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# EVLUATION OF HEPATOPROTECTIVE ACTVITY OF *CASSIA TORA* ROOT

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**Abstract:-**Plant derived drugs came into use in the modern medicine through the uses of plant material as indigenous cure in folklore or traditional systems of medicine. Plant drugs are known to play a vital role in the management of liver disease. Liver diseases are among the major diseases affecting mankind. In spite of the tremendous advances made in allopathic medicine, no effective hepatoprotective medicine is available till date. Thus the aim of the study is to evaluate hepatoprotective activity of methanol and petroleum ether extracts of Cassia tora. A Cassia tora possesses hepatoprotective activity.

**Keywords:** Liver diseases, hepatoprotective activity, *Cassia tora*

## INTRODUCTION

Plants have been major contributors to human welfare since the dawn of civilization. Besides food, shelter and clothing, they are an important source of fine chemicals which find their applications in pharmaceutical industries across the globe. Nature indeed serves as a rich storehouse of herbal remedies to cure various ailments. Plant derived drugs came into use in the modern medicine through the uses of plant material as indigenous cure in folklore or traditional systems of medicine.1-10 Plant drugs are known to play a vital role in the management of liver disease. There are numerous plants and polyherbal formulations claimed to have hepatoprotective activity. Nearly 150 phytoconstituents from 101 plants have been claimed to possess liver protecting activity. In India, more than 87 medicinal plants are used in different combinations in the preparation of 33 patented herbal formulations.11-14

Liver is the largest and most complex internal organ in the body. It plays an important role in maintenance of internal environment through its multiple and diverse functions. It is involved in the intermediary metabolism of proteins, fats and carbohydrates as well as in the synthesis of number of plasma proteins such as albumin, fibrinogen and in the production of various enzymes, formation and excretion of bile. It acts as storage depute for proteins, glycogen, various vitamins and metals. It also has a role in regulation of blood volume by transferring blood from portal to systemic circulation and its reticuloendothelial system particularly in immune mechanism. It plays central role in detoxification and excretion of many endogenous and exogenous compounds. Hence any injury to liver or impairment of its function will have grave implication on the health of the person. Although viral infections are of main cause of hepatic injury xenobiotics, excessive drug therapy, environmental pollutants and chronic alcohol ingestion can also cause severe liver injury. Since it plays a central role in processing, abolishing and disposition of foreign chemicals it is susceptible to their injurious effect15.

Liver diseases are among the major diseases affecting mankind. In spite of the tremendous advances made in allopathic medicine, no effective hepatoprotective medicine is available till date. The roots of Cassia tora has not been evaluated for the hepatoprotective activity. Thus the aim of the study is to evaluate hepatoprotective activity of methanol and petroleum ether extracts of Cassia tora.

Cassia tora (Family- Caesalpiniaceae) is a wild crop and grown in most parts of India as a weed. It is an annual foetide herb, 30-90cm high. Traditional it is used as tonic, carminative and stimulant. As a folk remedy, the

In India, cassia tora is used as a natural pesticide in organic farms. Roasted seeds are substituted for coffee, like tephrosia seeds. According to Chinese Material Medica, it promotes blood circulation, and its cold nature makes it effective in the treatment of heat syndromes. Seed tarts ailments due heat such as blindness, conjunctivitis, hyperdacryosis, and others. 16-18

## MATERIAL AND METHOD

### Collection of plant materials19-20

The roots of Leucas aspera was collected from Ananthagiri forest region, Vishakapatnam District, Andhra Pradesh, India. The plant species were authenticated by Dr. K. Madhava Chetty, Department of Botany, Shri Venkateshwara University, Tirupati, India.

### Extraction of plant materials21

The fresh roots were cleaned and shade dried at room temperature and was chopped into small pieces. Dried plant were powdered and packed in air tight container. The coarse powders of both plant materials were packed in soxhlet column for 6 hr successively with methanol and petroleum ether. Thereafter, the extracts were concentrated using rotary flash evaporator (50̊C).

### Experimental Animals

Albino wistar rats weighing 150-220g were maintained under controlled condition of temperature at 27 ± 2 ̊C and 12-h light-dark cycles and relative humidity of 50 ± 15%). All the studies conducted were approved by the Institutional Animal Ethical Committee (IAEC) of according to prescribed guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals, Govt. of India. (Regd. no. 769/2011/CPCSEA) They were housed in polypropylene cages and had a free access to standard pellets and water ad libitum.

