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Protective Effects of Ginger Extract against Lead Induced Hepatotoxicity in Male Albino Rats

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Abstract: *Ginger (Zingiber officinale) is used traditionally for many therapeutic purposes. . Oxidative stress may be the main reason behind most histological and cellular effects of lead. The aim of this study was to investigate the possible hepatoprotective role of ginger against lead acetate induced hepatotoxicity in rats. . In the present investigation, lead acetate (200 mg/kg b.wt) was given orally to male rats for eight weeks to induce hepatotoxicity. The ginger was found to contain zingerone, gingerdiol, zingibrene, gingerols and shogaols. Lead-induced oxidative stress in liver tissue was indicated by significant decreased levels of liver reduced glutathione (GSH) and superoxide dismutase (SOD). Histologically, the liver showed several histological alterations such as degeneration of hepatocytes by necrosis and apoptosis, fatty changes and inflammatory cells infiltration. Ginger-I (200 mg/kg b.wt) and Ginger-II (300 mg/kg b.wt) markedly attenuated the previous lead-induced biochemical alterations in liver tissues as well as the histological and cellular changes. From this study, it can be concluded that the Zingiber officinale showed effective hepatoprotective and antioxidative action against lead acetate-induced hepatotoxicity in rats.*

Keywords: *Ginger, Lead acetate, Oxidative stress, Antioxidants*

I. Introduction

The liver plays an astonishing array of vital functions in the maintenance and performance of the body. Some of these major functions include carbohydrate, protein and fat metabolism, detoxification and secretion of bile. Therefore, the maintenance of healthy liver is vital to overall health and well being[1]. Unfortunately, the liver is often abused by environmental toxins, poor eating habits and over the counter drug use, which can damage and weaken the liver and eventually leads to hepatitis, cirrhosis and liver disease. Conventional medicine is now pursuing the use of natural products such as herbs to provide the support that the liver needs on a daily basis[1].

Medicinal plants are part and parcel of human society to combat diseases from the dawn of civilization[2]. Medicinal plants have continued providing valuable therapeutic agents, both in modern and in traditional medicine[3]. With the associated side effects of modern medicine, traditional medicines are gaining importance and are now being studied to find the scientific basis of their therapeutic actions[4]. Ginger, the rhizomes of the plant Zingiber officinale (Family Zingiberaceae), is arguably one of the most widely used culinary agent and spice in the world[5]. Phytochemical studies have shown that the unique culinary and medicinal properties of ginger are due to the presence of phytochemicals like zingerone, shogaols, gingerols, pardols, β-phellandrene, curcumene, cineole, geranyl acetate, terphineol, terpenes, borneol, geraniol, limonene, β-elemene, zingiberol, linalool, α-zingiberene, β-sesquiphellandrene, β-bisabolene, zingiberenol and α-farmesene[6]. Preclinical studies carried out with laboratory animals have also shown that ginger to possess hepatoprotective effects, and to protect the liver against the toxic effects of heavy metals[7], All Ginger's major active ingredients, such as zingerone, gingerdiol, zingibrene, gingerols and shogaols, are known to possess anti-oxidant activities[8].

Lead (Pb) exposure is considered to be a major public health problem; therefore it has been paid attention by researchers in probing further into its toxicity. This heavy metal has been found to induce a wide range of behavioural, biochemical and physiological effects[9].The liver, kidneys, and brain are considered to be the target organs for the toxic effects of lead[9].Toxicity of lead is mainly attributed to the induction of oxidative stress by elevation of reactive oxygen species (ROS) such as superoxide radicals, hydrogen peroxide and hydroxyl radicals and lipid peroxides, therefore, increased interest among phytotherapy investigators to use medicinal plants with antioxidant activity for protection against metal, especially lead, toxicity has been noted[10].

As far as our literature survey could ascertain, no attempt has been made to study the protective effects of Zingiber officinale against lead toxicity. The aim of the present work was to investigate the hepatoprotective action of Zingiber officinale against lead acetate-induced hepatotoxicity in rats and finding the exact mechanism for this protection.

II. Materials And Methods

1. 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 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.

2. 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).

3. 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[11].

4. Treatment

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.

5. 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). Liver 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 levels of liver antioxidant enzymes like Glutathione (GSH) and Superoxide dismutase (SOD) activities were measured in liver tissue of albino rats by methods of Ellman's [12] and Soon and Tan[13] respectively.

6. Histopathology

The histological sections of the liver of rats were taken by adopting the procedure as described by humason[14]. 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. Photomicrographs of the section preparations were taken using Magnus photomicrographing equipment.

