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Research Article

HISTOPATHOLOGICAL CHANGES IN ADHATODA VASICA TREATED MICE STOMACH AFTER GAMMA-IRRADIATION.

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ABSTRACT

In the present study, *Adhatoda vasica* extract administered and radiation induced changes in the stomach of Swiss Albino male mice were studied. Animals were divided into four groups: Group I containing normal mice served as control for each experimental stage, mice of Group II received oral administration of ***Adhatoda vasica*** extract.(900mg/kg body weight),mice of group III received oral administration of *Adhatoda* extract and were irradiated with 4Gy γ –rays, mice of group IV were irradiated with 4Gy γ-radiation. *Adhatoda* extract was adminstred orally to the animals (900mg/kg body weight) for a period of 28 days. After 7 days of extract administration mice were irradiated with 4 Gy γ-rays. 24 hours after irradiation mice were sacrificed by cervical dislocation. on days 7,14,21and 28. Excised tissue was fixed in 10% neutral formalin. Sections of 5µm thickness were stained with hematoxylin and eosin for histopathological examination. Histological changes in the mice stomach were observed between 7-28 days of investigation. Extract treated group of mice showed no alterations in the architecture of gastric mucosa. Mice which were pretreated with extract and then irradiated showed continuous mucosal layer and also disruption is minimized. In the irradiated group the damaged mucosal layer with lesions at different regions of mucosal lining i.e gastritis is pronounced. Gastric glands are disorganized showing large intracellular spaces. Muscularis mucosal slips become irregular.

Keywords: Radiation, *Adhatoda vasica*, Gastric Mucosa, Swiss Albino Mice.

INTRODUCTION:

All the physical and chemical agents present in the environment, radiation is undoubtedly known to produce deleterious effects on living organisms. Man may be exposed to radiation emanating from detonation of nuclear weapons, travel in outer space or nuclear vehicles, employment in nuclear power installations, utilizing radiation for industrial use or in hospitals for diagnostic and therapeutic purposes. Radiation is often used to treat malignant tumours, or in combination with surgery or chemotherapy. Despite the advantage of radiotherapy and the improvements in techniques, many patients experience moderate to severe side effects including xerostomia, diarrhoea, mucositis, dermatitis, ulceration and fibrosis (Dormand *et al*., 2005).These days due to total dependence on allopathic medicinal system, our immune system has become so adaptive that allopathic medicines have no positive effects on body; rather, various side effects on body are emerging day by day (Kaur *et al.,* 2013). The Indian system of medicine offers a large number of plants in the treatment of different diseases including cancer. The herbal drugs have been used by mankind since time immemorial to treat various ailments and offer an alternative to the synthetic compounds, as they are considered either non-toxic or less toxic than their synthetic counterparts. Reports are available for radioactive properties of various plants like ocimum sanctum (Devi, 2007) *Adhatoda vasica* (Kumar *et al*.2003, Emblica officinalis. Singh *et al* 2006) ,Tinospora cardifolia(Sharma & Goyal 2014). Herbal drugs like triphala,abana,cystone and mentat have also been reported to protect mice against radiationa induced lethality (Jagetia *et al*.,2002and 2003;Jagetia and Baliga, 2002,2003). *Adhatoda vasica* is a well known plant drug in Ayurvedic and Unani medicine, well documented for therapeutic potentials and is described as anti-bleeding and anti-asthamatic. *Adhatoda vasica*, an evergreen, gregarious stiff and perennial shrub of family Acanthaceae has been used as herbal medicine in treating a wide variety of diseases in

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India. It grows throughout the Indian peninsula upto an altitude of 1300 m on wastelands in a variety of habitats and types of soil. It has been used as traditional medicine for over 2000 years. It possesses a wide spectrum of medicinal properties. The drug is employed in different forms such as fresh juice, decoction, infusion and powder; also given as alcoholic extract and liquid extract or syrup. The leaf juice is stated to be for diarrhoea, dysentry and glandular tumor. A number of different principles including alkaloids vasicine, vasicinone, vasinol, essential oil: betane vitamins: vitamin C, B-carotene, a non crystalline steroid: vasakin and a mixture of fatty acids have been identified as contributing to the observed medicine effects of the plants.(Wealth of India, 1989). The powder of *A. vasica* is reported to be used as poultice on rheumatic joints as counter irritant on inflammatory swelling ,on fresh wounds, urticaria and in neuralgia (Claeson *et al* .,2000). In vivo, investigations have revealed that 90% ethanolic extract of A.Vacica possesses promising teratologic effects in rats (Nath *et al*., 1992). *A. vasica* has antioxidant and hepatoprotective properties (Dhuley, 1999).One of the principal mechanisms of the radiation damage is the production of free radicals by by conjugation phase II enzymes results in radioprotection .Singh *et al.,* 2000 showed that hydroalcoholic extract of A. vasica modulate the phases I and II enzyme system and thus results in cancer chemoprevention in mice model system. Stomach is light grey sac, wide curved situated a bit obliquely on left side of anterior part of abdomen. The stomach walls are made of three layers mucosa, submucosa, muscularis externa and serosa.The cellular component of stomach consists of a mixedpopulation of cells of three main types:acid secreting cells (parietal cells),mucus secreting cells and pepsin secreting cells (zymogenic cells)(Heath *et al*.,1999) The major function of the stomach is to temporarily store food and release it slowly into the duodenum. The present study is designed to investigate the histopathological effect of *Adhatoda vasica* extract on irradiated stomach of mice.