### In vivo Hepatoprotective Activity:

1. Evaluation of Hepatoprotective Activity in Paracetamol-Induced Hepatotoxicity: 22-24
In the dose response experiment, albino rats were randomly assigned into 9 groups of 6 individuals each.
Group-I: Animals (-ve control) were administered normal saline 1ml/kg p.o., for 7 days
Group-II: Animals (+ve control) were administered normal saline 1ml/kg p.o., for 7 day
Group-III: Animals were administered with silymarin 100 mg/kg p.o., for 7 days.
Group-IV: Animals were administered with MECT 200 mg/kg p.o., for 7 days.
Group-V: Animals were administered with MECT 400 mg/kg p.o., for 7 days.
Group-VI: Animals were administered with MECT 600 mg/kg p.o., for 7 days.
Group-VII: Animals were administered with PECT 200 mg/kg p.o., for 7 days.
Group-VIII: Animals were administered with PECT 400 mg/kg p.o., for 7 days.
Group-IX: Animals were administered with PECT 600 mg/kg p.o., for 7 days.

On 5th day, 30 min after the administration of normal saline, 100 mg/kg silymarin, 200, 400 and 600 mg/kg of MECT and PECT to Group- II, III, IV, V, VI, VII, VIII and IX respectively, paracetamol 2g/kg was given orally. After 48 hours of paracetamol feeding rats were sacrificed under mild ether anaesthesia.

Blood samples were collected for evaluating the serum biochemical parameters and liver was dissected out, blotted off blood, washed with saline and stored in 10% formalin and preceded for histopathology to evaluate the details of hepatic architecture in each group microscopically. The blood so collected was centrifuged immediately to get clear serum and was subjected to various biochemical studies.

2. Evaluation of Hepatoprotective Activity in Thioacetamide-Induced Hepatotoxicity: 25
In the dose response experiment, albino rats were randomly assigned into 9 groups of 6 individuals each.
Group-I: Animals (-ve Control) were administered distilled water (1ml/kg, p.o) for 9 days.
Group-II: Animals (+ve Control) were administered distilled water (1ml/kg, p.o) for 9 days.
Group-III: Animals were administered with silymarin 100 mg/kg p.o., for 9 days.

Group-IV: Animals were administered with MECT 200 mg/kg p.o. for 7 days.
Group-V: Animals were administered with MECT 400 mg/kg p.o. for 9 days.
Group-VI: Animals were administered with MECT 600 mg/kg p.o. for 9 days.
Group-VII: Animals were administered with PECT 200 mg/kg p.o. for days.
Group-VIII: Animals were administered with PECT 400 mg/kg p.o., for 9 days.
Group-IX: Animals were administered with PECT 600 mg/kg p.o., for 9 days.

On 9th day, 30 min after the administration of distilled water, 100 mg/kg silymarin, 200, 400 and 600 mg/kg of MECT and PECT to Group-II, III, IV, V,VI,VII, VIII and IX respectively, received thioacetamide (100 mg/kg, s.c) which was prepared in distilled water (2% solution). Food was withdrawn 12 hr. before thioacetamide administration to enhance the acute liver damage in animals of groups II, III, IV, V, VI, VII, VIII and IX. The animals were sacrificed 24 hr. after the administration of thioacetamide under mild ether anesthesia. Blood samples were collected for evaluating the serum biochemical parameters and liver was dissected out, blotted off blood, washed with saline and stored in 10% formalin and preceded for histopathology to evaluate the details of hepatic architecture in each group microscopically. The blood collected was centrifuged immediately to get clear serum and was subjected to various biochemical studies.

**A) Physical Parameters:**

**1) Determination of Wet Liver Weight:**

Animals were sacrificed and livers were isolated and washed with saline and weights determined by using an electronic balance. The liver weights were expressed with respect to its body weight i.e. gm/100gm.26

**2) Determination of Wet Liver Volume:**

After recording the weight all the livers were dropped individual in a measuring cylinder containing a fixed volume of distilled water or saline and the volume displaced was recorded.26

**B) Estimation of biochemical markers to assess liver functions:**

**1. Estimation of Serum SGPT (UV- Kinetic method):27**

| Pipette Sample (µl) | Sample (µl) |
|---|---|
| Working reagent | 1000 |
| Sample | 100 |

Mix well and read the initial absorbance A0 after 1 minute and repeat the absorbance reading after every 1, 2 & 3 minutes. Calculate the mean absorbance change per minute (A/min).

**2. Estimation of Serum SGOT (UV- kinetic method):**

| Pipette Sample (µl) | Sample (µl) |
|---|---|
| Working reagent | 1000 |
| Sample | 100 |

Mix well and read the initial absorbance A0 after 1 minute and repeat the absorbance reading after every 1, 2 & 3 minutes. Calculate the mean absorbance change per minute (A/min).

**3. Estimation of Serum Alkaline Phosphatase (ALP):**

| Pipette Sample (µl) | Sample (µl) |
|---|---|
| Working reagent | 1000 |
| Sample | 20 |

Mix well and read the initial absorbance A0 after 1 minute and repeat the absorbance reading after every 1, 2 & 3 minutes. Calculate the mean absorbance change per minute (A/min).

