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Luffa acutangula - A Hepatoprotective Medicine

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ABSTRACT

Medicinal plants play a very crucial role in maintaining human health. People are dependent on use of conventional medicine obtained from plant materials (WHO, 1993). A very common target for toxicity by oxidative stress, drugs and xenobiotics, is liver (Jaeschke H *et al.*,2002). *Luffa acutangula (LA)* was investigated as a hepatoprotective medicine. Wistar rats (180-200 g) were given extract of *LA* at various doses along with hepatotoxic constituents. ie. 1:1 (v/v) mixture of CCl4 and olive oil (1 ml/kg, i.p.).Separated serum was estimated for serum AST, ALT, ALP and TP. Histopathological investigations was done. Liver tissue homogenate was used for determination of liver LPO, GSH, CAT and SOD. The liver section of animals treated with CCl4 showed moderate degree of centrilobular necrosis, a moderate degree of fatty infiltration, periportal lymphocytic infiltration and distorted architecture of hepatocytes. Lesions noted in the livers of Silymarin treated animals were of much milder degree, while the liver in the *LA*-100, *LA*-200and *LA*-400, the moderate degree of centrilobular fatty infiltration with leucocytic infiltration and regeneration of hepatocytes having a prominent nucleus with no or lower signs of necrosis and inflammatory infiltration were found. These findings suggested that the herbal drug named *Luffa acutangula* is a potential agent for the prevention and treatment of liver damages due to various hepatotoxic components.

INTRODUCTION

Liver regulates the body homeostasis. It also controls almost all the biochemical pathways related to growth and involved in nutrient supply, fight against disease, energy production and reproduction. It is having a unique metabolism and relationship to the gastrointestinal tract and so it is a chief target for toxicity due to oxidative stress, xenobiotics and drugs (Jaeschke H*et al.,* 2002). Most of the hepatotoxic chemicals damage the liver. Excessive exposure to hazardous chemicals, generate free radicals leading to hepatic damage and cause jaundice, cirrhosis and fatty liver. Production of the reactive species depletion manifests in tissue thiol depletion, lipid peroxidation, plasma membrane damage etc., results into severe hepatic injury (Gupta Amartya K*et al*., 2009)**.**

Protection and treatment of liver diseases is a challenge to novel medicine. Conventional drugs used in the treatment of liver diseases are often inadequate. It is therefore necessary to search for alternative drugs for the treatment of liver diseases to replace the currently used drugs of doubtful efficacy and safety (Seakins A *et al.,*1963). Numerous medicinal plants and their formulations are used for liver disorders. But still we do not have satisfactory remedy for serious liver diseases. Herbal drugs are used for the natural healing process of liver. So, search for effective hepatoprotective drug continues. The survey has shown not much of the work reported for *Luffa acutangula* var.amara family Cucurbitaceae for the hepatoprotective activity.

MATERIALS AND METHODS

Preparation of herbal medicines

Luffa acutangula (LA) of family Cucurbitaceae was cultivated and collected from the fields of H. H. Shri. MurlidharaSwamiji College of Agriculture premises, Loknete Vyankatrao Hiray Marg, Malegaon Camp, Malegaon, Dist. Nashik, India. Herbaria were prepared and were authenticated from Botanical Survey of India, Pune, Maharashtra.

Dried powder of both crude drugs were extracted successively by using petroleum ether chloroform and ethanol as solvents in Soxhlet apparatus and finally extracted with alcohol water by maceration. The extracts were screened for the presence of various constituents by chemical tests and by TLC technique.

ETHICS

All experimental procedures were carried out in strict accordance with the guidelines prescribed by the Committee for the Purpose of Control and Supervision on Experimentation on Animals. Wistar rats (180-200 g) were obtained from National Toxicology Center, Pune, of either sex.