MATERIALS AND METHODS

Animals:

The present investigation was carried out on stomach of mice. Adult sexually mature Swiss albino mice weighing between 20 – 30 g were procured from Central Research Institute (CRI), Kasauli (H.P.). They were maintained in polypropylene cages in the animal house of Department of Biosciences, H.P.University, under hygienic conditions with proper temperature and light (24±2˚C, 12:12 hours light dark cycle). Mice were fed upon Hindustan lever pellets diet and water *ad libitum*. All experimental procedures were conducted after Institutional Animal Ethics Committee Approval (IAEC/Bio/2009/11)of H.P.University, Shimla.

PREPARATION OF *ADHATODA VASICA* LEAF EXTRACT

Leaves of *Adhatoda vasica* were collected from herbal garden Joginder Nagar, H.P and were properly identified by the taxonomist of Biosciences, H. P .University, Shimla . Leaves were washed thoroughly and dried under shade for one month. Dried leaves were grinded to a coarse, green coloured powder.

Extraction:

Dried leaf powder was extracted 5 times with 80% ethanolic solution. Extraction was done after every twenty four hours. Collected suspension was concentrated under reduced pressure.

Source of Irradiation:

2-3 weeks old mice were irradiated in “Gamma Chamber-900” (BARC) with automatic timer having Cobalt 60 as the source of gamma rays.

Grouping of Animals:

Mice were randomly divided into 4 groups of 8 animals each.

(i) First group i.e. designated as control: Group I containing normal mice served as control for each experimental stage.

(ii) Second group i.e. designated as treated: Mice of Group II were maintained under identical conditions and received oral administration of ***Adhatoda vasica*** extract (900mg/kg body weight).

(iii) Third group i.e designated as treated and irradiated: Mice of group III were maintained under identical conditions and received oral administration of *Adhatoda* extract and irradiated with γ –rays.

(iv) Fourth group- i.e designated as irradiated only:- Mice of group IV were maintained under identical conditions and irradiated with γ-radiation.

Determination of Optimum dose of extract:

Mice were given *Adhatoda* extract orally (600 mg/kg body weight) for 7 consecutive days. One hour after last administration animals were exposed to whole body 6.0 Gy gamma radiation. Only the mortality rate was studied in this group.

Mice were given *Adhatoda* extract orally (900mg/kg body weight) for 7 consecutive days and one hour after last administration animals were exposed to whole body 6.0 Gy gamma radiation. Only the mortality rate was studied in this group.

Modification of Radiation Response:

Adhatoda extract was adminstred orally to the animals (900mg/kg body weight) for a period of 28 days. After 7 days of extract administration mice were irradiated with 4 Gy γ-rays. 24 hours after irradiation mice were sacrificed by cervical dislocation. Similarly they were sacrificed by cervical dislocation on days 7, 14, 21 and 28. Stomach of normal, treated, treated+irradiated and radiated mice were excised, kept in refrigerator & then processed for further investigations.

Body and Organ Weight:

Body and organ weight of normal and treated mice were recorded at various stages of investigation. Thereafter 8 animals at each stage were sacrificed for further investigation. The excised tissues were employed for histological and biochemical investigations.

Histological Studies:

The stomach was excised immediately after sacrificing the animals. Tissue was fixed in aqueous bouin's fixative for 24 hours. Tissue was then washed thoroughly in running tap water till excess of fixative got washed away. Tissues were dehydrated finally in different grades of alcohol.(30%,50%,70%,90%,100% for 30 min each) cleared in xylene (15min.) and lastly embedded in paraffin wax (58-60˚C). Thin sections (5-6µ) were cut on a rotary microtome and subjected to haematoxylin eosin staining.

Haematoxylin eosin staining:

Ribbons of tissue sections were cut and stretched on albuminised coated slides in warm water. These were subjected to dewaxing in xylene at 37˚ C overnight followed by dehydration in descending grades of alcohol (100%, 90%, 70%, 50% and 30%) for 30 minutes each. Sections were then finally kept in distilled water and subjected to haematoxylin eosin stain for 20-40 minutes. Sections were passed through acid water (0.1% of HCl in distilled water) and alkali water (81% NH_3 in distilled water). Tissues were again washed in distilled water and dehydrated in ascending grades of alcohol (30%, 50%, 70%, 90% and 100%) for 30 min. each. Counterstaining was done in 2% alcoholic eosin for 2-3 min. Excess of stain was removed in 90% alcohol. Sections were then dehydrated completely in absolute alcohol. These were cleared in xylene and mounted in DPX. The permanent slides were dried in oven, examined and photographed for further studies.

RESULTS AND DISCUSSIONS

Body weight and organ weight changes are depicted in table 1 & 2.

Adhatoda extract treatment causes a slight increase (14.34%) in body weight upto 28 days of treatment. Irradiated animals reveal a decrease in body weight (14.09%) as compared to control upto 28 days of treatment. Adhatoda extract treated and irradiated mice exhibits an increase of 12.00% in body weight upto 28 days of treatment. Adhatoda extract causes a small increase in the organ weight (stomach) from 1.20% to 1.51 %. Irradiated stomach results in decline of 3.35% and 1.86% respectively in comparison to control. Adhatoda extract + Irradiation treatment causes an increase in stomach weight as compared to only irradiated group.

