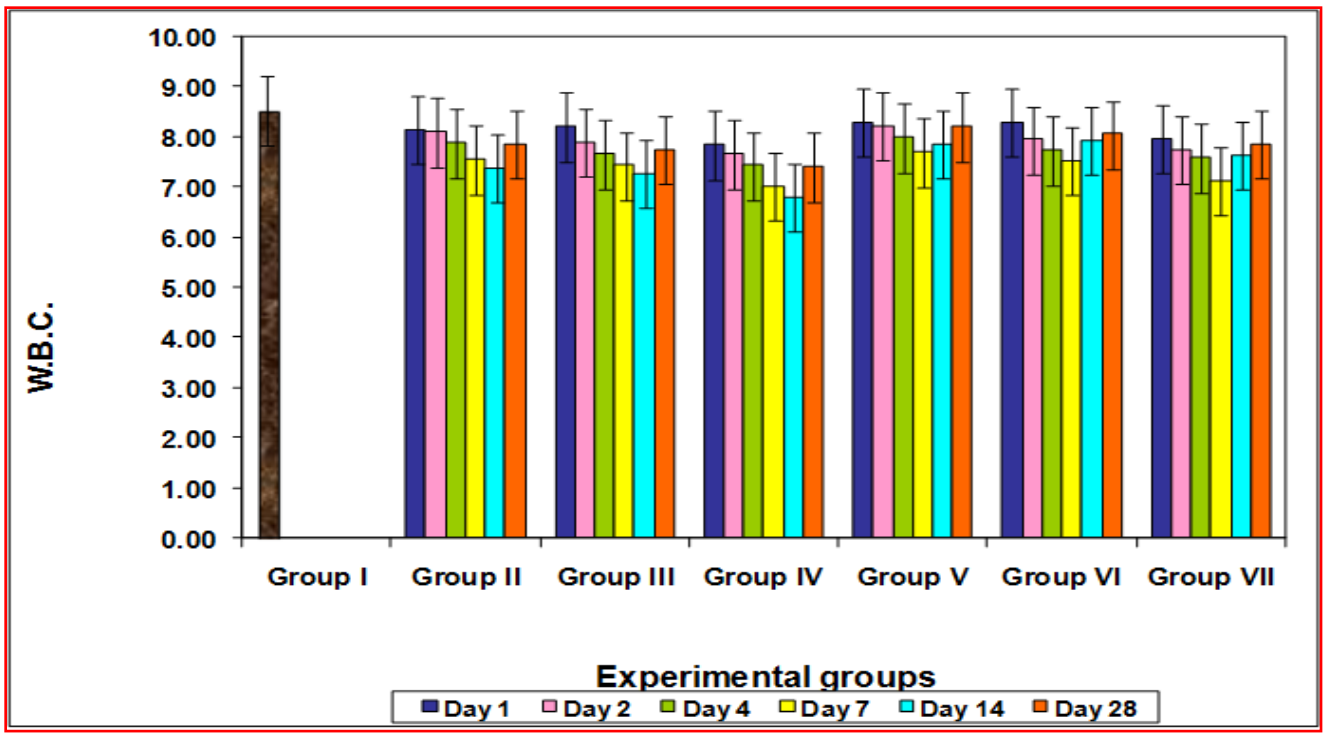

Fig.-2: Variations in the W.B.C. (thousand /cu.mm) of mice in various groups

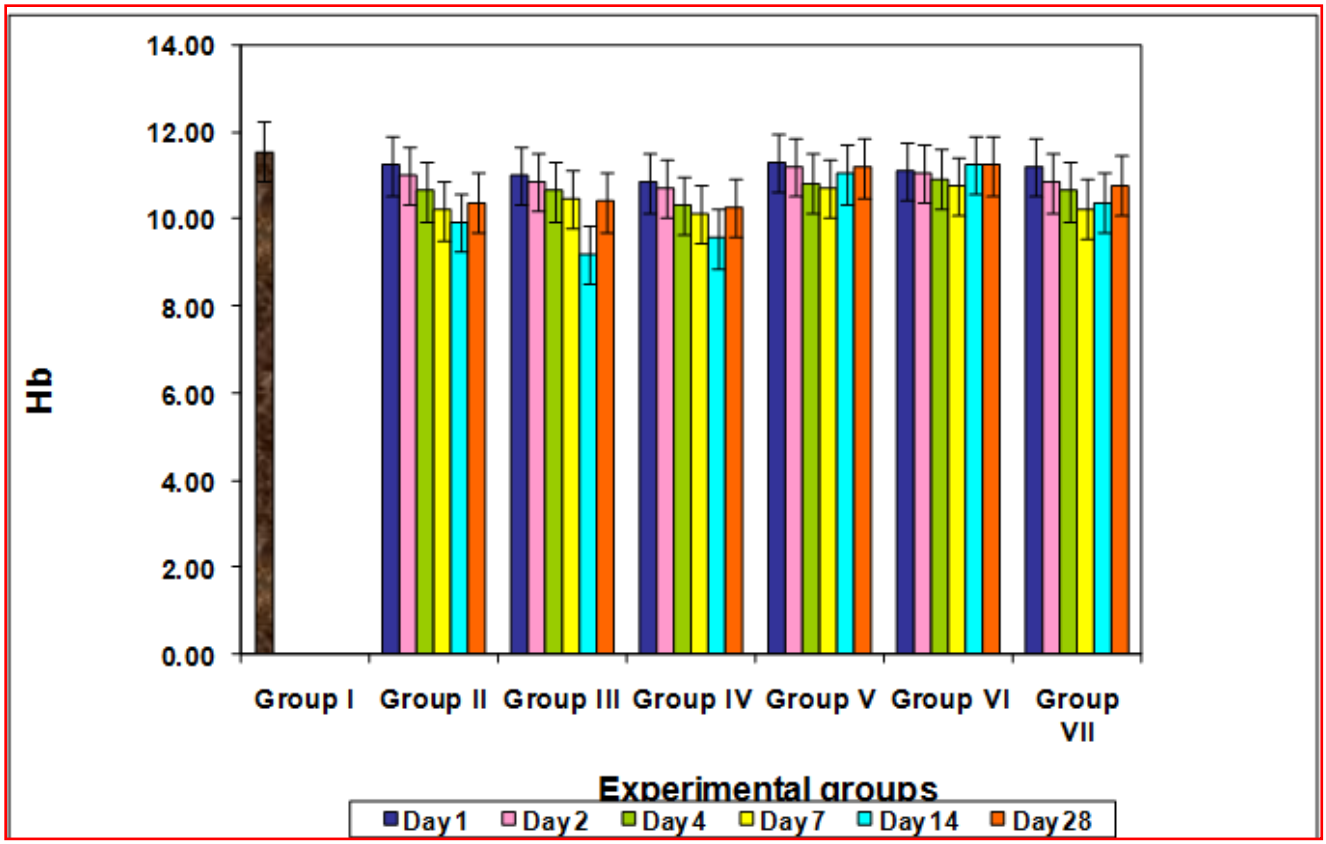

Fig.-3: Variations in the Hb (gms/100ml. of blood) of mice in various groups

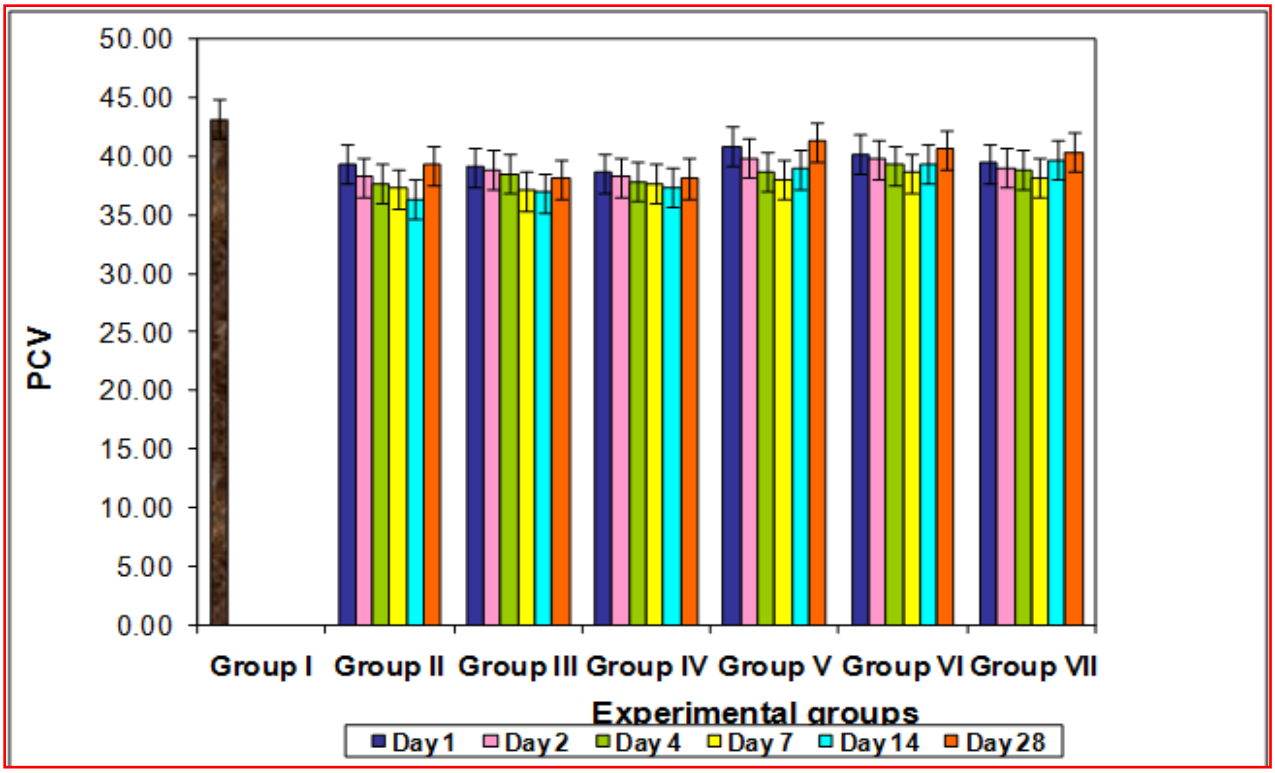

Fig.-4: Variations in the PCV (%) of mice in various groups

Discussion

Inbuilt antioxidants system like superoxide dismutase (SOD), reduced glutathione (GSH) and so forth protect the tissue from free radical attack. Excessive release of ROS powers over this system resulted in organ damage. Strengthening of inbuilt protective mechanisms or exogenous administration of antioxidants may be useful in the protection of the organs from ROS damage (Flora et *al.,* 2006).

Due to lack of an effective protective agent, newer compounds are currently under investigation as possibly adjuvant in the radiation treatment of cancer, while herbal medicines have only recently begun to receive some attention as possible modifiers of the radiation response (Weiss & Landauer, 2003). Studies carried out in the past fifteen years have shown that herbal preparations