CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187
https://zenodo.org/records/10285713

Available online at: http://www.iajps.com *Research Article*

ANTI-OXIDANT AND HEPATOPROTECTIVE EFFECT OF *LANTANA CAMARA* LEAF EXTRACT IN ALCOHOL-INDUCED HEPATOTOXICITY

Mahendar Boddupally*[1], S. Shobha Rani[2]

[1]Research scholar, Centre for Pharmaceutical science, Jawaharlal Nehru Technological University, kukatpally Hyderabad-500 085, Telangana, India

[2]Professor, Department of Pharmaceutical Analysis, Centre for Pharmaceutical science, Jawaharlal Nehru Technological University, kukatpally, Hyderabad-500 085, Telangana, India

Abstract:

A study on the protective effect of lantana camara leaf extract in acute alcohol-induced hepatotoxicity in rats was evaluated. Rats fed alcohol only produced significant increase in the levels of enzyme markers of tissues damage (ALT, AST and ALP), lipid peroxidation and (TBARS) levels compared to normal control rats. Pretreatment with 200 and 400mg/kg body weight of extract significantly decreased the levels of enzyme markers, lipid peroxidation and markedly increased serum vitamin C level in a dose-dependent manner. Post-treatment with 400mg/kg body weight of extract significantly enhanced the recovery of animals from hepatic damage compared to untreated control. Lipid peroxidation due to oxidative stress could be the possible mechanisms of alcohol induced toxicity and the protective effect of the extract could be as a result of its ability to inhibit lipid peroxidation.

Key words: *lantana camara, Lipid peroxidation, hepatotoxicity, alcohol induced toxicity*

Corresponding author:

Mahendar Boddupally,

Research scholar, Centre for Pharmaceutical science,
Jawaharlal Nehru Technological University
kukatpally Hyderabad-500 085, Telangana, India
Mobile No: +91-7780231956
Email id: mahipharmacist@gmail.com

QR code

Please cite this article in Mahendar Boddupally et al, ***Anti-Oxidant And Hepatoprotective Effect Of Lantana Camara Leaf Extract In Alcohol-Induced Hepatotoxicity****, Indo Am. J. P. Sci, 2023; 10 (11).*

INTRODUCTION:

Alcohol abuse is a major health problem worldwide. Alcoholic liver disease is responsible for 15-30% of all admissions in many general hospitals in South Wales [1]. Although important progress has been made in understanding the pathogenesis of alcoholic liver disease, current therapies for this disease are not effective. Novel therapeutic approaches such as utilizing agents that successively correct the fundamental cellular disturbances resulting from excessive alcohol consumption are attractive [2]. Alcohol administration has been found to cause accumulation of reactive oxygen species, which in turn causes lipid peroxidation of cellular membranes and proteins and DNA oxidation resulting in hepatocyte injury. Based on the hypothesis that oxidative stress occurs only when the antioxidant capacity is insufficient to cope with the generation of prooxidants many studies have focused on the alcohol-associated changes in the liver antioxidants. In spite of the tremendous advances made in allopathic medicine, no effective hepatoprotective medicine is available. Plant drugs are known to play a vital role in the management of liver diseases. At the same time, surprisingly, we do not have readily available plant drugs/formulations to treat severe liver disease [3]. Focus on plant research has increased all over the world and a large body of evidence has been collected to show immense potential of medicinal plants used in various traditional systems [4]. Such scientific studies have led to isolation of chemical substances with therapeutic properties. And many of the isolates have found use as modern drugs while others have served as substrates for the synthesis of drugs. Unfortunately, a greater proportion of plants known traditionally to possess medicinal properties and which are used in herbal medicine have not been subjected to scientific evaluation which is necessary not only because of the need to discover new drugs but also the need to assess the toxicity risks. Besides, it is important that traditionally claimed therapeutic properties of such plants are confirmed even if the active principles are not ultimately discovered [5] As a consequence of an increasing demand for the biodiversity in screening programs, seeking hepatoprotective therapeutic drugs from natural products, there is the need to develop interest at locally screening medicinal plants used in the treatment of liver problems.

