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Research Article

NEPHROPROTECTIVE EFFECT OF GINGER (*Zingiber officinale*) EXTRACT AGAINST LEAD INDUCED RENAL TOXICITY IN MALE ALBINO RATS

Pratap M*[1]., Jyothi M[2] and Baburao G[3]

[1]Department of Zoology, Sri Krishnadevaraya University, Anantapuramu, Andhra Pradesh, India
[2]Department of Botany, Sri Krishnadevaraya University, Anantapuramu, Andhra Pradesh, India
[3]Department of Zoology, NB Science College, Hyderabad, Telangana, India

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ABSTRACT

The aim of this study was to investigate the nephroprotective effects of ginger extract against nephrotoxicity induced by lead acetate in male albino rats. Adult 42 healthy male albino rats were divided into 7 groups, each of six rats were used. Lead acetate induced kidney damage showed deleterious histological changes such as significant glomerular and tubular degenerations varying from, glomerular basement thickening, pycnotic nuclei, medullary vascular congestion and moderate to severe necrosis. Treatment with ginger structural organisation of the kidney showed regenerated atropic glomeruli, regeneration of renal tubular epithelial cells and the nuclei are conspicuous centrally located without any vacuolization. It can be concluded that, the lead acetate had adverse effects on the kidney. Ginger showed effective nephroprotective action against lead acetate induced nephrotoxicity in male albino rats.

INTRODUCTION

Lead is considered as one of the most hazards and cumulative environmental pollutants that affect all biological systems through exposure from air, water and food sources (Patra *et al*., 2000). Lead is a non-threshold multi-targeted toxicant that causes alterations in different organs of the body, including the kidney (Jarrar, 2003). The absorbed lead is conjugated in the liver and passed to the kidney, where a small quantity is excreted in urine and the rest accumulates in various body organs and interferes with their function specially the kidney as a target site for lead toxicity (Jarrar *et al*., 2006).

Zingiber officinale is the most widely used spice worldwide. It has been reported as an antioxidant and detoxifying agent against alcohol abuse (Shati and Elsaid, 2009) and bromobenzene intoxication (Islam and Choi, 2008) and evaluated its antidiabetic and antihyperlipidemic activity (Matsuda *et al*., 2009).

The kidney is vital organ with several functions; serve essential regulatory roles in most animals, including vertebrates and some invertebrates. They are essential in the urinary system and also participate in whole-body homeostasis functions such as the regulation of electrolytes, maintenance of acid–base balance, and regulation of blood pressure. Kidney damage occurs with exposure to high levels of lead, and evidence suggests that lower levels can damage kidneys as well (Grant, 2009). The toxic effect of lead causes nephropathy and may cause Fanconi syndrome, in which the proximal tubular function of the kidney is impaired. Long-term exposure at levels lower than those that cause lead nephropathy have also been reported as nephrotoxic in patients from developed countries that had chronic kidney disease or were at risk because of hypertension or diabetes mellitus (Ekong *et al*., 2006). Lead poisoning inhibits excretion of the waste product urate and causes a predisposition for gout, in which urate builds up. This condition is known as saturnine gout. The present study is an attempt to characterize histological alterations induced by lead acetate in the kidney of the male albino rats.

MATERIALS AND METHODS

Animals

Adult male albino rats wistar strain (Rattus norvegicus) weighing 150±30gms obtained from Sri Raghavendra Animal Supplier, Bangalore, Karnataka. The rats were housed in clean

Corresponding author:* **Pratap M
Department of Zoology, Sri Krishnadevaraya University, Anantapuramu, Andhra Pradesh, India

polypropylene cages having 6 rats per cage and maintained under temperature controlled room (25±2^{0}C) with 12 hrs dark/light photoperiod. The rats were given standard pellets diet supplied by Sai Durga Feeds and Foods, Bangalore and water adlibitum throughout the experimental period. They were allowed to laboratory conditions for seven days after arrival before use.