Histological Study:

Administration of Adhatoda extract did not alter the architecture of gastric mucosa. Mucosal epithelium is intact and gastric glands and gastric pits are arranged properly. Sections of irradiated mice stomach at 7 days stage show disorganized arrangement of gastric cells. Due to the disruption of gastric glands, large intracellular spaces between the gastric cells are observed. At 14 days stage, erosions or lesions are seen as breaks in mucosa. The lamina propria is damaged and glands

are ruptured. Thin slips of muscularis mucosa are observed. At 21 days stage sections demonstrates the disturbed arrangement of gastric cells. Large intracellular spaces are noticed. Clustering of parietal cells and irregular muscularis mucosal slips are observed. The 28 days stage demonstrates the damaged mucosal layer with lesions at different regions of mucosal lining i.e gastritis is pronounced. Transverse sections of stomach of Adhatoda extract treated and irradiated mice at 7 days stage reveals almost normal and continuous mucosal layer and formation of the epithelial layer. The arrangement of gastric cells is compact. No intracellular spaces are visualized. Gastric pits lying parallel to one another are observed. At 14 days stage, the mucosa shows more compact and well organized arrangement of cells. Gastric glands and gastric pits are clearly witnessed. At 21 days stage, sections of stomach show the restoration of gastric mucosa. Mucus secreting cells, parietal cells and regular purple stained strips of muscularis mucosa are observed. At 28 days stage, the mucosal layer is compact and thick as compared to the normal and only irradiated mice. Disruption of mucosa is minimized. Arrangement of cells is compact and organized.

Table 1:

	Days			
	7	**14**	**21**	**28**
Normal	22.10±0.07	22.70±0.06	22.80±0.05	23.00±0.04
AE	23.00 ± 0.04*	24.80±0.05*	25.60±0.11	26.30 ±0.07*
%Increase	4.07%	9.25%	12.28%	14.34%
IR	19.00± 0.10	19.60±0.06	20.20±0.10	21.00±0.05
AE+IR	20.95±0.04*	21.80±0.06*	22.76±0.09*	23.76±0.06*
%Increase	9.33%	11.22%	11.27%	12.00%

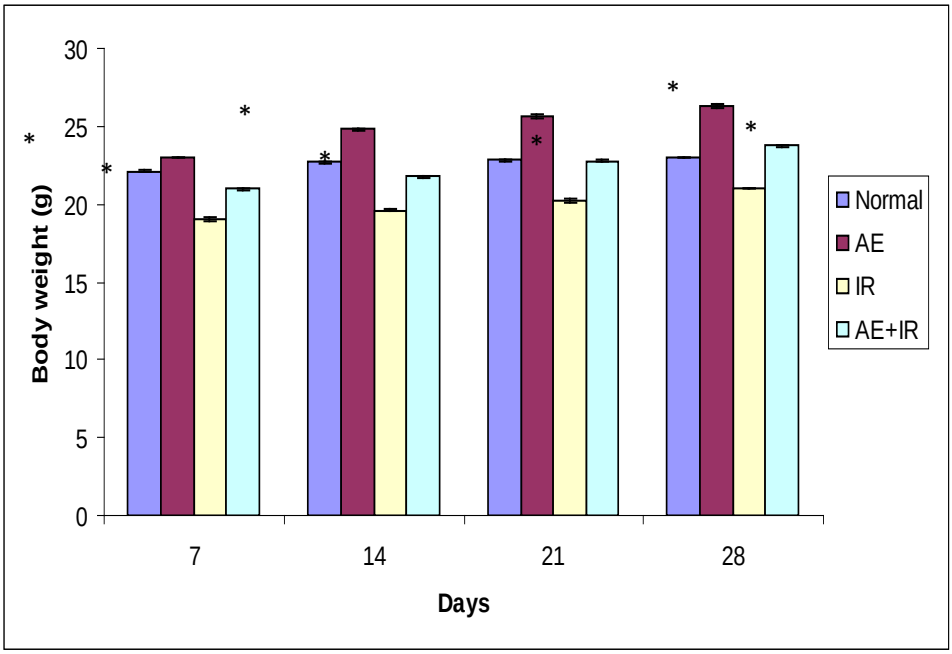

Table 1 and Figure 1: Change in Body weight (g) of normal, Adhatoda extract treated (AE), irradiated (IR) and Adhatoda extract treated+ irradiated (AE+IR) mice during 7-28 days period. Value are mean ± SEM; n=3 (P*<0.05)

Table 2:

	Days			
	7	**14**	**21**	**28**
Normal	131.40±6.50	131.75±1.12	131.99±1.03	132.00±4.13
AE	133.10±1.60	133.20±2.20	133.70±1.02	133.99±4.00*
%Increase	1.2%	1.10%	1.30%	1.51%
IR	127.00±6.40	127.35±0.50	127.86±4.10	128.10±4.90
AE+IR	129.15±3.30*	129.80±2.20*	130.15±1.70*	130.55±2.10
%Increase	1.69%	1.92%	1.80%	1.91%