III. Results

Liver Reduced Glutathione (GSH) and Superoxide dismutase (SOD) levels were presented in table1.

Table 1: levels of Reduced Glutathione and Superoxide dismutase in liver of normal and all experimental rats.

In the present study male albino rats treated with lead acetate once daily for 8 weeks. The data presented in Table: 1 shows levels of reduced glutathione and Superoxide dismutase in liver. GSH and SOD in normal control (group-I) rats were found to be 20.4150µg/mg, 11.4033U/mg/min respectively. In group-IV (lead control), these levels were significantly decreased to 10.4400 µg/mg, 3.9283 U/mg/min respectively.

Histological Analysis

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

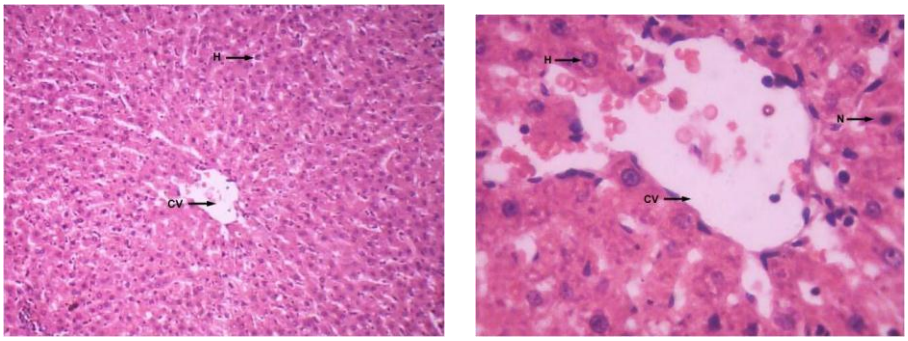

Figure1. A Transverse section of the liver of Normal Control (Group-I) clearly shows hepatocytes (H), Neucleus (N), and Central Vein (CV). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

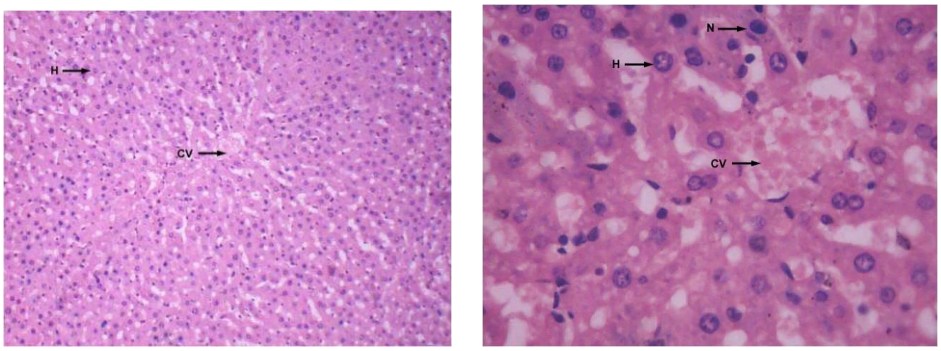

Figure 2. A Transverse section of the liver of Ginger Control-I (Group-II) clearly shows hepatocytes (H), Neucleus (N) and Central Vein (CV). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

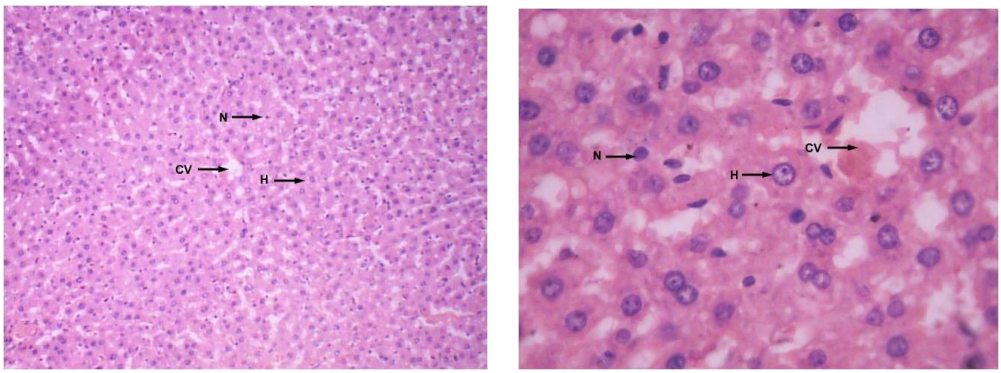

Figure 3. A Transverse section of the liver of Ginger Control-II (Group-III) clearly shows hepatocytes (H), Neucleus (N) and Central Vein (CV). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