Animal Ethical Clearance

Local Institutional Animal Ethical Committee of our University, obtained ethical clearance for conducting experiments on animals from committee for the purpose of control and supervision of experiments on Animals (CPCSEA) (REGD.No.470/01/a/CPCSEA, DT.24th Aug 2001).

Preparation of ethanolic extract of rhizome of Zingiber officinale

The ginger was collected from local market and cut into small pieces and dried under ceiling fan for 5 to 6 days. The dried ginger was ground in an electronic grinder and powder was collected. 50g of powder was extracted in 250ml ethanol for 18hrs in soxhlet apparatus. The extract was dried at reduced pressure, stored at 0-4^{o}C and used for the experimentation.

Experimental design

The animals were divided into 7 groups of 6 rats each and treated as follows:

- ***Group- I****:* Normal control (Nc): This group of rats received vehicle solution (5% Tween 80).
- ***Group-II****:* Ginger treatment (Gt1): Rats received ethanolic extract of ginger (200mg/Kg body weight) orally for 8 weeks.
- ***Group-III****:* Ginger treatment (Gt2): Rats received ethanolic extract of ginger (300mg/Kg body weight) orally for 8 weeks.
- ***Group-IV****:* Lead treatment (Lt): Rats received lead acetate orally at a dose of 200mg/Kg body weight orally for 8 weeks.
- ***Group-V****:* Lead treatment + Ginger treatment (Lt+Gt1): This group of rats received both lead acetate and ginger as described in group II and group IV for 8 weeks.
- ***Group-VI****:* Lead treatment + Ginger treatment (Lt+Gt2): This group of rats received both lead acetate and ginger as described in group III and group IV for 8 weeks.
- ***Group-VII****:* Lead treatment + Silymarin treatment (Lt+St): This group of rats received both lead acetate and silymarin. Lead as described in group IV and Silymarin (100mg/Kg body weight) orally for 8 weeks.

Lead acetate was dissolved in distilled water before administration. Food was withdrawn 12hr before Lead acetate administration. Ginger was suspended in 5% Tween 80.

Analytical procedures

After completion of 8 weeks treatment the animals were sacrificed by cervical dislocation and immediately liver tissues were excised at 4^{o}C. The tissues were washed thoroughly with ice-cold 0.9% sodium chloride solution (saline). Kidney tissue of every animal were suspended in 0.15 M potassium chloride in polypropylene containers, sealed with parafilm, labelled carefully and stored at -20^{o}C until assays were carried out.
In the present investigation the effect of lead toxicity, protective activity of ginger-I, ginger-II and standard drug silymarin treatment for 8 weeks on histological sections of kidney in male albino rats were observed

Histopathology

The histological sections of the kidney of rats were taken by adopting the procedure as described by humason. The tissues were isolated and gently rinsed with physiological saline solution (0.9% NaCl) to remove mucus and other debris adhering them. They were fixed in Bouin's fluid (75 ml of saturated aqueous picric acid, 25 ml of 40% formaldehyde and glacial acetic acid) for 24 hours. The fixative was removed by washing through running tap water for overnight. Then the tissues were processed for dehydration. Ethyl alcohol was used as the dehydrating agent, as it is the most suitable and economical besides its hardening effect. The alcoholic transfer schedules were so arranged as to utilize both dehydration and hardening effect. The tissues were passed through successive series containing 30%, 50%, 70%, 80%, 90%, 95% and absolute alcohols. Then the tissues were cleaned in methyl benzoate and embedded in paraffin wax. Sections of 5µ thickness were cut using "SIPCON" rotatory microtome. The sections were stained with Harris hematoxylin and counter stained with eosin, dissolved in 95% alcohol. After dehydration and cleaning, the sections were mounted in Canada balsam.