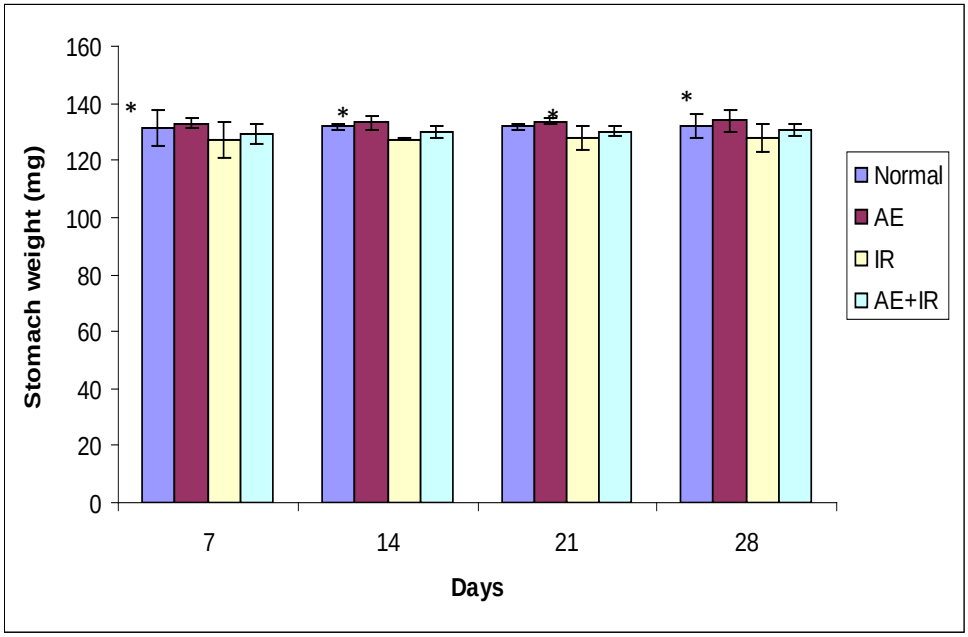

Table 2 and Figure 2: Changes in stomach weight (mg) of normal, Adhatoda extract treated (AE), irradiated (IR), Adhatoda extract treated + irradiated mice during 7-28 days period. Values are mean ± SEM; n=3 (P*< 0.05).

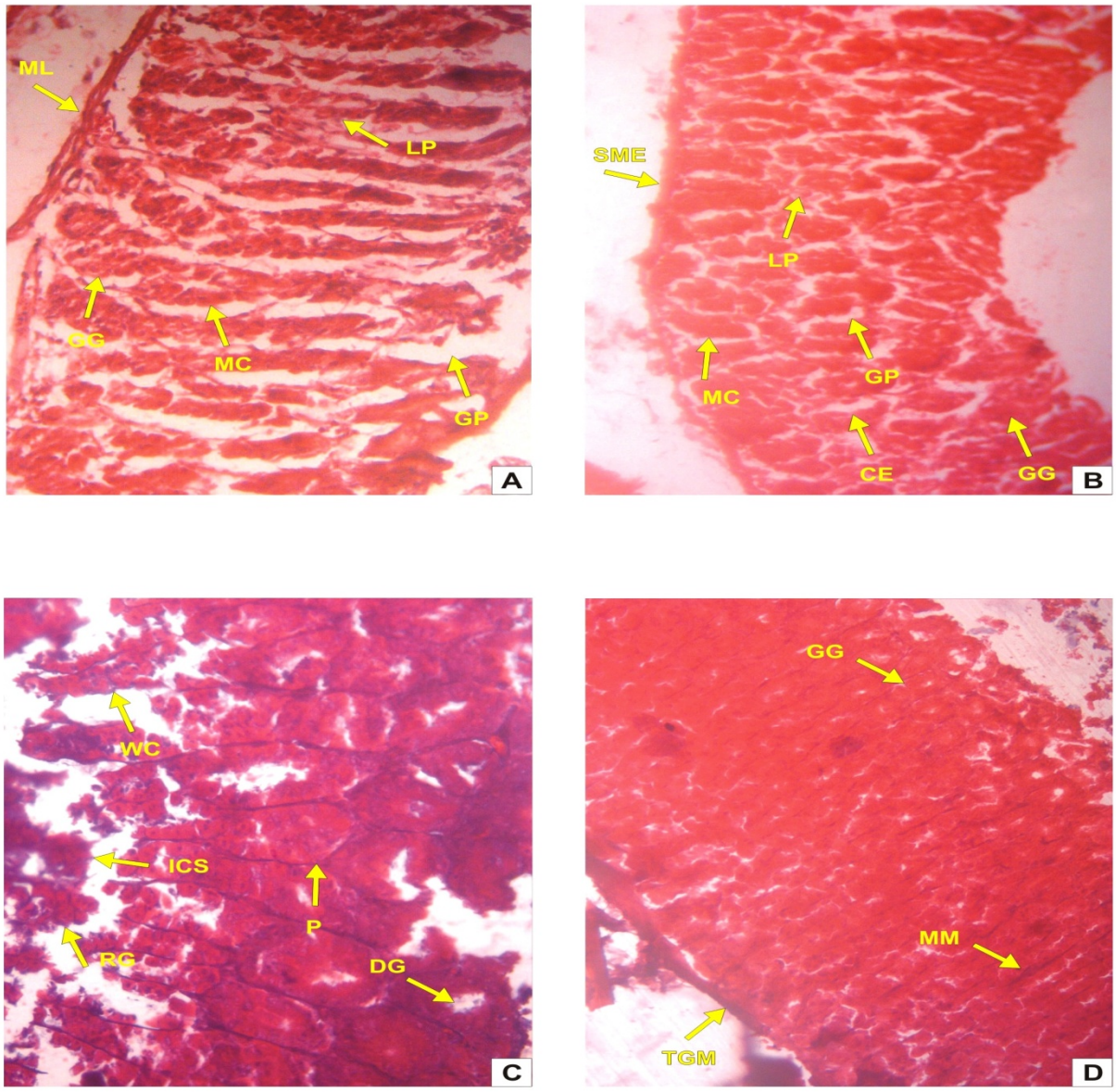

Figure 3:

A) T.S of normal mice stomach at 7 days stage showing the gastric mucosal layer (ML). Mucosa with a layer of connective tissue lamina propria (LP) which fills the narrow spaces between the gastric glands can be identified. Gastric glands (GG) and gastric pits (GP) occupying the entire thickness of mucosa are also seen X400.