such as Liv.52, Brahmarasayana, Podophyllum , *Ocimum sanctum*, Triphala , *Emblica officinalis* , *Rosemarinus officinalis* reduced radiation -induced damage in mammals. (Sharma and Purohit 2012; Kumar *et al*., 1996; Jagetia *et al.,* 2002; Goel *et al.,* 1999; Umadevi *et al.,*1999, Singh *et al.,* 2005 and Jindal *et al.,*2006)

The most important of metabolic parameter for cadmium uptake is a person's possible lack of iron. People with low iron supplies showed a 6 per cent higher uptake of cadmium than those with a balanced iron stock (Flanagan *et al.,* 1978). This is the main reason for the higher cadmium resorption in people with anemia and habitual iron deficit, such as children or menstruating women. Low iron blood levels stimulate the expression of DCT-1, a metal iron transporter in the GI tract, serving as a gate for cadmium resorption (Gunshin *et al.,* 1997).

The Blood concentration of cadmium serves as reliable indicator for a recent exposition, while the urinary concentration reflects past exposure, body burden and renal accumulation (Jin et *al.,* 2002).

Although molecular mechanisms of cadmium induced carcinogenesis are not yet understood, several factors may contribute to it like, up regulation of mitogenic signaling, perturbance of DNA–repairing mechanism and acquisition of apoptotic resistance by cadmium exposure (Goyer *et al.,* 2004). A substitution of zinc by cadmium in transcription-regulating proteins is also in discussion. Furthermore, new data showed that cadmium is able to change the conformation of E-Cadherin, a transmembrane Ca (II) - binding glycol- protein. E- Cadherin plays an important role in cell-cell adhesions, especially in epidermal cells (Prozialeck & Lamar, 1999). These results are consistent with the hypothesis that E–cadherin may be a direct molecular target for Cd^{2+} toxicity.

Examining the nature of the membrane injury in gamma irradiated erythrocytes in the dose range 2.0 to 200Gy Shaprio & Kollmann (1968) concluded that the sulphydryl group is the major target in radiation induced alteration of sodium and potassium ion permeability. Using fluorescent probes Yonei and Kato (1978) found that X-irradiation readily induces significant changes of the erythrocytes membrane structure.