ANIMAL EXPERIMENTS

Animals were housed in group of 5 to 6. All the animals were maintained at standard laboratory conditions. The animals were fed with standard pellet diet and cleaned tap water *ad libitum*. The animals were maintained at (22 ± 1º C) with relative humidity and kept under 12 h light and dark cycle. The animals were allowed to acclimatize to laboratory conditions prior to experimentation. Acute toxicity study (OECD Guidelines-425, 2001) for *Luffa acutangula* was carried outon Wistar rats (180-200 g). The animals were fasted overnight and maintained with water *adlibitum*. The animals received various doses of extract of *LA*up to 2000 mg/kg. After administration of the test compounds, animals were observed continuously for 24 h and then monitored for any mortality. Based on the findings in acute toxicity studies with the maximum tolerable dose (2000 mg/kg), various doses including 100, 200 and 400 mg/kg, p.o. were taken for the detailed evaluation.

Screening of Hepatoprotectiveand Antioxidant activity:

Carbon-tetrachloride Induced Hepatotoxicity (Naik and Panda, 2007)

The animals in group I served as normal control had received Olive oil (1ml/kg, i.p; o.d.) from day 1 to day 7. The animals in group II served as negative control had received 1:1 (v/v) mixture of Carbon tetrachloride (CCl4) and Olive oil (1 ml/kg, i.p.) once daily for 7 days from day 4 to 10. The animals in group III served as positive control had received Silymarin (200 mg/kg, p.o; o.d.) for 10 days and 1:1 (v/v) mixture of CCl4 and olive oil (1 ml/kg, i.p.) once daily for 7 days from day 4 to 10. The animals in group IV, V and VI which served experimental groups had received ethanolic extract of *Luffa acutangula (LA)* at the dose of 100, 200 and 400 mg/kg, p.o; o.d. respectively for 10 days and 1:1 (v/v) mixture of CCl4 and olive oil (1 ml/kg, i.p.) once daily for 7 days from day 4 to 10.

Serum Biochemical Studies:

Animals were sacrificed 24 hr after the administration of the last dose under ether anesthesia and blood was withdrawn by retro-orbital puncture and collected in plain sterile centrifuge tubes and allowed to clot. Serum was separated by centrifugation at 7000 rpm for 15 min at 5^0C. The separated serum was used for estimation of serum AST and ALT, ALP and TP.

Histoarchitectural studies and determination of hepatic LPO, non-enzymatic(GSH) and enzymatic (CAT and SOD) antioxidants:

Each animal was sacrificed 24 h after the administration of the last dose under ether anesthesia and abdomen was cut open. The liver, heart and kidneys was surgically removed, sliced, accurately weighed and cut into small pieces. One part of the tissue followed the histochemical studies where the tissue sections were fixed in 10 % formalin solution and further processed for the histopathological investigations using hematoxylin-eosin staining under light microscope at x 400magnifications. Other part of tissue was washed and homogenized in ice cold Tris buffer (10Mm, pH 7.4). The homogenate was used for determination of liver LPO, GSH, CAT and SOD.

Assay of Lipid Peroxidation (LPO) (S*LA*terand Sawyer, 1971):

Quantitative estimation of Lipid Peroxidation (LPO) was performed by determining the concentration of Thiobarbituric acid reactive substances (TBARS) in the tissue homogenate:

For the blank specimen, 1.5 ml of distilled water and 1.5 ml of trichloroacetic acid (20 %) were added in a test tube. While for the test specimen, 2 ml of tissue homogenate and 2 ml of trichloroacetic acid (20 %) were added in a another test tube. Both the specimen solutions (blank and standard) were cooled for 15 min in a refrigerator and centrifuged. Then, 0.5 ml of supernatant liquid from both the blank and test tubes was removed. To the blank supernatant, 3 ml and to the test supernatant, 2 ml of thiobarbituric acid (67 mg /10 ml Hot water) was added. Both of these specimens were kept in boiling water bath for 10 minutes. The solutions were cooled and the absorbance of both blank and test specimens was measured at 535 nm.

The amount of malondialdehyde (MDA) formed was quantified by reaction with thiobarbituric acid (TBA) and used as an index of lipid peroxidation. The results were

expressed as nmol of MDA/g of wet tissue using molar extinction coefficient of the chromophore (1.56 x 10-5 /M/cm).