B) T.S of stomach of adhatoda extract treated mice at 7 days stage revealing normal architecture of mucosa surface mucinous epithelium (SME) and lamina propria (LP) can be identified. Mucus secreting cells (MC) of gastric glands (GG) and gastric pits (GP) can also be observed. Columnar epithelium lining gastric cells can also be observed X400.

C) T.S of stomach of irradiated mice at 7 days stage demonstrating large intracellular spaces (ICS) between gastric cells. Some dilated glands (DG) lined by mucus cells can also be noticed. Arrangement of cells is wrinkled (WC) and some polygonal cells (PC) are also observed. Large number of ruptured glands (RG) are also noticed X400.

D) T.S of stomach of mice given adhatoda extract for 7 days and irradiated depicting thick gastric mucosa (TGM) with compactly arranged gastric cells (GG). Thin slips of muscle from muscularis mucosa (MM) extend into lamina propria between gastric glands (GG) are also observed X400.

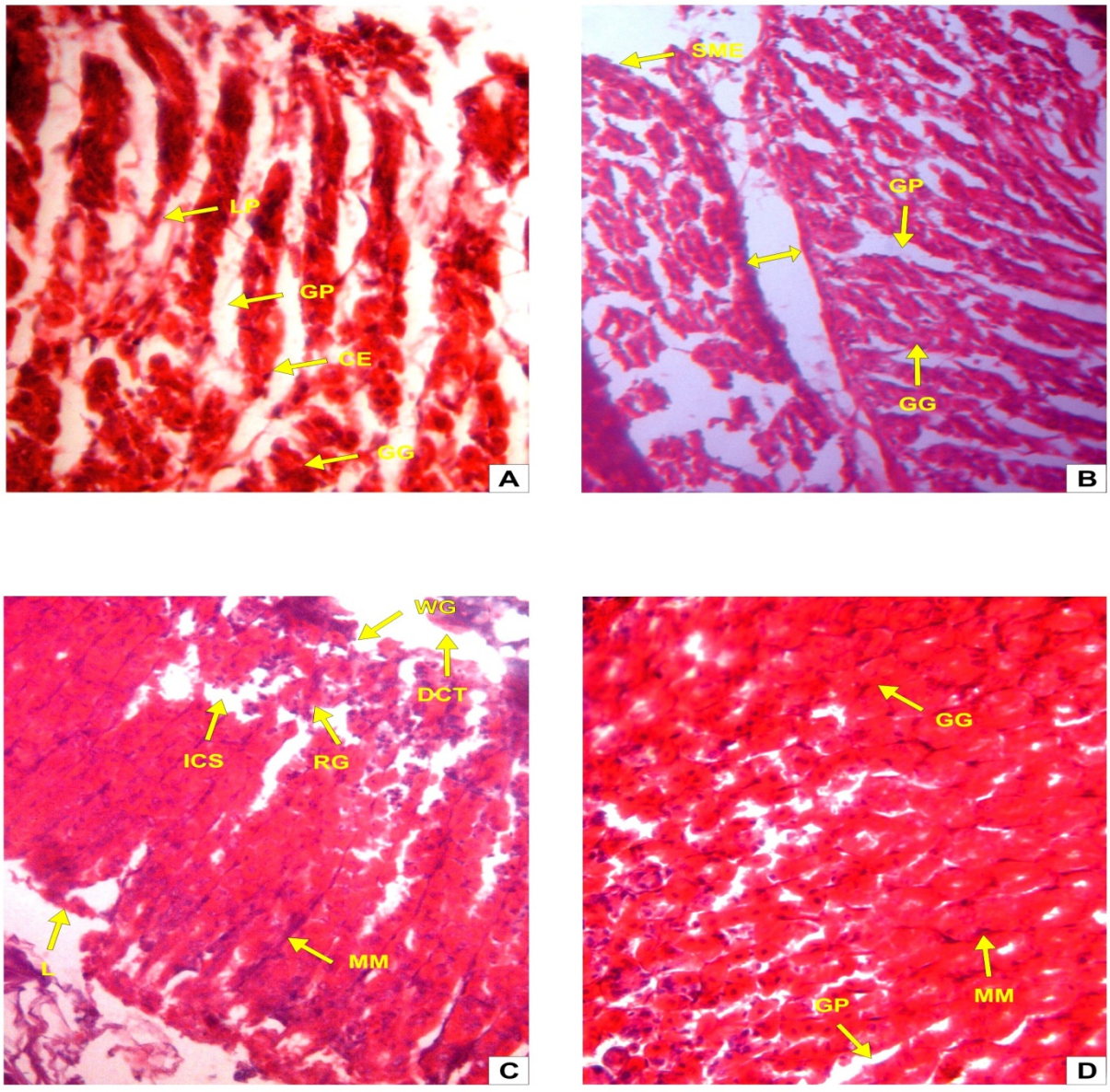

Figure 4:

A) T.S of normal mice stomach at 14 days stage showing mucosa with compactly arranged gastric glands (GG) and gastric pits (GP). Lamina propria (LP) and columnar epithelium (CE) lining gastric cells surface can also be observed X400.