Lantana camara is a species of flowering plan within the verbena family (Verbenaceae), native to the American tropics. Other common names of L. camara include Big-sage, wild-sage, red-sage, white-sage, tick berry, West Indian lantana, and umbelanterna. *L. camara* was probably introduced before 19th century. Currently *L. camara* is distribute throughout India where there is a moderate to high summer rainfall and well-drained sloping sites *L. camara* is a well-known medicinal plant in traditional medicinal system and recent scientific studies have emphasized the possible use of *L. camara* in modern medicine Phytochemical investigation of this plant was indicated by the presence of essential oil i.e., Sabiene (19. 6- 21.5%), 1, 8- Cineole (12.6- 14.8%), ß-caryophyllene (12.7-13.4%), α-humulene (5.8-6.3%), two rare sesqui terpenoids humulene epoxide-III and 8-hydroxy bicyclo-germacrene 11, 1, 8-cineol (15.8%), sabinene (14.7%) and caryophylene (8.9%). Phytochemical screening revealed that leaf, stem and root of *Lantana camara* contained tannin, catachin, saponin, steroids, alkaloids, phenol, anthroquinone, protein, several tri-terpenoids, flavonoids, alkaloids, glycosides and reducing sugar. which are mainly responsible for exerting diverse biological activities. The leaves of lantana camara are known to possess highest antioxidants chemical constituents like flavonoids, vitamin c

MATERIALS AND METHODS:

Selection of plant

The medicinal plant of *lantana camara* leaves was selected based on the literature survey.

Plant collection and authentication

Lantana camara leaves were obtained from the local places of tirupati, ap. *Lantana camara* leaves plants was authenticated by Dr. K. Madhava Chetty, M.Sc., M.Ed., M.Phil., Ph.D., PG DPD, Assistant professor, Department of Botany, sri venkateshwara university, Thirupathi, A. P

Extraction by maceration

Fresh leaves of *lantana camara* leaves washed with water to get rid of contaminants like dirt and other impurities and were shade-dried.

These dried leaves and fruits were ground and sieved to get a uniform coarse powder. Powdered plant material was weighed (1kg) and is immersed in methanol and kept for maceration for a period of 7 days with occasional stirring. On the 8th day, the solvent was filtered by pressing with a muslin cloth and was evaporated in a rotary evaporator at 40oc. The resultant extract was put in a desiccator to remove any ethanol left in it. The dried methanolic extract of *lantana camara* (MELC) was packed in an air-tight bottle and put in a dry place for further studies.

Phytochemical screening

Phytochemical screening of the leaves of *lantana camara* was carried out using standard protocols. Plants were screened for carbohydrates, proteins, amino acids, alkaloids, phenolic compounds, tannins, flavonoids, steroids, saponins and glycosides.

Experimental animals
Male Wistar albino rats weighing 200 to 250 g body weight each were maintained at standard laboratory conditions such as temperature at (25-27°C), humidity (45-55%) and 12 h light-dark cycle with proper access to the standard rat pellet diet and water, *ad libitum.* Post acclimatization, the animals were divided into 5 groups, each group with 6 rats.

Evaluation of hepatoprotective activity in alcohol-induced hepatotoxicity:
Wistar Albino Rats (Wistar Strain) of either sex weighing 150-200g were selected and divided into five groups of six animals each. Group I: Vehicle treated rats were kept on normal diet and served as control for 15 days. Group II: Rats orally received 30% alcohol (1.5 ml/ Rat / twice a day) for 15 days. Group III: Rats orally received Silymarin (25 mg/kg b. w/day) and alcohol as group II, for 15 days. Group IV: Rats orally received *MELC* (200 mg/kg b. w/day) and alcohol as group II, for 15 days. Group V: Rats orally received *MELC* (400 mg/kg b. w /day) and alcohol as group II, for 15 days.

This period of treatment, the rats were maintained under normal diet and water. The blood was collected from the retro orbital plexus of the rats of all groups 24 h after the last dose administration, under light anesthetic ether. The blood samples are centrifuged at 3000rpm for 30min to separate the serum. The serum was analysed for various biochemical parameters such as SGOT, SGPT, ALP, BIT, BID and ALB. Liver was dissected out and subjected for morphological study such as liver weight and liver volume of each animal. Further the liver was placed in 10% formalin solution for histopathological study.