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 (Purohit et *al.,* 2010).

In one of the earlier study on cell membrane permeability of erythrocytes reported the kinetics of the diffusion of the salts into an out of X –irradiated Erythrocytes. The X irradiation of erythrocytes was reported to cause osmotic disturbance. It has been shown that at 330Gy, the effect of X-rays was not due to hemolytic disturbance in the red blood cells but rather to a "disturbance within the cells". This manifested itself, slow swelling of the cells (Ting & Zircle, 1940).

Lymphocytes have been found to be one of the most radiosensitive mammalian cells (Vanbekkum, 1974). Although irradiation has been shown to alter neither lymphocyte count nor their viability, Wong *et al.* (1979) reported impairment of their function following a 30Gy radiation dose, as evidenced by a decrease in response to phytohaemagglutinin and mixed leukocyte culture. In fact Pelezynski et *al.* (1991) reported that to effectively inactivate lymphocytes in red blood cell units, a minimal gamma radiation dose of 25Gy is required.

In another investigation of a relationship between yields of micronuclei and radiation dose, micronuclei were induced in lymphocytes by exposing human blood samples *in vitro* to various doses of Cs-137 gamma-rays. It seems, according to (Balasem & Ali, 1991) that there is a correlation between the yields of micronuclei in mononuclear cells and the corresponding doses of radiation.

In studies on enzyme systems in leucocytes, alkaline phosphates activity is enhanced following a 500Gy radiation dose (Wagner *et al.,* 1957). The inherent ageing process of leucocytes is probably enhanced by change in the cell envelope. Alpha glycerophosphate dehydrogenase (one of the most important respiratory enzymes in leukocytes) activity is similarly enhanced by radiation. The glycolytic system in leukocytes remains intact at 500 Gy.

A comparative study of survival of peripheral blood lymphocytes from neonatal umbilical cord blood or from children and adults after exposure to gamma irradiation (up to 4.0 Gy) was made (Waugh et *al*., 1991). Mean activation of doses were calculated from survival rates in the cloning assay. Cord blood samples showed a strong tendency towards lower mean inactivation dose (1.54Gy) relative to comparison (1.90Gy). Based on survival rates of different doses, it was noted that cord blood samples shows increasing radio sensitivity above 1.0Gy. Thus, it was concluded that these results confirm greater T-Lymphocyte radiosensivity in newborns, which may have implications for prenatal radiation protection.

Leitman & Holland (1985) argue that since the mean lethal dose of radiation for lymphocytes and haematopoietic stem cells in less than 2.0Gy (Hall, 1978) well below the dose used in irradiating blood products, there is no possibility for sustain proliferation of cell with radiation-induced carcinogenic potential. They conclude that all such cells will die during subsequent mitosis.

Ambe *et al.* (1961) reported that 1kGy irradiation caused two percent loss in cattle haemaglobin in anoxic aqueous solution, when expressed as total nitrogen in scission products. A 10 kGy radiation dose caused a 15 percent loss; 600Gy caused a 29 percent loss. At 100kGy there was complete destruction of the chromophore group and the functional properties of the haemaglobin, with a 30 to 45 percent loss of these properties at 10kGy. The essential effects of radiation in aqueous solution were formation of insoluble protein aggregates, and formation of scission products.

In a further study (Kollmann et *al.,* 1969) haemolysis was evident following the gamma irradiation, in the dose range 162 to 500Gy, of erythrocytes suspended in isotonic sodium chloride solution. No haemolysis was observed in isotonic choline chloride solution (although there was a loss of potassium ions), nor in hypertonic sodium chloride or potassium chloride. The results indicate that radiation induced haemolysis is an osmotic effect due to destruction of the barrier to sodium and potassium ions (caused by a decrease in membrane sulphydryl groups), and movement across the cell membrane.

Preliminary investigation by Nisnevitch *et al.* (1994) has shown the possibility of cryoradaition sterilization of blood serum and plasma. They showed that following a 25kGy gamma-radiation dose, there was less than ten percent degradation of

the fibrinogen content of the plasma, and one percent degradation of albumin content. The protein composition of the globulins (alpha1and 2, beta and gamma) in the plasma were generally well within 10 percent of the controls. Similar findings were reported for the immunoglobulin content of the cryoirradaited serum. Kitchen *et al.* (1989) based on their investigation of the effect of gamma irradiation on HIV and human coagulation proteins, coupled with the absence of gross changes in other plasma proteins, concluded that irradiation of frozen raw plasma is likely to be highly effective as a means of inactivation of infectious agents present in human plasma while apparently causing minimal deleterious effects on plasma proteins.