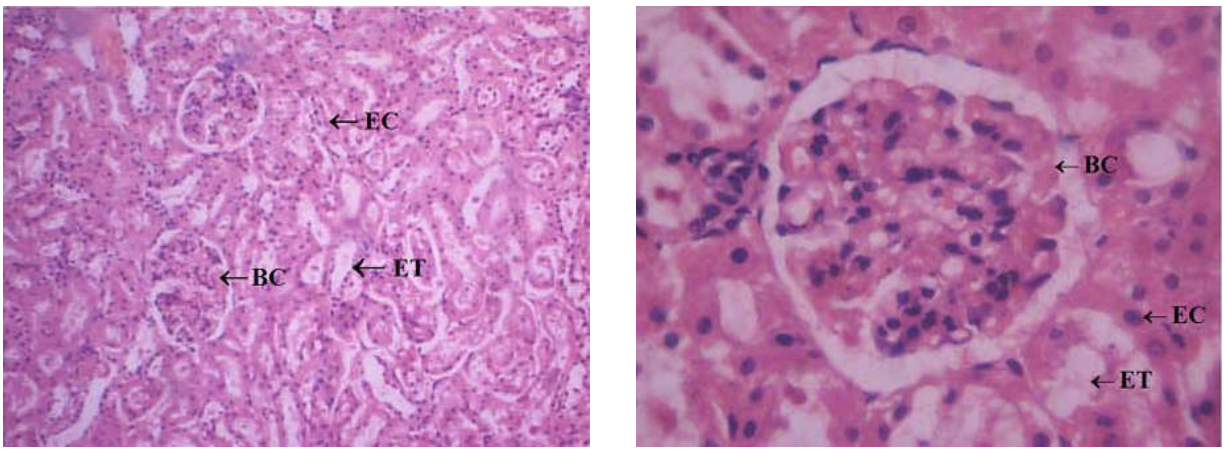

Figure 1 A Transverse section of the kidney of Normal Control (Group-I) clearly shows enlarged tubules (ET), Bowman's capsule (BC), epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

Photomicrographs of the section preparations were taken using Magnus photomicrographing equipment.

RESULTS

Oral administration of lead acetate toxicity, protective effect of ginger and silymarin on histopathological changes of kidney tissues was studied in all experimental groups for 8 weeks treatment.

Histological Analysis

DISCUSSION

Oral administration of lead acetate toxicity, protective effect of ginger and silymarin against lead acetate toxicity were described in kidney histopathological changes in all experimental rat groups for 8 weeks treatment.

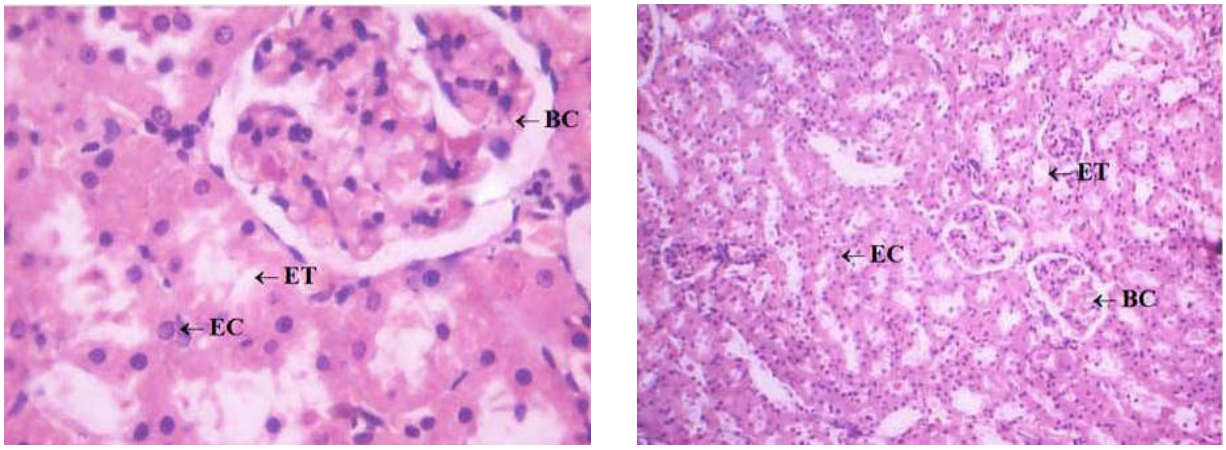

Figure2 A Transverse section of the kidney of Ginger Control-I (Group-II) clearly shows enlarged tubules (ET), Bowman's capsule (BC), epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