B) T.S of stomach of adhatoda extract treated mice after 14 days stage revealing gastric folds (↔) in the mucosa. Surface mucinous epithelium (SME), gastric glands (GG) and gastric pits are also visible X400.

C) T.S of stomach of irradiated mice after 14 days stage demonstrating the lesions in the mucosa (L), Ruptured glands (RG) and wrinkled arrangement of gastric glands (WG). Muscularis mucosal slips (MM) and degenerative connective tissue (DCT) is also observed X400.

D) T.S of stomach of mice given adhatoda extract for 14 days and then irradiated depicting the thick mucosa with compactly arranged cells. Gastric glands (GG) and Gastric pits (GP) are also observed. Muscularis mucosal slips (MM) are also noticed X400.

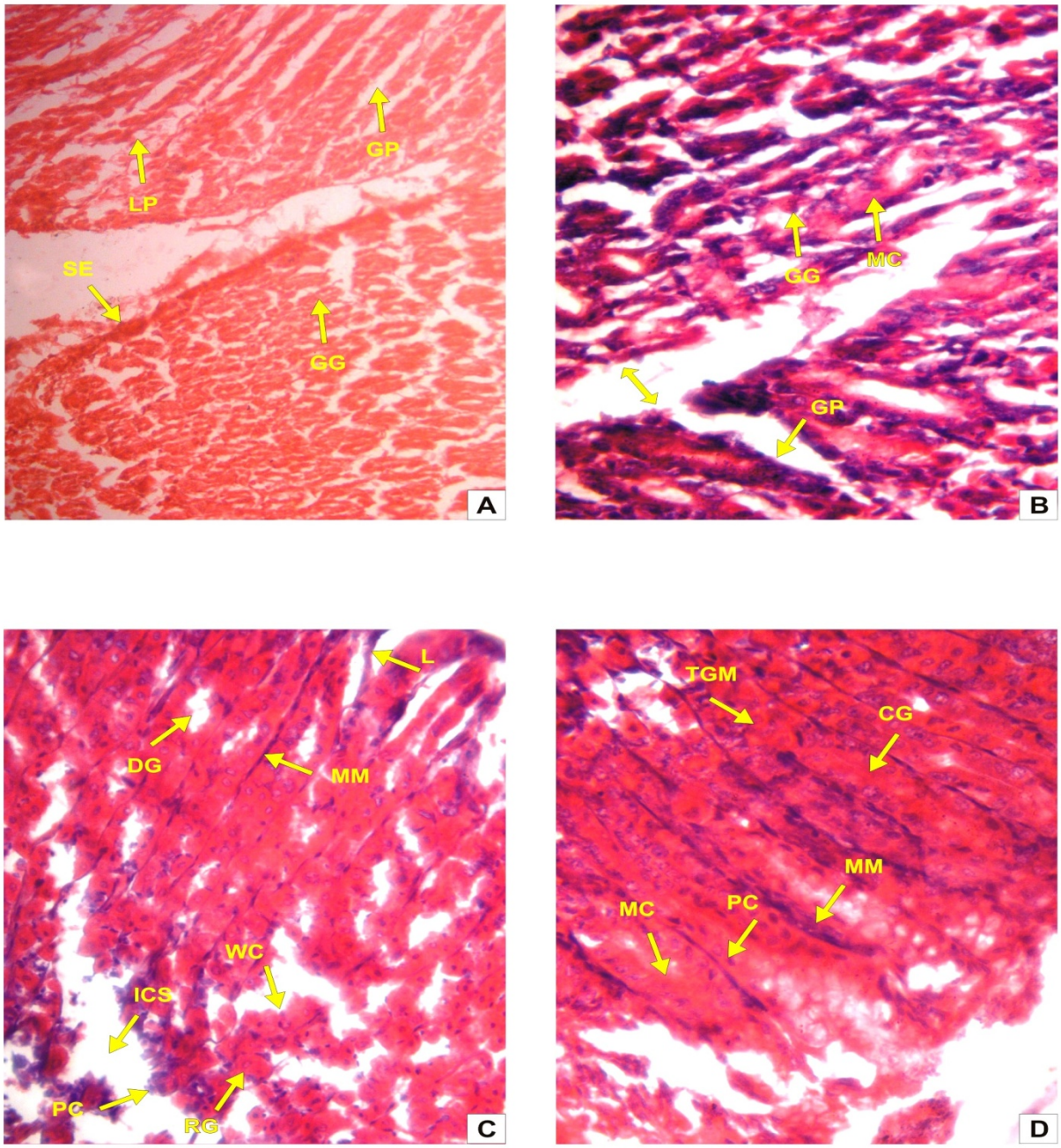

Figure 5:

A) T.S of normal mice stomach at 21 days stage demonstrating normal architecture of gastric mucosa with well arranged gastric glands (GG) and gastric pits (GP) X400.

B) T.S of stomach of adhatoda extract treated mice at 21 days stage depicting gastric folds (↕) and well arranged gastric glands (GG) and Gastric pits (GP). Mucus secreting cells (MC) are also observed X400.