Assay of Glutathione (GSH) (Ellman, 1959):

Glutathione (GSH) was estimated in tissue homogenate using 5, 5'-dithiobis(2- nitrobenzoic acid) (DTNB):

For the blank specimen, 1 ml distilled water and 1 ml trichloroacetic acid(10%) were added in a test tube. While for the test specimen, 1 ml of tissue homogenate and 1 ml of trichloroacetic acid were added in another test tube. Both of them (blank and test) were cooled for 10 minutes in refrigerator and then centrifuged to obtain 0.5 ml of supernatant. To these supernatant, 4 ml of DTNB (6 mg /10 mlSodium citrate) and 1.5 ml of phosphate buffer (0.2 M pH-8) were added. The absorbance of resultant blank and test specimen was measured at 412 nm and expressed as µmol of GSH/ g of wet tissue.

Assay of Catalase (CAT) (Aebi, 1974):

The tissue homogenate was diluted 20 times with phosphate buffer. To the blank specimen, 4 ml of diluted homogenate and 2 ml of phosphate buffer were added whereas to the test specimen, 1 ml of hydrogen peroxide was added to 2 ml of diluted homogenate just before taking the absorbance. The absorbance was read at 240 nm initially at 0 minute and finally at 15 minutes. The results were expressed in µmol of hydrogen peroxide /g of wet tissue/ min., as catalase is the marker for the conversion or breakdown of hydrogen peroxide (H_2O_2) into H_2O and O_2.

Assay of Superoxide dismutase (SOD) (Mishra andFridovich, 1972):

Activity of SOD in liver tissue was assayed:

To the blank specimen, 1.5 ml of distilled water, 0.38 ml of ethanol and0.15ml of chloroform were added whereas to the test specimen, 0.5 ml of tissue homogenate, 0.5 ml of distilled water, 0.25 ml of ethanol and 0.15 ml of chloroform were added. The resultant solutions were shaken and centrifuged at 2000 rpm. After that the supernatant was separated. Thereafter, to 1.2 ml of blank supernatant, 3.6 ml of carbonate buffer (pH- 10.2) and 1.2 ml of EDTA were added whereas, to 0.5 ml supernatant, 1.5 ml of Carbonate Buffer (pH- 10.2), 0.5 ml of EDTA and 0.4 ml of epinephrine were added. Epinephrine was added just before taking

absorbance. The absorbance was read at 480 nm for 3 minutes with 60 seconds interval and the results were expressed as units/g of wet tissue.

STATISTICAL ANALYSIS:

The results of hepatoprotective and antioxidant activity were expressed as(Mean ± S.E.M.) and results were assessed by analysis of variance and Dunnett's multiple comparison test. Values of $p< 0.05$ were considered to be statistically significant.

RESULTS

Effect of *Luffa acutangula* on Carbon tetrachloride induced hepatotoxicity:

Serum Biochemical Studies:

The effects of *LA* on serum biochemical parameters including AST, ALT, ALP and TP were summarized in Table. There was a marked increase in the serum enzymes such as AST, ALT and ALP while decrease in TP level in CCl^s- treated group as compared with the normal control group, which was reversed with *LA*. The effects of *LA* were comparable with CCl4-treated group.

The analyzed data was expressed as - CCl4- treated group (Negative control group) showed significant increase serum levels of AST, ALT and ALP with (p<0.001) and significant decrease serum level of TP (p<0.01), when compared with normal control group. Silymarin treated group (Positive control group) showed significant decrease in serum levels of AST, ALT and ALP with (p<0.01) and significant increase in serum level of TP (p<0.01).Experimental groups (*LA* 100, 200 and 400 mg/kg) when compared with CCl4-treated group, group *LA*-100 and *LA*-200 showed no significant decrease in serum levels of AST, ALT and ALP and increase in TP was observed (p<0.05). Group *LA*-400 showed significant decrease in serum levels of AST, ALT and ALP (p<0.01) and significant increase in serum level of TP (p<0.01).