ALP Activity in U/L = A/min×2754

**4. Estimation of Serum Bilirubin: 28**

| Addition sequence | B(ml) | T(ml) |
|---|---|---|
| Direct Bilirubin Reagent ($L_1$) | 1.0 | 1.0 |
| Direct Nitrite Reagent ($L_2$) | - | 0.05 |
| Sample | 0.1 | 0.2 |

Mix well. Incubate for 5 minutes at Room temperature for direct bilirubin and 10 minutes for Total bilirubin. Read absorbance at 546 nm against Reagent blank.

Total or Direct Bilirubin in mg/dl = Abs. T × 13

**5. Estimation of Serum Total Proteins29-34**

| Pipette into tubes marked | Blank | Standard | Test |
|---|---|---|---|
| Reagent | 1000µl | 1000µl | 1000µl |
| Distilled water | 20µl | - | - |
| Standard | | 20µl | |
| Test | - | - | 20µl |

Incubate for 10 minutes at 370C. Read absorbance of the Standard and each test at 546 nm (520-560 nm) against reagent blank.

**Calculation:**

$$\text{Total Protein} = \frac{\text{Absorbance of Test}}{\text{Absorbance of Standard}} \times 6.0\ \text{g/d}$$

**C) Histopathological Study35**

**Processing of Isolated Pancreas**

The animals were sacrificed and the pancreas of each animal was isolated. The isolated pancreas was cut into small pieces and preserved and fixed in 10% formalin for two days. Following this was the washing step where by the pancreas pieces were washed in running water for about 12 hours. This was followed by dehydration with isopropyl alcohol of increasing strength (70%, 80% and 90%) for 12 hours each. Then the final dehydration is done using absolute alcohol with about three changes for 12 hours each. The clearing was done by using chloroform with two changes for 15 to 20 minutes each. After clearing, the pancreas pieces were subjected to paraffin infiltration in automatic tissue processing unit. The pancreas pieces were washed with running water to remove formalin completely. To remove the water, alcohol of increasing strengths was used since it is a dehydrating agent. Further alcohol was removed by using chloroform and chloroform removed by paraffin infiltration.

**Embedding in Paraffin Vacuum:**

Hard paraffin was melted and the hot paraffin was poured into L-shaped blocks. The pancreas pieces were then dropped into the molten paraffin quickly and allow cooling.

**Sectioning:**

The blocks were sectioned by using microtome to get sections of thickness of 5?. The sections were taken on a micro slide on which an egg albumin (sticking substance) was applied. The sections were allowed to remain in an oven at 600C for 1 hour. Paraffin melts and egg albumin denatures, thereby fixes tissues to slide.

**Procedure:**

1.Finally washed with water.
2.Stained with haematoxylin for 15 minutes.
3.Rinsed in tap water.
4.Differentiated in 1% acid alcohol by 10 quick dips. Checked the differentiation with a microscope. Nuclei were distinct and the back ground was very light (or colourless).
5.Washed in tap water.
6.Dipped in (Lithium carbonate) until sections become bright blue (3-5 dips).
7.Washed in running tap water for 10 to 20 minutes, if washing is inadequate eosin will not stain evenly.
8.Stained with eosin for 15 seconds – 2 minutes depending on the age of the eosin and the depth of the counter stain desired. For even staining results, dip slides several times before allowing them to set in the eosin for the desired time.
9.Dehydrated in 95% isopropyl and absolute isopropyl alcohol until excess eosin is removed, 2 changes of 2 minutes each (check under microscope).
10.An absolute isopropyl alcohol 2 changes of 3 minutes each.
11.Chloroform 2 changes of 2 minutes each.
12.Mounted in DPX (Desterene dibutyl phthalate xylene).

All the sections of the tissues were examined under microscope for the analyzing the altered architecture of the pancreas tissue due to streptozotocin treatment and improved pancreas architecture due to pretreatment with test extracts and standard drug.

**Statistical Analysis:**

The values are expressed as Mean ± SEM. The data was analysed by using one way ANOVA followed by Tukey multiple comparison tests using Graph pad prism software. Statistical significance was set at $P \leq 0.05$.

**RESULT**

**I) Effect of MECT and PECT on Paracetamol Induced Hepatotoxicity:**

**1. Physical Parameters**

**a) Wet Liver Weight and Wet Liver Volume:**

Paracetamol treatment in rats resulted in enlargement of liver which was evident by increase in the wet liver weight and volume. The groups were treated with Silymarin and MECT and PECT showed significant restoration of wet liver weight and wet liver volume nearer to normal. These values are tabulated in the Table No.1 and graphically represented in Figure No.1 and 2.