C) T.S of stomach of irradiated mice at 21 days stage demonstrating dilated glands (DG) lined by mucus cells. Wrinkled cell arrangement (WC) and large intracellular spaces are observed (ICS). Lesions in mucosal layer (L) and clumping of parietal cells (PC) are also seen. Gastric glands are ruptured (RGG) and thin muscularis mucosal slips (MM) can also be noticed X400.

D) T.S of stomach of mice given adhatoda extract for 21 days and irradiated mice stomach showing thick gastric mucosa (TGM) with compactly arranged gastric cells (GC). Mucus secreting cells (MC), parietal cells (PC) and muscular mucosal slips (MM) can also be noticed X400.

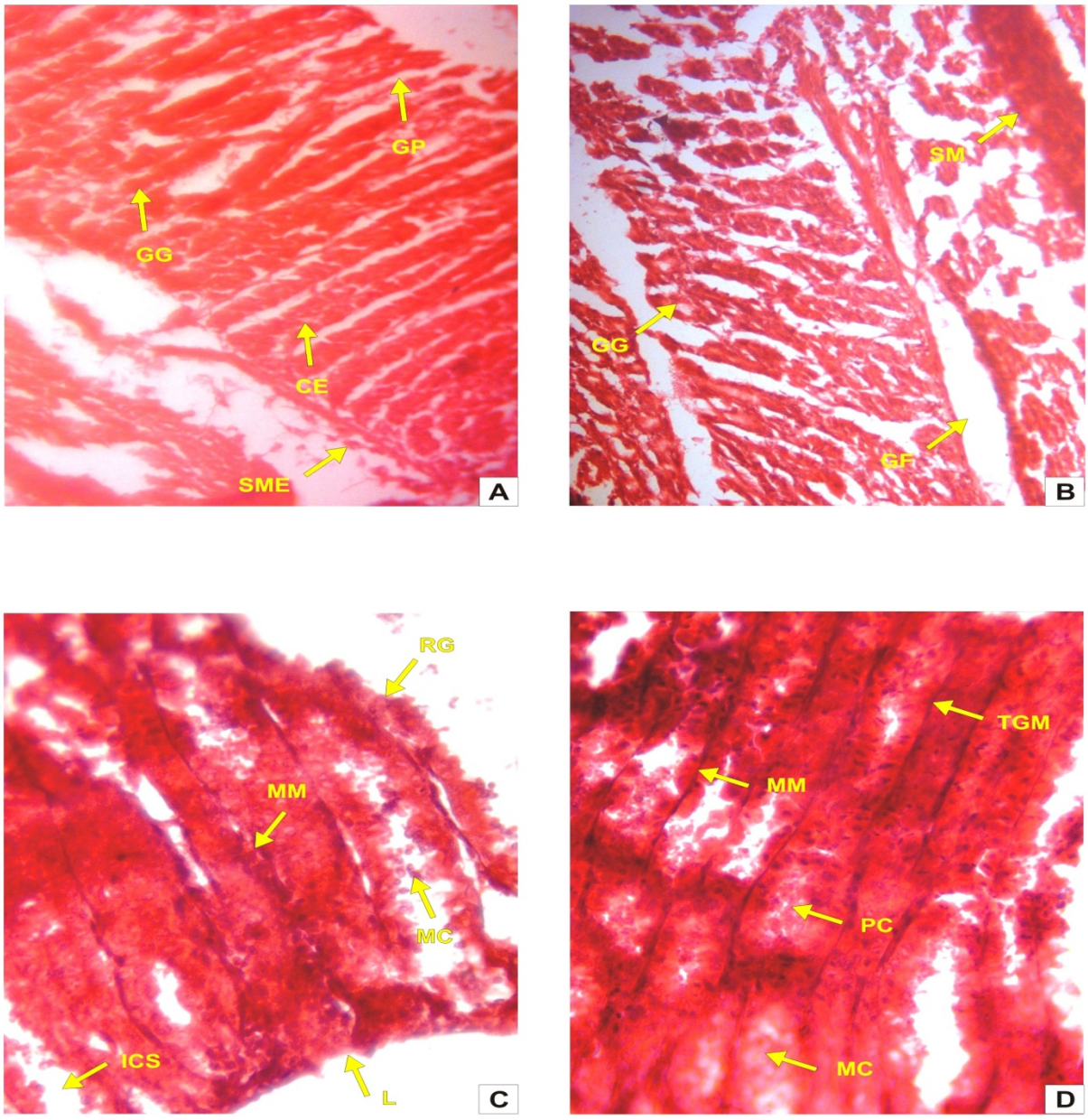

Figure 6:

A) T.S of normal mice stomach at 28 days stage showing intact mucosa with surface mucinous epithelium (SME), neatly arranged gastric glands (GG) and gastric pits (GP). Columnar epithelium (CE) lining the gastic glands can also be observed X400.

B) T.S of stomach of adhatoda extract treated mice at 28 days stage depicting gastric folds (↔), gastric glands (GG) and gastric pits (GP) in the mucosa. Submucosal layer can also be noticed X400.

C) T.S of stomach of irradiated mice at 28 days stage demonstrating the damaged mucosal layer. Ruptured gastric cells (RG) and mucus cells (MC) are observed. Large intracellular spaces (ICS) and muscularis mucosal slips (MM) are also seen. Lesions (L) at different places of mucosa are also noticed X400.