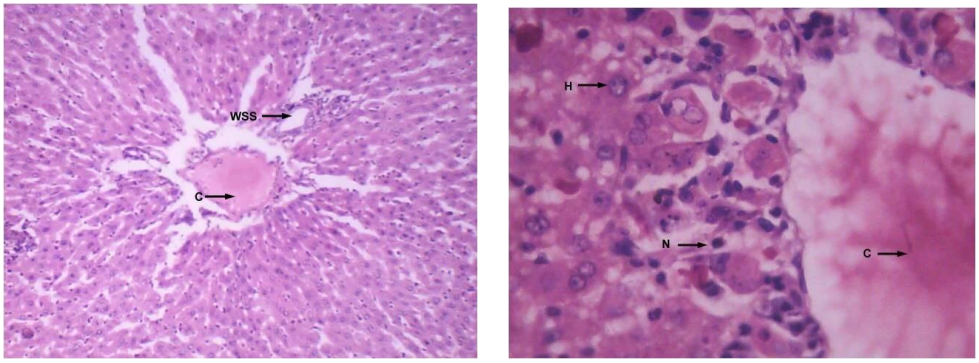

Figure 4. A Transverse section of the liver of Lead Control (Group-IV) clearly shows Degenerated hepatocytes (H), Neucleus (N), Wending sinusoid space (WSS), and Conjetion **(C**). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

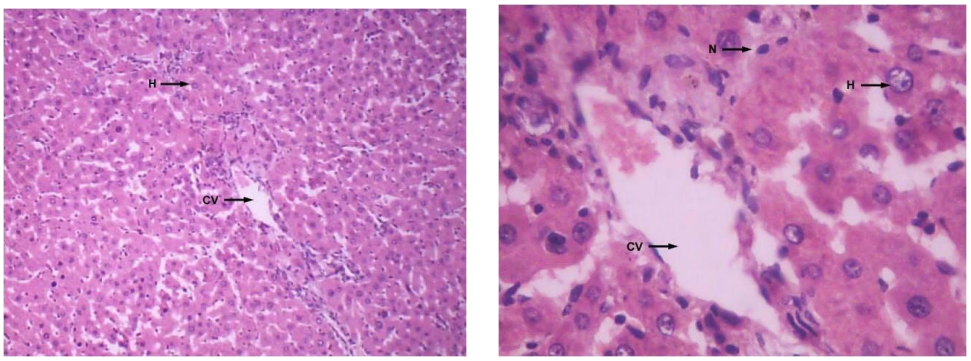

Figure 5. A Transverse section of the liver of Lead + Ginger-I treated (Group-V) clearly shows hepatocytes (H), Neucleus (N), Sinusoids (S), and Central Vein (CV). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

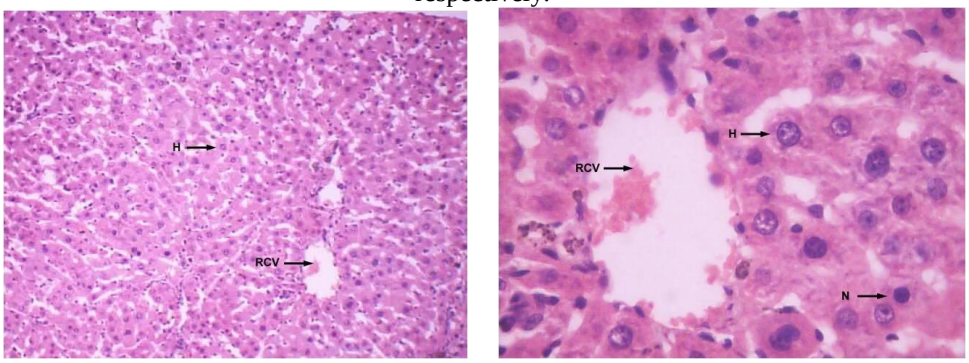

Figure 6. A Transverse section of the liver of Lead + Ginger-II treated (Group-VI) clearly shows hepatocytes (H), Neucleus (N), and Regenerated Central Vein (RCV). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