Estimation of serum bio-chemical parameters
Different biochemical parameters were estimated like SGOT, SGPT, ALP, bilirubin and albumin

Assessment of *in vivo* antioxidant potential
Effects of the extract, MELC and standard drug, silymarin on the levels of antioxidant enzymes were assessed by standard method described by [6].

Assay for reduced glutathione content
A 500 mg of tissue from liver was homogenized in 0.02 M EDTA (5 ml) and was added 4 ml of cold water to it. A 1 ml of 50% trichloroacetic acid was added into it and shaken for 10 min from time to time via Vortex mixer. All the contents were poured to a centrifuge tube to centrifuge at 6000 rpm for 15 min. The supernatant (2 ml) was mixed with 0.4 M Tris buffer (pH 8.9, 4 ml). Whole of the contents was mixed well and 0.01 M DTNB (0.1 ml) was added to it. After five minutes, absorbance was read at λ_{412} against a suitable blank. Glutathione (GSH) solution (50 µg/ml) was applied as standard. The µg GSH/mg of protein = ($A_{412} \times C_{standard\ soln}$ in µg/ml × dilution factor)/(A_{412} × mg/ml of protein)].

Assay for catalase activity
A 19 mM H_2O_2 (2.95 ml) was added in a cuvette. A 10% tissue homogenate prepared in potassium phosphate buffer (pH 7.4, 2 ml) was centrifuged at 3000 rpm for 15 min. A 50 µl of supernatant (cytosolic) was poured into it and the absorbance change at 240 nm (ΔA_{240}) was measured for 3 min at each 1 min interval. Catalase activity = (volume of assay × ΔA_{240} per min) / (mg of protein × volume of homogenate × 0.081).

Assay for superoxide dismutase activity
A 100 µl of liver's cytosolic supernatant was poured to buffer, Tris–HCl and final volume of 3 ml was made. Pyrogallol (25 µl) was poured to it and the change in A_{420} was measured at an interval 1 min for 3 min. After pyrogallol addition, increase in A_{420} should be inhibited by SOD presence. SOD units per ml of sample = {100 × (A – B)} / (50 × A), where, A is absorbance difference in 1 min in control and B is absorbance difference in 1 min in test sample.

Assay for thiobarbituric acid reactive substances
Suspension (1 ml) was taken in a tube from 10% liver tissue homogenate´s supernatant and centrifuged at 10,000 rpm. A 30% trichloroacetic acid (0.5 ml) and 0.8% TBA (0.5 ml) was added to the tube. The tubes after cover with aluminium foil were shaken for 30 min at 80 °C on water bath. Then, tubes were kept for 10 min in ice-cold water and further, centrifuged for at 3000 rpm 15 min. A_{540} against blank was read at room temperature and TBA calculated. Amount of Thiobarbituric acid reactive substances present in the sample (nmol TBA/mg protein) = (final volume of test solution × A_{540}) / 0.156].

Assessment of histopathology
Before histopathological examination and for the preservation of isolated livers of rats of different groups, 10% formalin solution was used. The liver was mounted by embedding it in paraffin; it was cut into size of 6 mm sections, put on slide and stained consequently with the

dyes eosin and haematoxylin and observed in the light microscope intended for PILD or hepatoprotection. They were observed for lymphocyte infiltration, centrilobular necrosis, fatty infiltration and fibrosis [7].

RESULTS AND DISCUSSION:

Table 1: Results of Phytochemical screening

S. No	Name of the Phytochemical	MELC
1	Carbohydrates	+
2	Amino acids	+
3	Proteins	+
4	Alkaloids	+
5	Cardiac glycosides	+
6	Triterpenoids	+
7	Saponins	+
8	Flavonoids	+
9	Phenolic compounds	+
10	Tannins	+
11	Steroids	-
12	Gums	-

Where, + means positive and - means negative.

The preliminary phytochemical screening showed the presence of various phytoconstituents like flavonoids, phenolic compounds, triterpenoids, tannins, saponins, amino acids, proteins, and carbohydrates in Methanolic extract of *Lantana Camara* (MELC).