D) T.S of stomach of mice given adhatoda extract for 28 days and irradiated after 28 days showing thick gastric mucosa (TGM) with compactly arranged gastric cells. Muscularis mucosal slips (MM), mucus cells (MC) and parietal cell (PC) are also observed X400.

DISCUSSION

Ionizing radiation is one of the most horrible ecological crisis to which living beings are subjected. The inadvertent exposure of human to various sources of radiation causes ionization of molecules that set off potential damaging reactions leading to different health disorders. The use of products from natural sources could be a better choice to reduce the effects of radiation. Herbal medicines are being used upto 80% of population in developing countries. *Adhatoda vasica* belonging to family Acanthaceae possesses a wide spectrum of medicinal properties. It is used as an herbal formulation owing to its antinflammatory, analgesic, antiasthmatic, antioxidant and antihaemorrhagic activities. It lowers the blood pressure, eases muscular cramps or convulsions and stimulates contraction of uterine muscle facilitating or speeding up child birth.

The present study demonstrated that *Adhatoda* extract treatment to mice causes a little effect on body weight of mice. Since changes in body weight have been used as an indicator of good health (Chauhan and Agarwal, 2008; Singh and Singh, 2009) Our results suggest that dose of Adhatoda extract administered orally is non –toxic to mice. Adhatoda extract pretreated and irradiated animals showed an increase in body weight. But irradiated mice showed loss in body weight. The weight loss may be due to the gastrointestinal damage following irradiation. The weight loss is also associated with decrease in water intake by animals (Nakamura *et al.*, 1968). The dose dependent weight loss in mouse has also been reported (Chapman and Jerome, 1956; Shinoda *et al.*, 1967). The stomach of extract treated mice showed very slight changes in their weight. The stomach weight of Adhatoda extract treated plus irradiated mice showed increase in organ weight. The organ weight is lowered in irradiated mice. One of the earliest effects of radiation is reduction in organ weight which reflects the histopathological changes in tissue. Mechanisms which cause reduction in muscle mass and muscle strength include physical inactivity, oxidative stress and chronic inflammation.

The effect of *Adhatoda vasica* extract and gamma radiations are studied on stomach by studying the histopathological changes. Stomach demonstrates well formed mucosa with gastric folds, innumerable gastric cells with gastric pits in between. Lamina propria fills the spaces between gastric glands. *Adhatoda* extract treated stomach demonstrates the normal architecture of gastric mucosa with no anatomical changes. *Adhatoda vasica* had patent antioxidant effect (Sarwat *et al.*, 2006; Kumar *et al.*, 2007). Antioxidants significantly strengthen the gastric walls and protect tissue from oxidative damage (Rajesh *et al.*, 2009). Irradiated stomach gastric mucosa is severely damaged. Irradiation causes thining of mucosa. The gastric cells arrangement is distorted; some dilated glands lined by mucus cells are noticed. Disruption of gastric cells lead to clumping of these cells and large intracellular spaces are observed. Lesions and erosions are also noticed in the mucosa. Present results are in agreement with Goldgraber *et al.,* (1954) who found that irradiation causes patchy loss of glandular architecture, marked architectural disorganization and loss of mucosal thickness. Degenerative changes in gastric cells (Chief, mucus and parietal cells of gastric mucosa) after irradiation are also explained by Michael and Alberts (1970).

Radiations cause frequent mucosal damage (Berthrong and Fajardo, (1981) with apoptosis, epithelial flattening and glandular dilatation. *Adhatoda* extract treated and irradiated mice stomach demonstrates the thick and intact gastric mucosa. The arrangement of gastric glands is compact and number of degenerating cells is also reduced. Gastric lesions began to heal. Pretreatment of mice with *Adhatoda* extract reduces the gastric damage and normalizes its architecture. Our results are in agreement with the findings of Mahmood *et al*., (2010) who reported that *Gynura procumbens* leaf exerts a protective effect against mucosal lesions through inhibition of neuotrophil infilteration in ulcerated gastric tissue. The gastro protective role of *A. vasica* is probably due its antioxidant properties. Similar results were shown by the study of Jindal *et al*., (2004) where pretreatment with plant extract inhibits mortality and protection against radiation induced deleterious alterations in intestinal mucosa of mice. Bhattacharya *et al*., (2004) demonstrated that pretreatment with *Emblica officinalis* modulates TNF-α and I-L-1B and prevent radiation

induced gastric damage. Geirforte, a polyherbal formulation containing Adhatoda as one of it constituent also protects against gastrointestinal and bone marrow death (Jagetia *et al.*, 2004).The stem bark extract of Ziziphus jujube has an effective activity against gastiric mucosal injury(Hamedi *et al*.,2015). The present study has convincingly demonstrated that stomach can be protected from radiation induced damage by *Adhatoda vasica* leaf extract.

Therefore radioprotective effects of Adhatoda extract are due to the antioxidant properties of its chemical constituents. The traditional use of *Adhatoda vasica* as herbal medicine has been very well documented. The drug has been used for a long period of time with no serious adverse effects reported or documented. However the plant can also be further explored against wide spectrum of microbes and can be developed into a powerful antibiotic.

CONCLUSION

The medicinal effects of ethanolic extract of *Adhatoda vasica* on deteriorating effects of gamma radiations on the cellular structure of stomach taking albino mice as a subject of study has been well accomplished. Pretreatment of mice with extract dose reduces gastric damage and normalize its architecture, the exposure to radiations causes damage to glandular architecture and disorganized structure in comparison to the control.

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