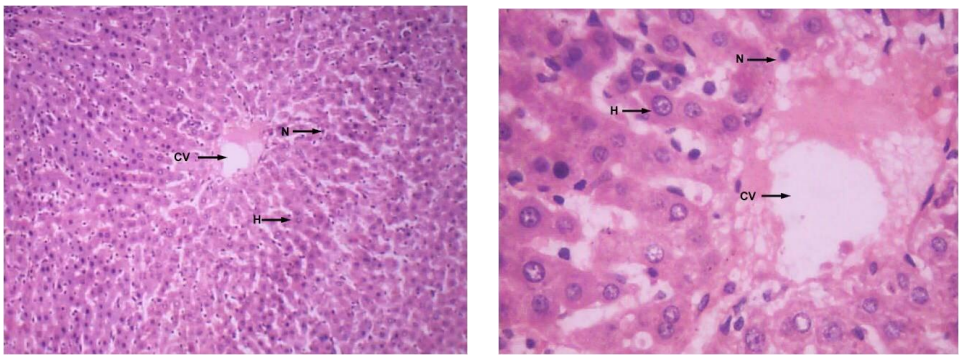

Figure 7. A Transverse section of the liver of Lead + Silymarin treated (Group-VII) clearly shows hepatocytes (H), Neucleus (N), and Central Vein (CV). Haematoxylin and Eosin (H&E) stain X100 and X 400 respectively.

IV. Discussion

The present investigation revealed significant ($p<0.05$) decrease of GSH and SOD levels in the liver of lead acetate treated (Group IV) rats in comparison to control (Group I). This means that it increased the oxidative stress in the lead treated rats. It is known that lead-induced oxidative stress tissue damage could be caused by two mechanisms: increased generation of ROS, and by causing direct depletion of antioxidant reserves[15]. Intense lipid peroxidation caused by lead exposure may affect the mitochondrial and cytoplasmic membranes causing more severe oxidative damage in the tissues and consequently releasing lipid hydroperoxides into circulation[16] which reflects the induction of oxidative stress[17].

Lead is conjugated in the liver with glutathione, where part of it and its conjugate accumulate in hepatic tissues and impair liver functions[18]. Lead can cause adverse effects to hepatic cells owing to its storage in the liver after Pb acetate exposure. Lead toxicity causes increased production of reactive oxygen species (ROS) in the liver[19]. These ROS decrease the levels of GSH and SOD in liver cells. Several studies supporting that lead toxicity decreases GSH levels in liver cells[20]. SOD is the primary antioxidant enzyme in the cell and cellular defense against superoxide radicals. The SOD catalyzes the dismutation of two superoxide (O_2-) radicals in to hydrogen peroxide (H_2O_2) and oxygen.). SOD, GPx, and CAT are potential targets for lead toxicity because these antioxidant enzymes depend on various essential trace elements for proper molecular structure and activity[21]. SOD requires copper and zinc for its activity. Copper ions play functional role in the reaction by undergoing alternate oxidation whereas zinc ions seem to stabilize the enzyme. Both the metal ions are replaced by lead, which decreases the activity of SOD.

Group V (lead+ginger-I), group-VI (lead+ginger-II) showed recovered levels of GSH and SOD when compared to lead controlled rats. Ginger compounds like gingerols, shagols and other pharmacological compounds of ginger as they have the capacity to reduce the free radical capacity. The antioxidant compounds like gingerols, shogals, ketone compounds and the phenolic compounds of ginger were responsible for scavenging the superoxide anion radicals[22]. In support of this authors Miller et al[23] and Ahmed et al[24] reported previously ginger extracts have been extensively studied for a broad range of biological activities, especially antioxidant activities found that ginger significantly lowered lipid peroxidation by maintaining the activities of the antioxidant enzymes like superoxide dismutase, catalase and glutathione in rats. Group VII also showed recovered levels of these antioxidants when treated with standard drug Silymarin over lead control and the results showed were as close to that of normal control and ginger treated ones.

In the present study liver 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. Liver histopathological observations showed in fig 1.liver sections of the group-I (normal control) healthy rats showed normal architecture of the liver. The hepatocytes were within normal limits and arranged in the form of cords without any vacuolization. Each hepatocyte is conspicuous with centrally located nucleus. The hepatocytes were separated by narrow blood sinusoids lined by endothelial cells. Portal tracts extend without fibrous tissue or lymphocytes deposition. Liver sections of the Group-II (fig. 2) and group-III(fig. 3) treatment with ginger ethanol extract showed there is no structural differences when compared with normal control(group-I). Histopathological examinations of liver of the Group-IV (lead treated rats) (fig. 4) revealed remarkable changes over normal controlled (group-I), ginger controlled (group-II & III) animals. Lead exposure produced pronounced hepatic histopathology evidenced by histological alternations in liver including focal necrosis with inflammatory cells, congestion at places, sinusoids not patent, centrilobular swelling, hepatocyte vacuolization and swelling, parenchyma disorganization, dilation of the inter hepatocyte space, and hemorrhagic clots.