Table 2: Liver weight and liver volume in Alcohol induced hepatotoxic rats

Group	Liver weight gm/100gm	Liver Volume ml/100gm
Normal control	3.68±1.08	6.49±1.15
Toxic control	4.38±1.10	8.93±1.05
Standard control	3.85±1.08**	7.52±1.12**
***MELC* 200 mg/kg**	4.24±1.13*	7.58±1.11**
***MELC* 400 mg/kg**	4.11±1.13**	7.48±1.10**

Alcohol treatment in rats resulted in enlargement of liver which was evident by increase in the liver weight and volume. The groups treated with standard group showed good restoration of liver weight and liver volume whereas test groups treated with extract showed significant effect on liver weight and liver volume compared to toxic control group. Results were showed in Table

Table 3: Effect of MELC on biochemical parameters

Groups and treatments	SGPT (IU/L)	SGOT (IU/L)	ALP (IU/L)	SBL (mg/dl)	LDH (U/L)	TP (g/L)	ALB (g/L)
Normal control	47.16 ± 1.32	87.17 ± 1.23	85.44 ± 3.43	0.73 ± 0.02	388.5 ± 9.54	6.67 ± 0.367	2.852 ± 0.067
Toxic control	153.54 ± 7.98#	159.35 ± 6.53#	253.37 ± 8.675#	1.73 ± 0.247#	608.67 ± 10.8#	2.99 ± 0.180#	1.40 ± 0.07#
Standard control	84.16 ± 7.44***	88.86 ± 3.65***	93.4 ± 2.558***	0.83 ± 0.05***	395.84 ± 5.49***	5.65 ± 0.23***	2.88 ± 0.06***
MELC *200 mg/kg*	130.54 ± 5.71**	128.17 ± 7.26***	212.3 ± 5.463*	1.11 ± 0.05*	545.76 ± 7.78*	3.98 ± 0.67*	2.11 ± 0.05*
MELC *400 mg/kg*	103.0.43 ± 5.08***	107.83 ± 1.65***	135.8 ± 12.376***	0.98 ± 0.05**	427 ± 8.84***	5.67 ± 0.76**	2.5 ± 0.32**

Rats treated with Alcohol developed a significant hepatic damage observed as elevated serum levels of hepatospecific enzymes like SGPT, SGOT and ALP when compared to normal control. Treatment with Silymarin had showed good protection against Alcohol induced toxicity to liver. Groups treated with Plant Extract showed significant effect which can be comparable with toxic control. Dunnet's test indicates a significant reduction in elevated serum enzyme levels with extract treated animals compared to toxic control animals. Results were showed in Table 7.

Assessment of antioxidant potential of methanolic extract of *lantana camara*

The effects of methanolic extract of *lantana camara* (MELC) on the levels of malondialdehyde (TBARS, MDA), superoxide dismutase (SOD), catalase (CAT) and glutathione (GSH) in hepatic homogenate is presented in Table 4. Group-II rats receiving Alcohol showed significant decrease in hepatic GSH ($P < 0.01$, 1.52 ± 0.12 µg/mg of tissue protein), CAT ($P < 0.01$, 8.07 ± 0.20 µmol H_2O_2/mg of tissue protein) and SOD ($P < 0.01$, 1.85 ± 0.23 Unit/mg of tissue protein) while enhancement in the level of hepatic MDA (7.37 ± 0.50 nmole/mg of tissue protein, $P < 0.01$) as compared to group-I rats of GSH (4.62 ± 0.14), CAT (14.83 ± 0.23), SOD (5.27 ± 0.06) and MDA (2.77 ± 0.07). The extract MELC in groups III and IV animals increased significantly the levels of GSH to (2.22 ± 0.20, $P < 0.05$ and 2.57 ± 0.15, $P < 0.05$), CAT to (10.20 ± 0.83, $P < 0.05$ and 12.16 ± 0.46, $P < 0.01$) and SOD to (2.82 ± 0.29, $P < 0.05$ and 3.56 ± 0.18, $P < 0.01$), while decrease in the level of hepatic MDA to (6.09 ± 0.26, $P > 0.05$ and 4.13 ± 0.21, $P < 0.01$) as compared to group-II animals where the levels were altered due to Alcohol administration. Silymarin in group-V rats significantly ($P < 0.01$) increased the levels of GSH, CAT and SOD to 3.75 ± 0.08, 13.62 ± 0.39 and 4.74 ± 0.24 respectively while significantly ($P < 0.01$) decreased the level of MDA to 4.13 ± 0.21 as compared to group-II rats. Extract MELC in groups III as well as in group IV rats showed insignificant activity in the levels of GSH, CAT, SOD and MDA compared to rats in group V rats. *L. Camara* at a dose of 400 mg/kg b. wt showed more protection to liver than that of 200 mg/kg b. wt but showed less protection than that of silymarin (25 mg/kg b. wt) in some marker enzymes like malondialdehyde.