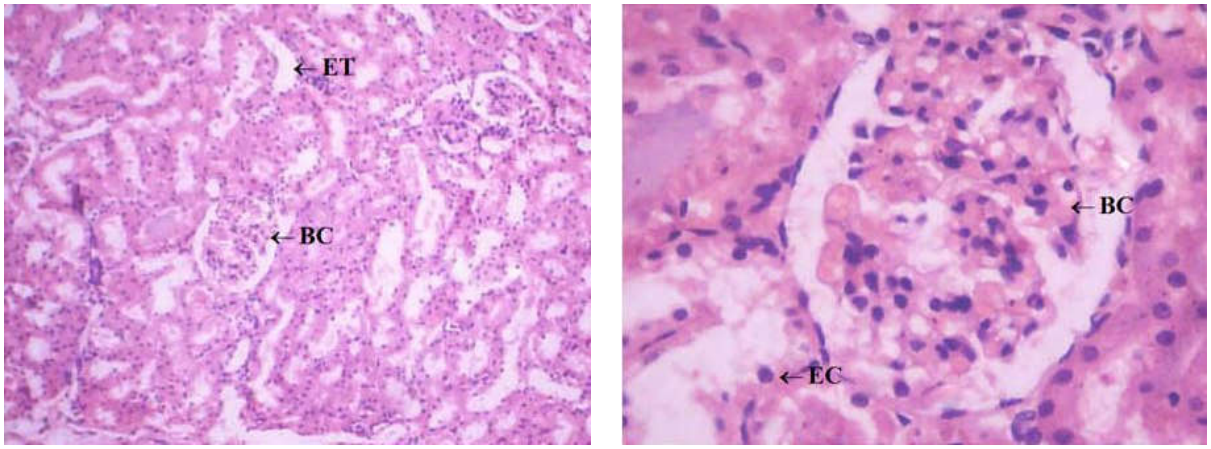

Figure 3 A Transverse section of the kidney of Ginger Control-II (Group-III) clearly shows enlarged tubules (ET), Bowman's capsule (BC), epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

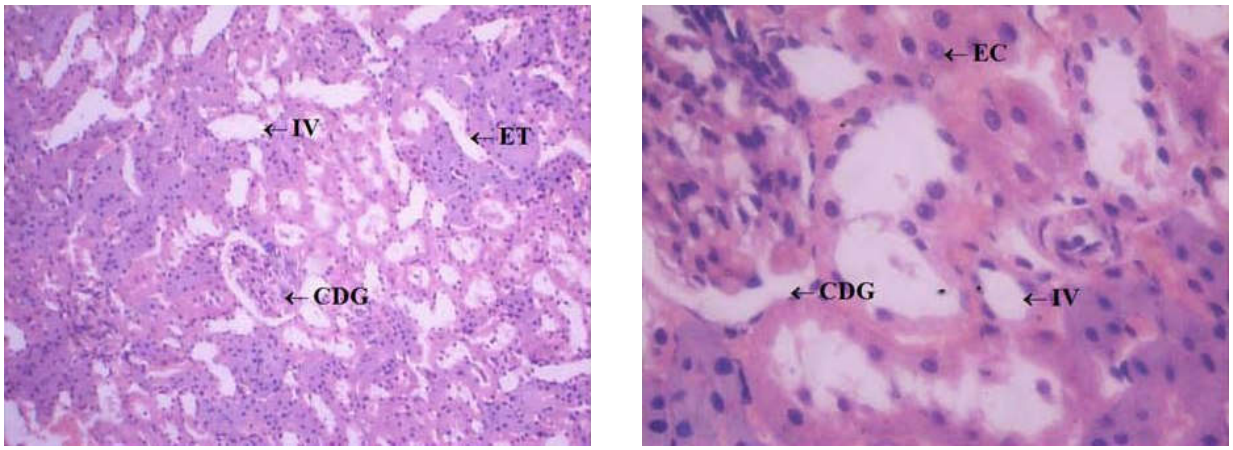

Figure 4 A Transverse section of the kidney of Lead Control (Group-IV) clearly shows enlarged tubules (ET), Degenerative Changes in Glomerulus (CDG), Increased Vacuolization (IV), epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