Group-V (lead+ginger-I) (Fig. 5) showed regenerated nucleated hepatocytes arranged in cord with obvious sinusoidal arrays, minimal fat vacuoles and minimal inflammatory lymphocytic infiltrations were observed. Group VI (lead+ginger-II) indicated ((Fig. 6)) that the structural organisation of the liver appeared almost normal with well defined hepatocytes having regeneration of central vein. The nuclei are conspicuous centrally located without any vacuolization between hepatocytes. So, ginger-II is well protected from lead acetate toxicity when compared with ginger-I. Group VII (lead+silymarin) (Fig. 7) also showed that the results were almost nearer to normal control with well defined hepatocytes and regenerative central vein.

Liver is a frequent target for many toxicants[25]. Continuous environmental and occupational exposure to lead can cause several changes in the structure of the liver[26]. Autopsy studies of lead-exposed humans indicate that among soft tissue, liver is the largest repository (33%) of lead, followed by kidney. Lead-induced hepatic damage is mostly rooted in lipid peroxidation (LPO) and disturbance of the prooxidant_antioxidant balance by generation of reactive oxygen species[27]. Lead is known to produce oxidative damage by enhancing peroxidation of membrane lipids, and LPO is a deleterious process carried out solely by free radicals. In fact, LPO is an outcome of the chain of events involving initiation, propagation, and termination reactions[28]. Lipid peroxidation, a reactive oxygen species mediated mechanism, has been implicated in the pathogenesis of various liver injuries and subsequent liver fibrogenesis in experimental animals and humans[29]. Unchecked peroxidative

decomposition of membrane lipids is catastrophic for living systems. The lipid peroxides produced are degraded into a variety of products, including alkanals, hydroxyl alkanals, ketones, and alkenes. All these products inactivate cell constituents by oxidation or cause oxidative stress by undergoing radical chain reactions ultimately leading to loss of membrane integrity. LPO can also adversely affect the function of membrane-bound proteins, such as enzymes and receptors.

The mechanism of hepatic injury may be due to inflammatory process, so the hepato-protective activity of ginger may be due to its content of volatile oils, which showed anti-inflammatory, analgesic and immunomodulatory effects[30]. Volatile oil of ginger is capable of inhibiting T lymphocyte dependent immune reactions[31]. Moreover the anti-inflammatory activity of ginger is due to its ingredients as the gingerols and gingerol analogs (shogaols and paradols). Previous reports have documented the ability of these compounds to directly inhibit prostaglandin and leukotriene synthesis[32].

Silymarin, an antioxidant flavonoid complex derived from the herb milk thistle (Silybum marianum), has long been used in the treatment of liver diseases[33]. These properties seem to be due to their ability to scavenge free radicals and to chelate metal ions[34]. Silymarin is frequently used in the treatment of liver disorders where it is capable of protecting liver cells directly by stabilizing the membrane permeability through inhibiting lipid peroxidation[35] and preventing liver glutathione depletion[36]. Silymarin prevents liver damage from butyrophenones, phenothiazines, acetaminophen, halothane, dilantin and ethanol due to membrane-stabilizing and free radical scavenging effects of Sily[37]. Thus, Silymarin acts by antioxidative, antilipid peroxidative, antifibrotic, antiinflammatory, membrane stabilizing, immunomodulatory and liver regenerating mechanisms.

V. Conclusion

In conclusion, the results generated from this study is suggestive of the fact that Lead acetate has adverse effects on antioxidant status and histology of liver tissue of rats which could lead to initiation of Liver Diseases and that Ginger (Zingiber officinale) has hepato- protective effect on Lead acetate -induced hepatotoxicity and this may due to the antioxidant properties possessed by Ginger.

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Sl. No.	Parameter		Group-I (Normal control)	Group-II (Ginger control-I)	Group-III (Ginger control-II)	Group-IV (Lead control)	Group-V (Lead+ Ginger-I)	Group-VI (Lead+ Ginger-II)	Group-VII (Lead+ Silymarin)
1.	GSH (µg/mg)	Mean S.D	20.4150^{a} ±0.6647	20.3283^{a} ±0.5755	20.1933^{a} ±0.5458	10.4400^{d} ±0.4985	16.223^{c} ±0.4649	18.2133^{b} ±0.2494	18.6233^{b} ±0.4448
2.	SOD (U/mg/ min)	Mean S.D	11.4033^{a} ±0.2459	11.2167^{a} ±0.2453	11.2817^{a} ±0.2911	3.9283^{d} ±0.1494	8.7683^{c} ±0.1628	9.9617^{b} ±0.1526	10.2517^{b} ±0.0868

Table 1: levels of Reduced Glutathione and Superoxide dismutase in liver of normal and all experimental rats.

Values are mean ± S.E.M
Values with different superscripts with in the column are significantly different at $P<0.05$ (Duncan's Multiple Range Test)