Table 4: Effects of MELC on GSH, SOD, CAT and TBARS levels

Groups	**GSH (µg/mg of tissue protein)**	**CAT (µ mol H_2O_2/mg of tissue protein)**	**SOD (Unit/mg of tissue protein)**	**TBARS (nmole/mg of tissue protein)**
Normal control	4.62 ± 0.14	14.83 ± 0.23	5.27 ± 0.06	2.77 ± 0.07
Toxic control	$1.52 \pm 0.12^{\#}$	$8.07 \pm 0.20^{\#}$	$1.85 \pm 0.23^{\#}$	$7.37 \pm 0.50^{\#}$
MELC *200 mg/kg*	2.22 ± 0.205*	10.20 ± 0.83*	2.82 ± 0.29*	6.09 ± 0.26^{ns}
MELC *400 mg/kg*	2.57 ± 0.15*	12.16 ± 0.46**	3.56 ± 0.18**	5.41 ± 0.44**
Standard control	3.75 ± 0.08**	13.62 ± 0.39**	4.74 ± 0.24**	4.13 ± 0.21**

Values are expressed as mean ± SEM of 5 rats in each group. # indicates $P < 0.01$ compared to respective normal control group-I *to $P < 0.05$ and ** to $P < 0.01$ compared to respective hepatotoxic group-II.

Assessment of effects of methanolic extract of *lantana camara* on histopathology

All findings of liver function tests, LFT were linked to histopathology changes observed in photomicrographs. Histopathology of liver tissues in experimental and control groups of rats is shown in (Figure 1). Histopathology of liver tissues in group-I rats displayed well defined vesicular nuclei and architecture, in group II displayed hepatocyte's necrosis and degeneration, group-III rats displayed elevated intercellular space and gentle degenerative changes in proliferative hepatocytes, in group-IV displayed clear nuclei and normal design, in group-V displayed normal architecture with well-defined nucleus. Infiltrating lymphocytes centrilobular cell degeneration and hepatic necrosis were well appeared in group-II intoxicated with Alcohol. Treatment of rats with MELC prevented the Alcohol induced histopathology changes in groups III and IV.