Table no. 1. Effects of *LA* treatment on serum marker enzymes and protein in CCl4 induced hepatotoxicity

Serum Biochemical parameter (n=6)	Normal Control	Negative Control	Positive Control	Ethanolic Extract of *Luffa acutangula*(*LA*)		
				100 mg/kg	200 mg/kg	400 mg/kg
Serum Glutamic Oxaloacetic Transaminase-SGOT/AST (U/L)	85.21 ±3.2	308.22 ±8.5	91.67 ± 4.6**	298.71 ±9.17	275.21 ± 2.14*	131.6 5±6.91**
Serum Glutamic Pyruvic Transaminase - SGPT/ALT (U/L)	37.12 ± 2.1	134.10 ±11.2	46.58 ±3.91**	109.87 ±9.09	83.18 ±7.63**	61.01 ± 5.56**
Alkaline Phosphatase-ALP (U/L)	2.54 ± 0.13	14.67 ± 1.04	4.12 ±0.67**	13.89 ± 1.01	11.78 ±0.98**	7.12 ± 0.09 **
Total Protein- TP (g/dl)	8.64 ± 0.67	5.31 ± 0.08	8.12 ±0.85**	6.21 ±0.08*	6.55 ±0.61**	6.86 ± 0.05**

***p<0.001, **p<0.01, *p<0.05

All experimental values were expressed as mean ± SD. Results were assessed by analysis of variance and Dunnett's multiple comparison tests. Differences were considered significant at $p < 0.05$.

Determination of liver LPO, non-enzymatic (GSH) and enzymatic (CAT and SOD) antioxidant:

The effects of *LA* on liver LPO, non-enzymatic (GSH) and enzymatic (CAT and SOD) antioxidant were summarized in Table no. 2. The levels of GSH and CAT with (p<0.01) as well as SOD (p<0.01) were decreased significantly in CCl4- treated group (Negative control group) while LPO levels were significantly get increased (p<0.01) when compared with normal control group. The free radical formation in lipid peroxidation was measured in terms of the MDA produced. The MDA content in the liver homogenate was increased in the CCl4-treated group in comparison with the normal group, which was significantly reversed by *LA*-100, 200 and 400 as well as Silymarin- treated group (positive control group) in dose dependent manner. Silymarin significantly increased the levels of GSH (p<0.01), CAT (p<0.01) and SOD (p<0.01) and decreased the level of LPO (p<0.01) whereas *LA*-100 showed moderate increase in the level of GSH (p<0.05), CAT (p<0.01) and SOD (p<0.01) and decreased the level of LPO (p<0.05). Group *LA*-200, *LA*-400 showed significant

increased the levels of GSH (p<0.01), CAT (p<0.01) and SOD (p<0.01) and decreased the level of LPO (p<0.01).

Table no. 2: Effect of *LA* treatment on liver LPO, non-enzymatic antioxidant GSH and enzymatic antioxidant enzymes including CAT and SOD in CCl4induced Hepatotoxicity

Liver Antioxidant Enzymes	Group n=6 Values are expressed in (Mean ± SEM)					
	Normal Control	Negative Control	Positive Control	Ethanolic Extract of *Luffa acutangula*(*LA*)		
				100 mg/kg	200 mg/kg	400 mg/kg
LPO (nM of MDA/g of wet tissue)	4.75 ± 0.83	27.62 ± 2.38	8.67 ± 1.13**	21.89 ± 2.3 *	15.34 ± 1.24**	11.67 ± 1.55**
GSH(µmol/g of wet tissue)	8.4 ± 0.64	3.2 ± 0.09	7.21 ± 0.43 **	4.05 ± 0.24*	4.89 ± 0.51**	6.34 ± 0.75**
CAT (µM of H2O2/g of wet tissue/min.)	36.67 ± 3.2	14.03 ± 2.09	36.89 ± 3.03**	18.74 ± 2.23**	28.52 ± 3.34**	34.96 ± 3.67**
SOD (Units/ g of wet tissue)	40.11 ± 3.87	16.79 ± 2.25	39.78 ± 4.56**	22.45 ± 2.13**	33.59 ± 3.38**	37.65 ± 3.74**

Figures showing Effect of *LA* treatment on liver LPO, non-enzymatic antioxidant GSH and enzymatic antioxidant enzymes including CAT and SOD in CCl4 induced Hepatotoxicity.