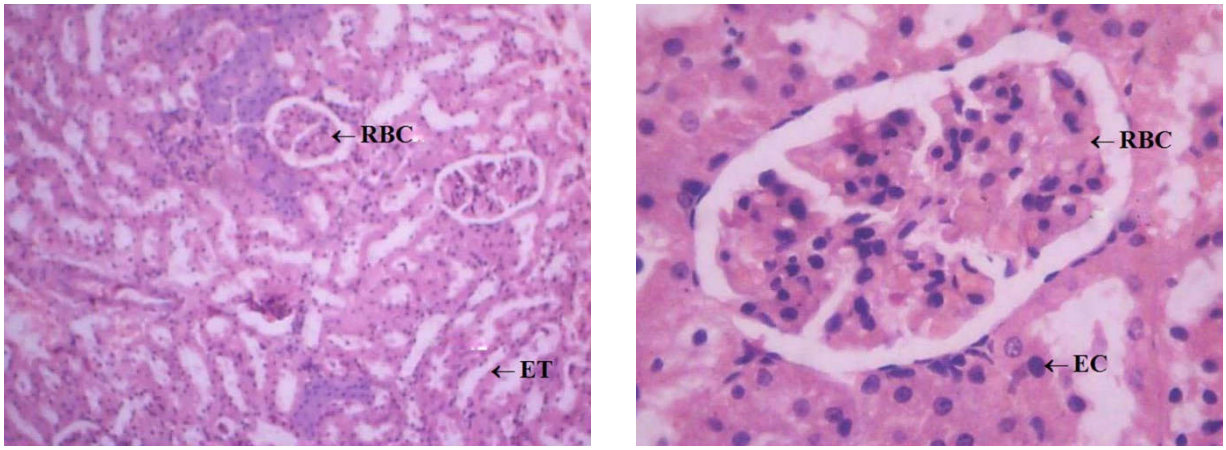

Figure 5 A Transverse section of the kidney of Lead + Ginger-I treated (Group-V) clearly shows regenerated Bowman's capsule (RBC), Enlarged tubules (ET), Epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

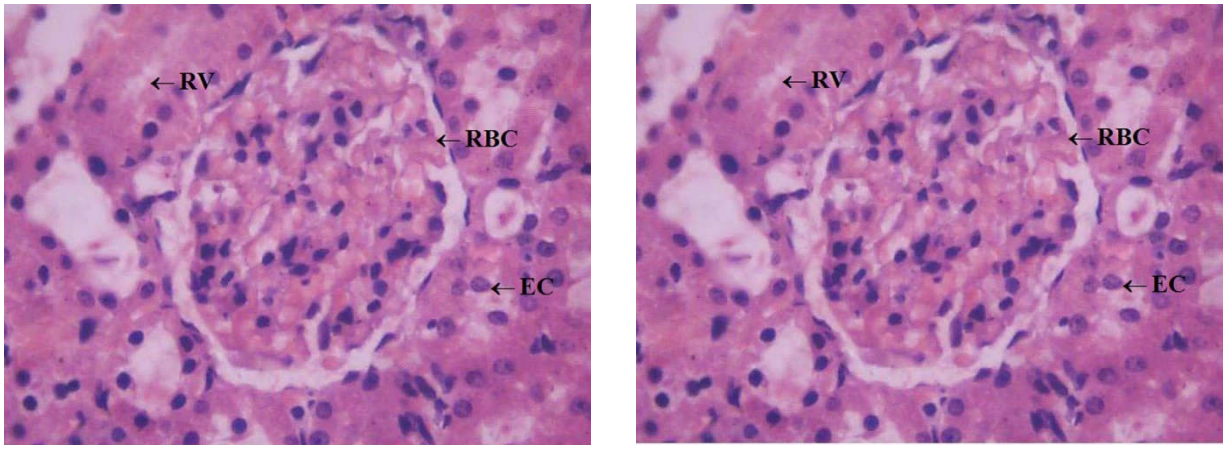

Figure 6 A Transverse section of the kidney of Lead + Ginger-II treated (Group-VI) clearly shows Enlarged tubules (ET), regenerated Bowman's capsule (RBC), Recovered vacuolization (RV), Epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