**Table No 1: Effect of MECT and PECT on Wet Liver Weight & Wet Liver Volumes in Paracetamol Induced Hepatotoxic Rats.**

| Groups | Treatment | Wet Liver weight (gm/100gm) (Mean ± SEM) | Wet Liver volumes (ml/100gm) (Mean ±SEM) |
|---|---|---|---|
| Group I | Negative Control (0.5ml saline) | 3.042 ± 0.079 | 3.180 ± 0.067 |
| Group II | Positive Control Paracetamol (2 g/kg p.o.) | 4.040 ± 0.141 | 4.312 ± 0.177 |
| Group III | Paracetamol + Standard (Silymarin) (2 g/kg p.o.+ 100 mg/kg p.o.) | 3.203 ± 0.098 *** | 3.330 ± 0.057*** |
| Group IV | Paracetamol + MECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 3.632 ± 0.105$^{ns}$ | 3.858 ± 0.080* |
| Group V | Paracetamol + MECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 3.458 ± 0.092** | 3.720 ± 0.114** |
| Group VI | Paracetamol + MECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 3.263 ± 0.058*** | 3.403 ± 0.068*** |
| Group VII | Paracetamol + PECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 3.752 ± 0.096$^{ns}$ | 3.967 ± 0.073 $^{ns}$ |
| Group VIII | Paracetamol + PECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 3.505 ± 0.096** | 3.753 ± 0.053** |
| Group IX | Paracetamol + PECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 3.370 ± 0.063*** | 3.513 ± 0.065*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to Paracetamol treated group. MECT- Methanolic extract of Cassia tora, PECT: Petroleum ether extract Cassia tora

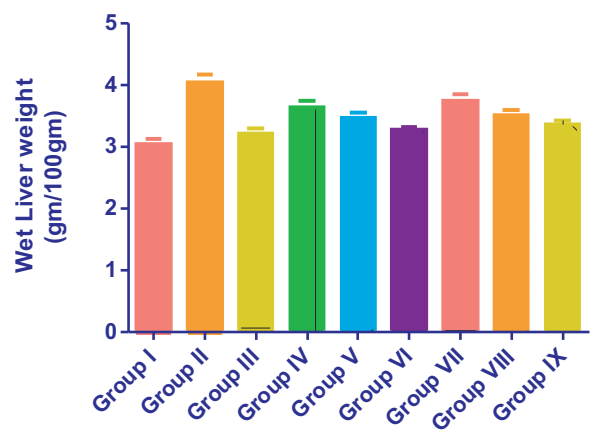



**Figure No.1: Effect of MECT and PECT on Wet Liver Weight in Paracetamol Induced Hepatotoxic Rats.**

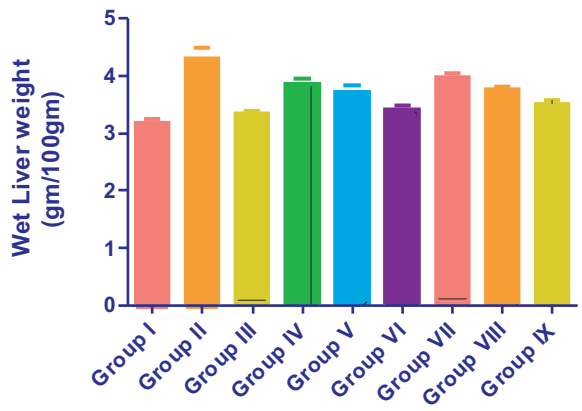



**Figure No.2: Effect of MECT and PECT on Wet Liver Volumes in Paracetamol Induced Hepatotoxic Rats.**

## 2 Biochemical Parameters

### 1 Effect on Serum Marker Enzymes:

There is a marked increase in SGPT levels observed in Paracetamol treated group. However the SGPT levels were decreased by MECT and PECT dose dependently. In addition the standard silymarin has restored the SGPT levels significantly. Serum SGOT levels have been also elevated in the Paracetamol treated groups. Treatment with standard silymarin has brought back the SGOT levels to the near normal levels. However treatment with the MECT and PECT has decreases the SGOT levels in a dose dependent manner, which statistically significant.

In case of total and direct bilirubin there is a noticeable rise in serum levels on Paracetamol treatment observed. Treatment with MECT and PECT has reversed the total and a direct bilirubin serum level by dose dependent manner, which is statistically significant when compared with Paracetamol treated group. Rise in ALP serum levels observed in Paracetamol treated group, and was remarkable decreased significantly by the MECT and PECT by dose dependent manner and standard silymarin treatment. The results are summarized in Table No.2 and graphically depicted in Figure No. 3 and 4.