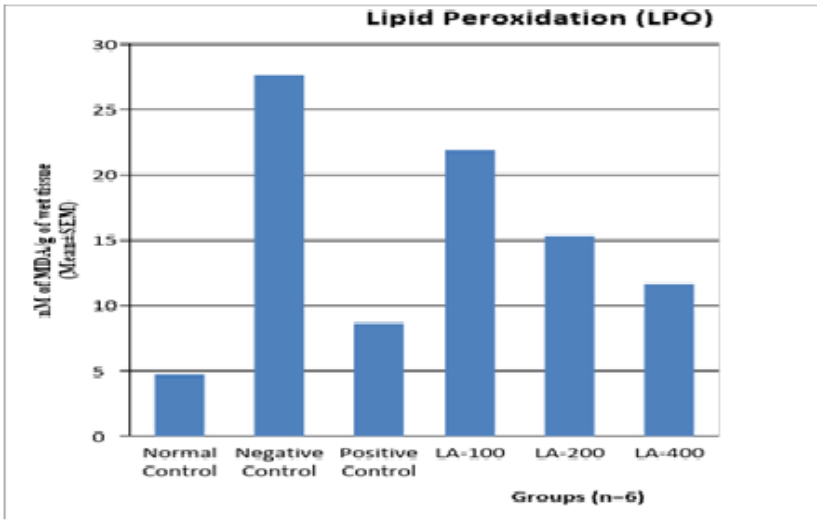

Figure 1. Effects of *LA* treatment on liver LPO in CCl4 induced Hepatotoxicity

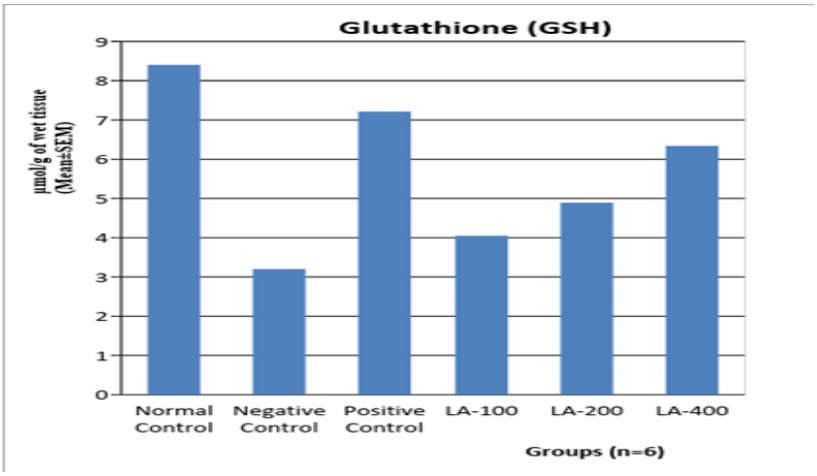

Figure 2. Effects of *LA* treatment on liver non-enzymatic antioxidant GSH in CCl4 induced Hepatotoxicity

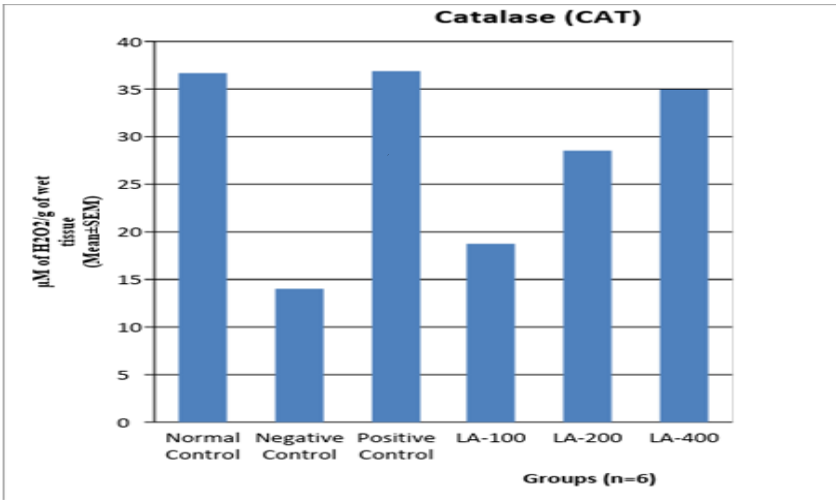

Figure 3. Effects of *LA* treatment on liver antioxidant enzymes CAT in CCl4 induced Hepatotoxicity