Topical aloe's anti- inflammatory properties do not appear to interfere with wound healing, but rather increase wound tensile strength (Davis *et al.*, 1994a) possibly due to the fibroblast stimulating activity of mannose-6-phosphate (Davis *et al.,* 1994b). *In vivo Aloe vera* gel (97.5%) significantly reduced UV-induced erythema after 48 hours, being superior to one per cent hydrocortisone in placebo gel. In contrast one per cent hydroxycortisone in cream was more efficient than *Aloe vera* gel (Reuter *et al.,* 2008). Aloe also has antithromboxane activity, yet it maintains prostaglandin ratio without causing injured blood vessels to collapse.

Anti-leukemic and Anti-mutagenic effects of Aloe *in vitro* have been attributed to di(2-ethylhexyl) phtalate (DEHP) (Lee *et al.,* 2000). Promotion of apoptosis has been reported *in vitro* as a possible anti-neoplastic mechanism(Pecere *et al.,* 2003). Aloe appears to affect detoxification of reactive metabolites by liver and other organs (Singh *et al.,* 2000).

Antioxidants properties have been attributed to aloesin derived from *Aloe vera* (Yagi *et al*., 2002, 2003 and Singh *et al.,* 2000).Based on cell-line research, APS-1, a polysaccharide from *Aloe vera var. chinensis*, also show free radical scavenging other antioxidant properties (Wu *et al.,* 2006). Aloe polysaccharides may have a radio protective effect on non-malignant cells via its ability to modulate cell cycle (Wang *et al.,* 2005).

Aloe vera may protect by different mechanisms because of its various physiological and biochemical properties. The depletion of intracellular glutathione (GSH) has been reported to be one of the causes of radiation induced damage while increase level of intracellular GSH is responsible for the radio protective action. The radio-protective activity of *Aloe vera* may be due to the inhibition of lipid per oxidation by increasing the level of a tocopherol and glutathione. Thus it can be concluded that *Aloe vera* inhibits the lipid per oxidation by reducing the formation of free radicals, destroying the free radical already formed, exudating the repair mechanism of damaged cell membrane (Goyal & Gehlot, 2009).

Agarwal *et al.* (2011) also studied protective efficacy of *Aloe vera* against radiation (2.0 and4.0Gy) and cadmium induced haematological changes in the Swiss albino mice. The values of RBC, WBC, Haemoglobin and PCV were found to decrease up to day-14 in non drug treated groups (II, III and IV), thereafter they increase on day-28. Whereas the values decreased up to day-7 in A*loe vera* treated groups (V, VI, VII) thereafter increased up to day-28.

Purohit and Joiya (2012) investigated protective role of polybion against radiation and cadmium induced haematological changes in the Swiss albino mice. They exposed the animals with 2.0 and 4.0 Gy of gamma radiation with or without cadmium chloride treatment. The values of RBC, WBC, haemoglobin and PCV were found to decrease in all the groups as compared to normal value, but decrease in these values was lesser in polybion treated groups. On the other hand, the value of MCV increased in all the groups at various intervals. When the animals were treated with radiation and cadmium chloride simultaneously synergistic effects were observed in all drug treated groups. Recovery started earlier than that in non drug treated groups. The polybion treated animals exhibited less severe damage and early recovery as compared to non drug treated groups.

Conclusion

Plants are naturally gifted with the ability to withstand the harmful radiations from the Sun. Therefore, it can be said that they are equipped with several defensive machineries to protect themselves from the radiation stimulated injuries and oxidative stress. The use of phytochemical in radioprotection has received much attention in the last decade owing to certain discoveries with special properties as antioxidants. Generally, they are popular because the phytochemicals are lower in toxicity in human beings (as many of these are used in alternative medicine in Asian countries for centuries), easy availability, inexpensive and good radioprotection exhibited in preclinical studies. The radioprotective activity of phytochemicals may be mediated through several mechanisms such as free radical scavenging, improvement in the antioxidant status, and antilipid-peroxidation potential, conferred due to presence of variety of phenolic hydroxyl groups attached to the ring structure. It is concluded from the present findings that *Aloe vera* pre treatment reduced the toxic effect caused by the cadmium and radiation.

Acknowledgements

Authors gratefully acknowledge the 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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