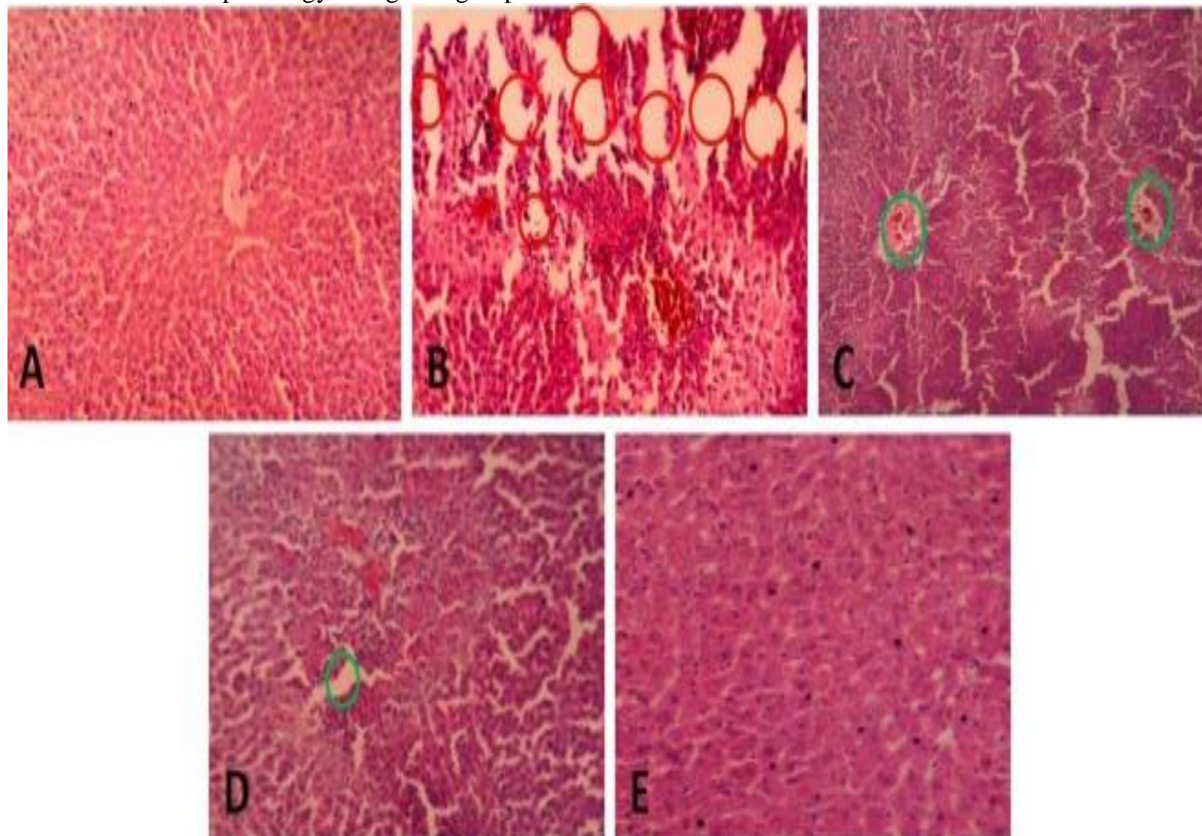

Figure 1: Histopathology of liver tissues in control and experimental groups of rats at 10X magnification of microscope (*circle marks indicated damage of liver cell*): (A) Normal control group-I. (B) Hepatotoxic control group-II. (C) Extract 200mg/kg treated group-III. (D) Extract 400mg/kg treated group-IV. (E) Standard drug treated group-V.

Discussion:

Alcohol is a commonly abused drug and acute ingestion of it may cause liver damage leading to other liver problems. Alcohol treatment of rats is known to cause the translocation of fat from the peripheral adipose tissue to liver, kidney and brain for accumulation [8]. The animals treated with alcohol only (group 1) had a significant hepatic damage as indicated by the elevated levels of serum enzyme markers of tissue damage studied. The rise in the ALT level is usually accompanied by an elevation in the levels of AST, which plays a role in the conversion of amino acids to keto acids [9]. Pretreatment with the extract of Moringa oleifera decreased levels of serum enzyme markers, thus suggesting that the extract possessed compounds that protected the hepatocytes from alcohol-induced liver injury and subsequent leakage of enzymes in to the circulation. Decreased levels of the enzyme markers in the post-treated group compared to control were an indication that the extract also possessed a curative effect. Acute alcohol ingestion is known to promote oxidative stress in animals and humans [10]. In the present study, significantly increased levels of lipid peroxidation in blood serum of rats treated with alcohol were observed, indicating the activation of the lipid peroxidation system. Lipid peroxidation is initiated by the abstraction of a hydrogen atom from the side chain of polyunsaturated fatty acids in the membrane lipids. The high vulnerability of neutral tissues to oxidative damage is partly due to its high lipid content [11]. Pretreatment with extract before alcohol administration significantly decreased the levels of lipid peroxidation in the blood. The antiperoxidative effect may be due to the presence of antioxidants in the leaves such as β carotene, α-tocopherol and vitamin C as earlier reported [12]. Post treatment with the extract also resulted in marked decrease in the level of lipid peroxidation compared to the group left without post treatment. Thus, the extract also has the ability to not only protect the animals from the effect of lipid peroxidation induced by alcohol but also to scavenge the already produced radicals and reverse the effect of the observed lipid peroxidation. Increased lipid peroxidation under ethanol treated conditions of rats left without pre or post treatment was due to increased oxidative stress as a result of depletion of the antioxidant scavenger system which might have resulted in changes in the cellular metabolism of the liver. The observed decreased in the level of serum vitamin C (an antioxidant) in alcohol treated group only could be as a result of increased utilization of this antioxidant in scavenging the free radicals generated or produced during acute alcohol induction [13]. Pretreatment of rats with the extract at the different doses administered resulted in significant increase in the levels of vitamin C. This indicates that the extract was able to raise the vitamin C levels of the pretreated animals, and increased the ability to combat produced free radicals. Raised level of serum vitamin C after post-treatment of extract enhance the recovery of the animals from alcohol-induced damage compared to untreated group