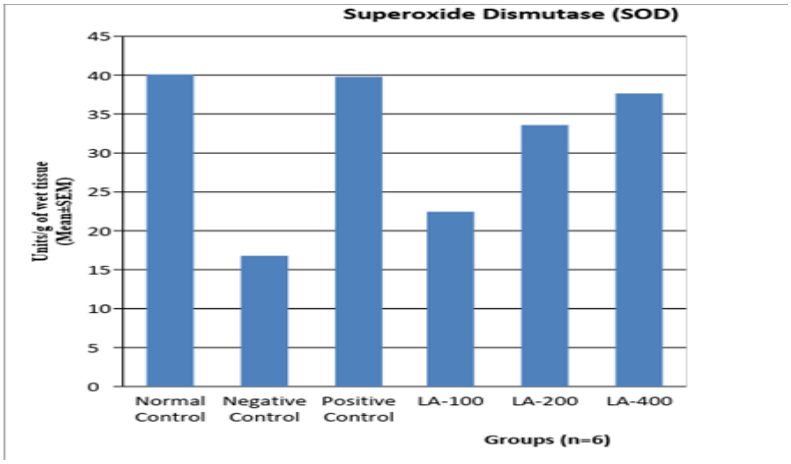

Figure 4. Effects of *LA* treatment on liver antioxidant enzymes SOD in CCl4 induced Hepatotoxicity

***p<0.001, **p<0.01, *p<0.05

All experimental values were expressed as mean ± SD. Results were assessed by analysis of variance and Dunnett's multiple comparison tests. Differences were considered significant at $p < 0.05$.

Histoarchitectural Studies:

The histoarchitectural overview of livers of normal control group, CCl4 treated group (negative control group), Silymarin- treated group (positive control group) and *LA*-100, 200, 400 were shown in figure.

The livers of animals of normal control group (group I) showed normal histology with normal architecture of hepatocytes having a prominent nucleus. The liver section of animals treated with CCl4 (group II) showed moderate degree of centrilobular necrosis. The midzonal areas surrounding the necrotic zones showed a moderate degree of fatty infiltration as well as periportal lymphocytic infiltration and distorted architecture of hepatocytes. Compared with the lesions observed in the CCl4 group, the lesions noted in the livers of Silymarin treated animals (group III) were of much milder degree. These animals showed a milder degree of centrilobular fatty infiltration as well as mild degree of lymphocytic infiltration and regenerating architecture of hepatocytes with mild degree of necrosis. The liver in the *LA*-100 (group IV) and *LA*-200 (Group V) showed the moderate degree of centrilobular fatty infiltration with leucocytic infiltration. Minimal regeneration of hepatocytes was noted. The liver in the *LA*-400 (Group VI) showed the regeneration of hepatocytes having a prominent nucleus with no or lower signs of necrosis and inflammatory infiltration.

Figures showing Effect of *LA* on histopathological examination of rat liver in CCl4-induced liver injury:

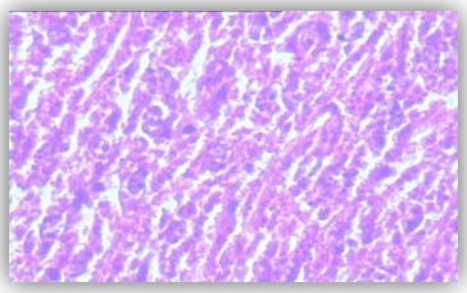

Figure 5. Group I Normal control

Normal histology with normal Architecture of hepatocytes with prominent nucleus (HxEx 400).

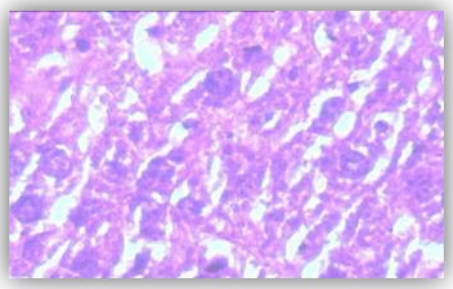

Figure 6.Group II Negative control

Moderate degree of centrilobular necrosis with fatty as well as lymphocytic infiltration showing distorted architecture of hepatocytes(HxEx 400).