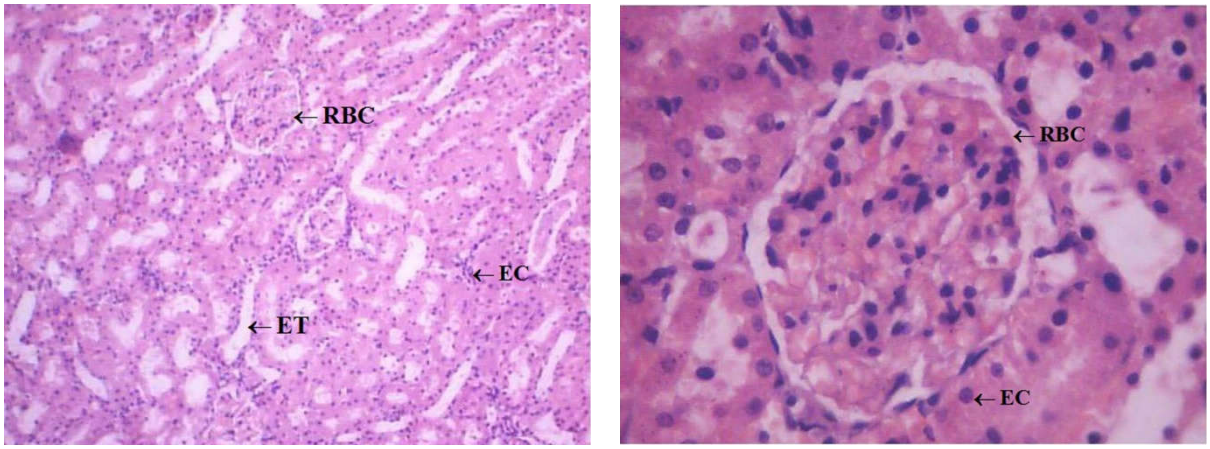

Figure 7 A Transverse section of the kidney of Lead + Silymarin treated (Group-VII) clearly shows Enlarged tubules (ET), regenerated Bowman's capsule (RBC), Epithelial cells (EC). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

In the present study kidney tissue of the normal control (group-I), ginger control (group-II,III), lead control(group-IV), ginger treated(group-V,VI) and silymarin treated(group-VII) rats were examined for structural changes under the light microscope using hemotoxylin and eosin staining. Kidney sections of the group-I (Fig.1) healthy rats revealed normal architecture of the kidney. Histological features of the kidneys showed clearly defined cortex and medulla. The cortex was distinguishable into two zones, an outer nephrogenic zone and inner deep part of cortex. The deep part of cortex contained convoluted tubules, renal corpuscles, straight tubules and medullary rays. The cortical portion of the kidneys showed many renal corpuscles consisting of glomeruli having loops of capillaries surrounded by Bowman's capsule. Group-II (Fig.2) and Group-III (Fig.3) were ginger treated animals. These groups also showed normal architecture of the kidney.

Group-IV (Fig.4) rats showed structural changes were observed when compared with normal control (group-I), ginger control-

I(group-II) and ginger control-II(group-III). In these groups of rats showed deleterious histological changes. The kidney sections showed significant glomerular and tubular degenerations varying from, glomerular basement thickening, tubular cell swelling, interstitial inflammation, pycnotic nuclei, medullary vascular congestion and moderate to severe necrosis. Ginger treatment with group-V (Fig.5) showed regenerated atropic glomeruli, regeneration of renal tubular epithelial cells and some cells showed picnotic nuclei. Treatment with ginger in group-VI (Fig.6) showed structural organisation of the kidney appeared almost normal with well defined kidney tubules and Bowman's capsule. The nuclei are conspicuous centrally located without any vacuolisation. In these ginger treated ones ginger-II is well protected from lead acetate toxicity when compared with ginger-I. Group VII (Fig.7) also showed almost nearer to normal with well defined kidney tubules and Bowman's capsule.