**Table No.2: Effect of MECT and PECT on SGPT, SGOT, ALP, Direct Bilirubin, Total Bilirubin levels in Paracetamol Induced Hepatotoxic Rats**

| Groups | Treatment | SGPT Levels ( U/L) (Mean± SEM) | SGOT Levels ( U/L ) (Mean± SEM) | Total Bilirubin Levels (mg/dl) (Mean ± SEM) | Direct Bilirubin Levels (mg/dl) (Mean ± SEM) | ALP Levels ( U/L ) (Mean± SEM) |
|---|---|---|---|---|---|---|
| Group I | Negative Control (0.5ml saline) | 57.43 ± 2.862 | 89.45 ± 3.293 | 0.892 ± 0.040 | 0.223 ± 0.018 | 112.7 ± 3.084 |
| Group II | Positive Control Paracetamol (2 g/kg p.o.) | 305.7 ± 9.145 | 427.5 ± 8.455 | 4.681 ± 0.427 | 1.612 ± 0.134 | 241.4 ± 6.359 |
| Group III | Paracetamol + Standard (Silymarin) (2 g/kg p.o.+ 100 mg/kg p.o.) | 65.78 ± 5.288*** | 122.5 ± 5.787*** | 1.105 ± 0.169*** | 0.327 ± 0.021*** | 98.55 ± 4.261*** |
| Group IV | Paracetamol + MECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 134.3 ± 6.633*** | 212.6 ± 6.684*** | 2.321 ± 0.346*** | 0.872 ± 0.041*** | 147.1 ± 4.175*** |
| Group V | Paracetamol + MECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 92.13 ± 4.786*** | 171.2 ± 4.086*** | 1.637 ± 0.203*** | 0.688 ± 0.037*** | 129.3 ± 4.022*** |
| Group VI | Paracetamol + MECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 73.55 ± 3.420*** | 131.7 ± 4.256*** | 1.193 ± 0.159*** | 0.394 ± 0.026*** | 103.4 ± 3.138*** |
| Group VII | Paracetamol + PECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 159.2 ± 7.012*** | 257.3 ± 7.631*** | 2.843 ± 0.270*** | 0.956 ± 0.045*** | 174.5 ± 5.813*** |
| Group VIII | Paracetamol + PECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 113.5 ± 5.238*** | 189.5 ± 4.972*** | 1.936 ± 0.258*** | 0.806 ± 0.029*** | 145.7 ± 4.227*** |
| Group IX | Paracetamol + PECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 79.30 ± 3.924*** | 152.8 ± 4.033*** | 1.513 ± 0.188*** | 0.471 ± 0.024*** | 122.8 ± 4.372*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to Paracetamol treated group. MECT-Methanolic extract of Cassia tora, PECT: Petroleum ether extract of Cassia tora.

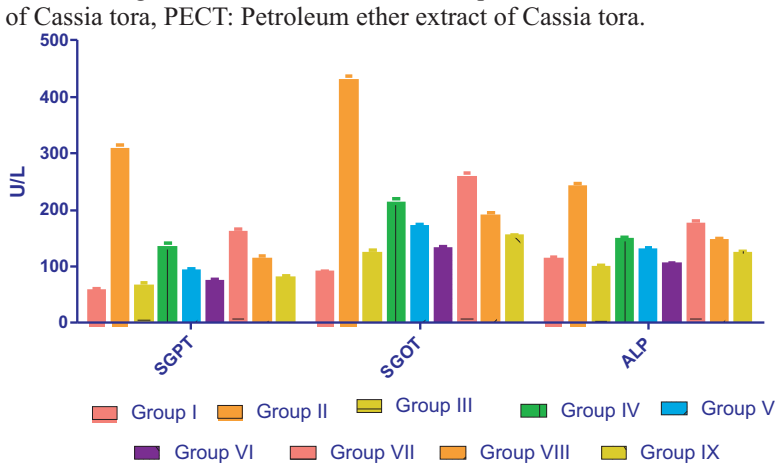



**Figure No.3: Effect of MECT and PECT on SGPT, SGOT, ALP, levels in Paracetamol Induced Hepatotoxic Rats**

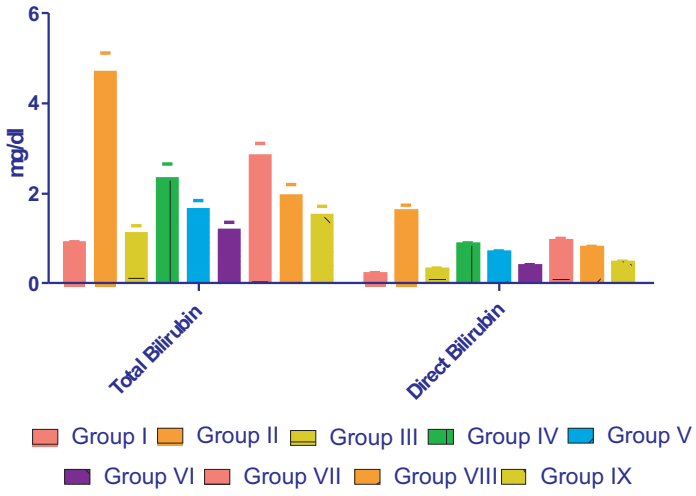



**Figure No.4: Effect of MECT and PECT on Direct Bilirubin, Total Bilirubin levels in Paracetamol Induced Hepatotoxic Rats**