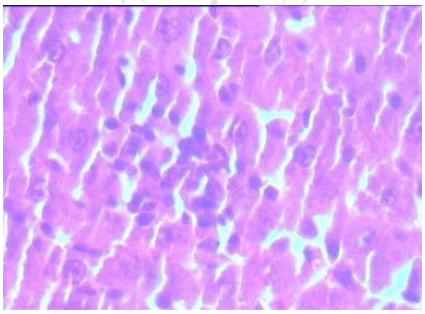

Figure 7. Group III Positive control

Milder degree of centrilobular

Fatty and lymphocytic infiltration

and regenerating architecture of

hepatocytes with mild necrosis

(HxEx 400)

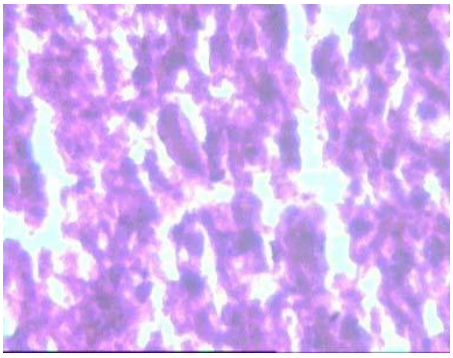

Figure 8. Group IV *LA* 100 mg/kg

Moderate degree of centrilobular fatty and leucocytic infiltration with minimal regeneration of hepatocytes (HxEx 400).

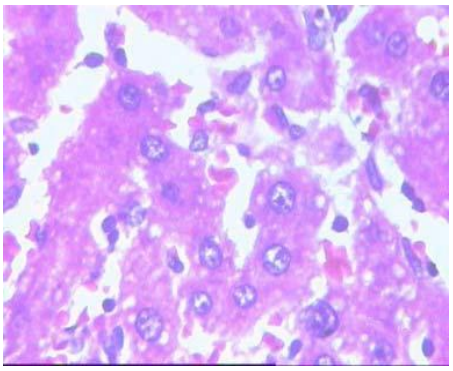

Figure 9. Group V *LA* 200 mg/kg

Milder degree of centrilobular Fatty and lymphocytic infiltration and regenerating architecture of hepatocytes with mild necrosis (HxEx 400).

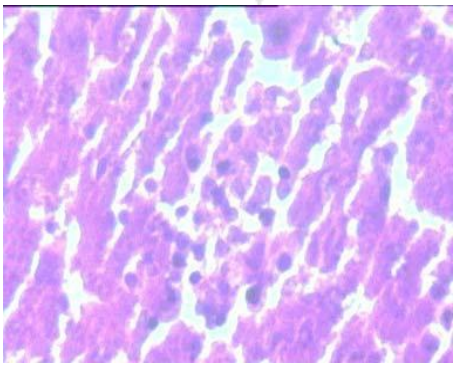

Figure 10. Group VI *LA* 400 mg/kg

Regeneration of hepatocytes with prominent nucleus and no signs of necrosis or inflammatory infiltrate.

(HxEx 400)

CONCLUSION

The present study shows that the liver section of animals treated with CCl_4 showed moderate degree of centrilobular necrosis, a moderate degree of fatty infiltration as well as periportal lymphocytic infiltration and distorted architecture of hepatocytes. Silymarin treated animals show much milder degree centrilobular necrosis, centrilobular fatty infiltration, lymphocytic infiltration and regenerating architecture of hepatocytes. The liver in the *LA*(low doses) showed the moderate degree of centrilobular fatty infiltration with leucocytic infiltration and minimal regeneration of hepatocytes was noted. Higher doses showed the regeneration of hepatocytes having a prominent nucleus with no or lower signs of necrosis and inflammatory infiltration. Based on these results, we conclude that *LA* extracts have potential novel agents for the prevention and treatment of various liver diseases.

CONFLICTS OF INTEREST

There are no conflicts of interest.

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