In the present study histopathological sections of kidney highly vulnerable to damage caused by reactive oxygen species (ROS), likely due to the abundance of polyunsaturated fatty acids in the composition of renal lipids. ROS are involved in the pathogenic mechanism of conditions such as glomerular necrosis and tubular interstitial fibrosis (Jose and Nova, 2002), Lead deposited predominantly in the proximal tubule was considered to be the main reason for its deleterious effects on the cortex of the kidney. Similar histopathological lesions have been reported in experimental lead acetate toxicity with different species (Rader *et al*., 1983).

Histological investigations revealed that lead exposure resulted in progressive glomerular and tubular alterations. These findings are in agreement with the results of previous investigations by Lin *et al*., (1993) who recorded alterations in renal histopathology due to environmental exposure to lead. Tubular vacuolization, necrosis and dilation found in the present study due to lead intoxication were reported previously by Karmakar *et al*., (1986). Tubular, interstitial and glomerular damage are also characteristic renal lesions due to lead toxicity. Tubular changes occur earlier than glomerular and interstitial changes, including development of pathognomonic intranuclear inclusions in the renal tubular epithelium (Jarrar, 2003). The toxic effect of lead causes nephropathy and may cause Fanconi syndrome, in which the proximal tubular function of the kidney is impaired (Ekong *et al*., 2006).

In support of our work Uz *et al*., (2009) reported that renal damage resulted from ischemia/perfusion injury in the kidney of rats was improved after administration of ginger. The nephroprotective effects of ethanol extract of Z. officinale alone and in combination with vitamin E (_-tocopherol) were evaluated using cisplatin induced acute renal damage in mice. The results indicated that Z. officinale significantly and dose dependently protected the nephrotoxicity induced by cisplatin (Ajith *et al*., 2007).

Ghasemzadeh *et al*., (2010) reported that young rhizome of Z. officinale had higher content of flavonoids with high antioxidant activity. Results of this study revealed that, ginger extract ameliorated metalaxyl induced nephrotoxicity. This effect is mediated by either preventing metalaxyl-induced decline of renal antioxidant defense system or by its direct free radicals scavenging activity. Ajith *et al*., (2007) reported that ginger ameliorated cisplatin- induced nerphrotoxicity and this protection is mediated either by preventing the cispaltin–induced decline of renal antioxidant defense system or by their direct free radical scavenging activity.

The kidney of group-VII (Fig.7) rats showed regenerated kidney tubules and Bowman's capsule. The protective effect of silymarin appeared to depend on many properties such as; its ability to inhibit the absorption of toxins, preventing them from binding to the cell surface and inhibiting membrane transport systems (Luper, 1998), its activity against lipid peroxidation (as a result of free radical scavenging), the ability to increase the cellular content of GSH, its ability to regulate membrane permeability and to increase membrane stability in the presence of xenobiotic damage (Pepping, 1999). Silymarin might help cells to withstand and overcome the stress response via stabilizing mitochondrial membrane potential. All these factors are favoring the survival and regeneration of the renal tissue.

Silymarin afford renal protection against lead acetate induced nephrotoxicity. This may be through preventing the necrotic changes and regulating the apoptotic process. The protective effect of silymarin is associated with its antioxidant properties, as it possibly acts as a free radical scavenger, lipid peroxidation inhibitor and as glutathione levels preservation factor.

CONCLUSION

From the previous discussion, it can be concluded that, the lead acetate had adverse effects on the kidney. *Zingiber officinale* showed nephroprotective action against lead acetate induced nephrotoxicity in male albino rats. Further studies are necessary to elucidate exact mechanism of protection of nephrotoxicity and potential usefulness of *Zingiber officinale* as a protective agent against lead acetate toxicity in clinical trials.

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