**2 Serum Total Protein**

**Table No. 3: Effect of MECT and PECT on Serum Total Protein Levels in Paracetamol Induced Hepatotoxic Rats**

| Groups | Treatment | Total Protein levels (gm/dl ) (Mean±SEM) |
|---|---|---|
| Group I | Negative Control (0.5ml saline) | 7.972 ± 0.255 |
| Group II | Positive Control Paracetamol (2 g/kg p.o.) | 3.488 ± 0.187 |
| Group III | Paracetamol + Standard (Silymarin) (2 g/kg p.o.+ 100 mg/kg p.o.) | 7.893 ± 0.094*** |
| Group IV | Paracetamol + MECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 6.483 ± 0.234*** |
| Group V | Paracetamol + MECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 7.473 ± 0.242*** |
| Group VI | Paracetamol + MECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 7.708 ± 0.141*** |
| Group VII | Paracetamol + PECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 5.685 ± 0.232*** |
| Group VIII | Paracetamol + PECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 6.997 ± 0.149*** |
| Group IX | Paracetamol + PECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 7.508 ± 0.080*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to Paracetamol treated group. MECT- Methanolic extract of Cassia tora, PECT: Petroleum ether extract Cassia tora

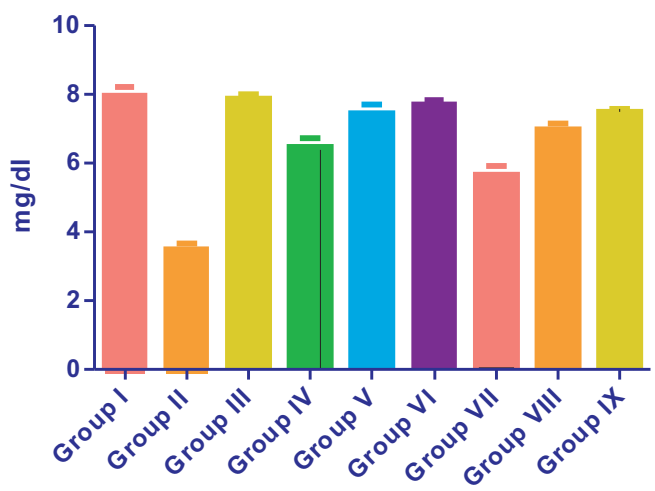



**Figure No.5: Effect of MECT and PECT on Serum Total Protein Levels in Paracetamol Induced Hepatotoxic Rats**

## 3 SERUM LIPID PROFILE

**Table No.4: Effect of MECT and PECT on Lipid Profile Levels in Paracetamol Induced Hepatotoxic Rats**

| Groups | Treatment | Serum Lipid Profile mg/dl | | | | |
|---|---|---|---|---|---|---|
| | | TC | TG | HDL-C | LDL-C | VLDL-C |
| Group I | Negative Control (0.5ml saline) | 102.6 ± 3.620 | 114.2 ± 2.743 | 29.53 ± 1.023 | 50.23 ± 2.048 | 22.84± 0.548 |
| Group II | Positive Control Paracetamol (2 g/kg p.o.) | 216.3 ± 5.433 | 192.8 ± 6.120 | 16.21 ± 1.138 | 161.53 ± 3.071 | 38.56 ± 1.224 |
| Group III | Paracetamol + Standard (Silymarin) (2 g/kg p.o.+ 100 mg/kg p.o.) | 110.9 ± 4.569*** | 122.5 ± 4.358*** | 28.97 ± 1.262*** | 57.42 ± 2.435*** | 24.50 ± 0.871*** |
| Group IV | Paracetamol + MECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 158.3 ± 5.087*** | 151.7 ± 4.863*** | 22.47 ± 1.202** | 105.4 ± 2.912*** | 30.34 ± 0.972*** |
| Group V | Paracetamol + MECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 133.5 ± 4.156*** | 135.3 ± 3.983*** | 27.88 ± 1.173*** | 78.56 ± 2.186*** | 27.06 ± 0.796*** |
| Group VI | Paracetamol + MECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 120.1 ± 3.270*** | 128.9 ± 3.382*** | 28.24 ± 1.041*** | 66.08 ± 1.552*** | 25.78 ± 0.676*** |
| Group VII | Paracetamol + PECT (2 g/kg p.o.+ 200 mg/kg p.o.) | 177.8 ± 6.120** | 162.5 ± 5.173** | 19.97 ± 1.372$^{ns}$ | 125.3 ± 3.713*** | 32.50 ± 1.034** |
| Group VIII | Paracetamol + PECT (2 g/kg p.o.+ 400 mg/kg p.o.) | 149.2 ± 4.236*** | 148.4 ± 4.088*** | 25.14 ± 1.139** | 94.38 ± 2.279*** | 29.68 ± 0.817*** |
| Group IX | Paracetamol + PECT (2 g/kg p.o.+ 600 mg/kg p.o.) | 133.5 ± 4.122*** | 142.0 ± 3.543*** | 27.43 ± 1.543*** | 77.67 ± 1.870*** | 28.40± 0.708*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to Paracetamol treated group. MECT-Methanolic extract of Cassia tora, PECT: Petroleum ether extract of Cassia tora