The extraction of plant material and its analysis play a significant role in the quality control of plant material [14]. Crude methanolic extract of the plant materials contains both nonpolar and polar phytoconstituents. [15]. Alcohol Its overdose in experimental rats and human causes hepatic necrosis, liver function failure (death of hepatocytes) and also death [16]. Laboratory traits of alcohol is alike to other types of liver ailment and acute inflammation in the company of foremost increase of serum transaminase enzymes such as aspartate transaminase (AST), alkaline phosphatase (ALP), alanine transaminase (ALT); lactate dehydrogenase (LDH), total cholesterol (TC), triglyceride (TG), serum bilirubin (SBL) and drop off of albumin (ALB) as well as total protein (TP) [17]. Results from present study evidently reflect hepatocellular damage in PILD in animal model and MELC at the doses of 200 and 400 mg/kg significantly lowered the AST, ALP, ALT, LDH, TC and SBL in the alcohol intoxicated rats of groups III and IV. alcohol was recognized as a direct hepatotoxin in the 1960s and if taken in toxic doses, converts to a toxic form which is further oxidized to a highly toxic and reactive metabolite by cytochrome P_{450} [18]. Toxic metabolite in turn causes liver damage which disturbs transport function of the hepatocytes resulting in the leakage of plasma membrane and thereby causing an altered level of enzyme in the serum. Thus, 3 g/kg b. wt p.o on the 8th day was used for the induction of hepatotoxicity in rats [19]. It is clear from the present study that the 3 g/kg p. o of paracetamol in hepatotoxic control group-II significantly decreased the levels of antioxidant enzymes namely hepatic GSH, CAT and SOD; and increased the level of hepatic MDA as compared to the normal control group-I leading to oxidative stress [20].

Results of present study clearly indicated that before paracetamol administration on 8th day, pretreatment of rats with 200 and 400 mg/kg/day p.o of MELC for seven days resulted in a significant enhancement in the levels of hepatic GSH, CAT and SOD; and decrease in the level of MDA as compared to hepatotoxic group-IV. MELC in 400 mg/kg dose showed better protection than in 200 mg/kg dose to restoring the liver markers parameter and antioxidant

markers towards normal. Hepatoprotective activity of 400 mg MELC/kg/day was comparable to that of 25 mg standard drug silymarin/kg/day. These demonstrated that inhibition of increased liver injury and normalization of liver function tests (LFT) markers might contribute to protective effect of MELC against Alcohol induced liver damage. *Lantana camara* contains pterostilbene (45%), alkaloids (0.4%), tannins (5%) and protein. Liquiritigenin, isoliquiritigenin, pterostilbene, pterosupin, gallic acid, epicatechin, catechin, kinotannic acid, kinoin, kino red, β-eudesmol, carsupin, marsupial, marsupinol, pentosan, *p*-hydroxybenzaldehyde are the primary phytoconstituents reported in *Lantana camara*. Flavonoids and phenolics are reported bioactives which decrease different destructive processes in human being due to their ability to scavenge free radicals and reduce its formation [21]. Hepatoprotection by MELC might be caused by the anti-oxidant activity of phyto-constituents available in MELC which reduced an oxidative stress incorporated by paracetamol and another similar analgesic and anti-inflammatory qualities preventing the inflammatory liver damage [22].

CONCLUSION:

Present study has demonstrated that Methanolic extract of *lantana camara* leaves (MELC) possesses a potent hepatoprotective effect against Alcohol-induced liver damage. Thus, *Lantana camara* may provide a novel potent hepatoprotective agent for liver damage, Alcohol which could be considered for further clinical studies for future drug development.

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