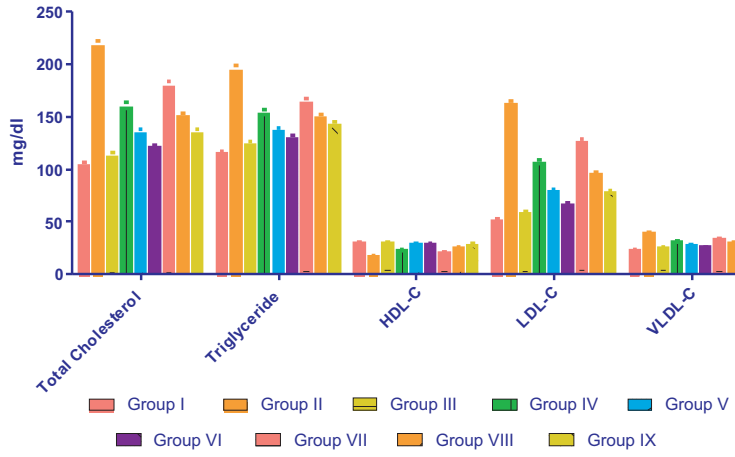
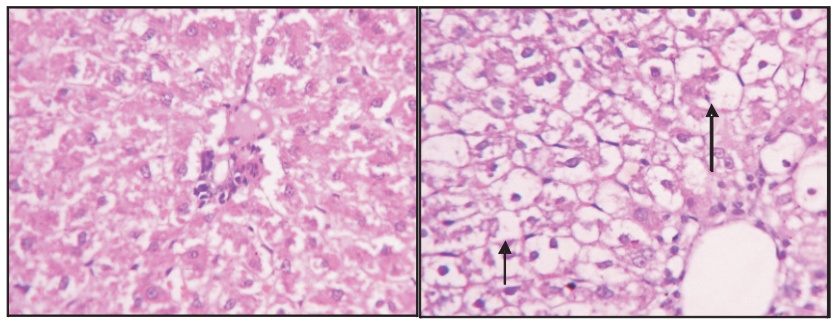


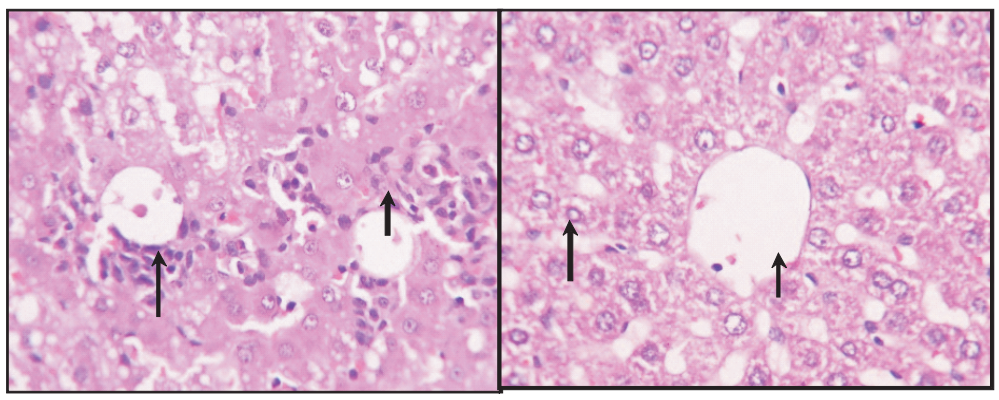

**Figure No.6: Effect of MECT and PECT on Lipid Profile Levels in Paracetamol Induced Hepatotoxic Rats**

**3. Histopathological Studies of the Liver in Paracetamol Induced Hepatotoxicity:**

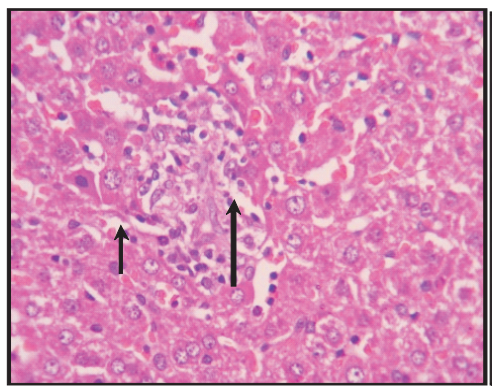
**Group I:** Section studied shows liver parenchyma with intact architecture. Most of the perivenular hepatocytes, periportal hepatocytes and midzonal hepatocytes appear normal. Within the hepatic parenchyma, the sinusoids appear normal.
**Group II:** Section studied shows liver parenchyma with effaced architecture. Most of the hepatocytes show macrosteatosis, while some show degenerative changes. There are seen focal aggregates of mononuclear inflammatory cells within the parenchyma.
**Group III:** Section studied shows liver parenchyma with partially effaced architecture. Most of the sinusoids appear dilated and congested. Most of the hepatocytes show microsteatosis, while few show macrosteatosis. There are seen scattered mononuclear inflammatory infiltrations within the parenchyma.
**Group IV:** Section studied shows liver parenchyma with effaced architecture. Some of the hepatocytes show degenerative changes, while some show regenerative changes. The central veins and sinusoids appear dilates. There are seen aggregates of mononuclear inflammatory cells within the parenchyma
**Group V:** Section studied shows liver parenchyma with partially effaced architecture. Some of the central veins and sinusoids appear congested. Also seen are few epithelioid granulomas within the parenchyma.
**Group VI**: Section studied shows liver parenchyma with intact architecture. The sinusoids and central veins appears unremarkable. Intervening the hepatocytes are seen scattered mononuclear inflammatory cells within the parenchyma.
**Group VII:** Section studied shows liver parenchyma with effaced architecture. Most of the hepatocytes show degenerative changes, while some show regenerative changes. The central veins and sinusoids appear dilates. There are seen periportal and perivenular aggregates of mononuclear inflammatory cells.
**Group VIII:** Section studied shows liver parenchyma with intact architecture. Few of the hepatocytes show microsteatosis. Some of the central veins and sinusoids appear congested
**Group IX:** Section studied shows liver parenchyma with intact architecture. Few of the central veins and sinusoids appear congested. Intervening the hepatocytes are seen scattered mononuclear inflammatory cells within the parenchyma



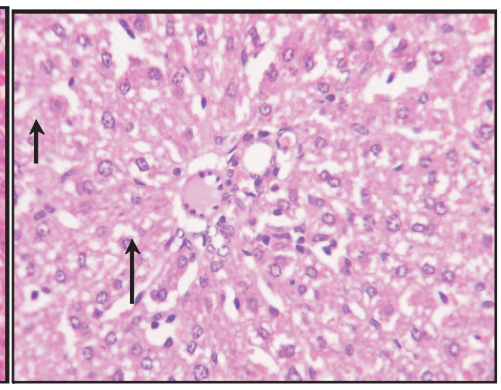
**Group I** **Group II**



Group III



Group IV



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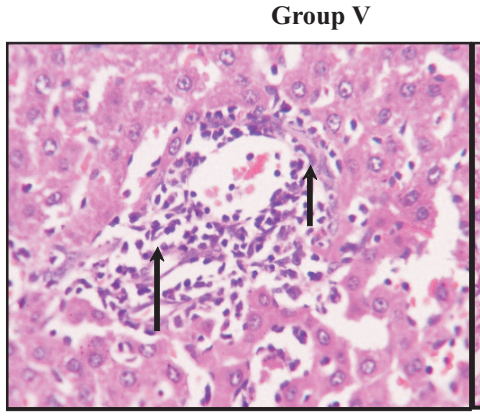

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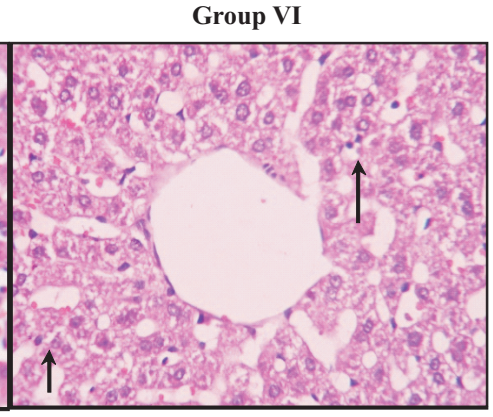

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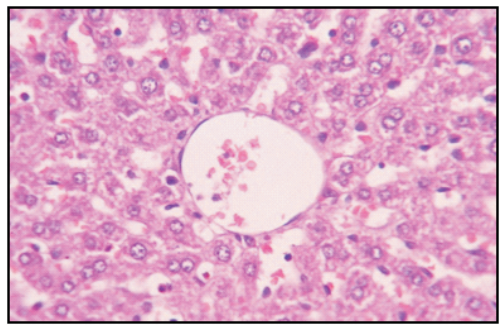


Group VIII

Group IX

**Figure No. 7: Histopathological Studies of the Rat Liver in Paracetamol Induced Hepatotoxicity**

Group –I(Negative Control - Saline)
Group –II (Positive Control Paracetamol [2 g/kg p.o.])
Group –III (Paracetamol [2 g/kg p.o.] + Silymarin [100mg/kg])
Group – IV (Paracetamol [2 g/kg p.o.] + MECT [200mg/kg])
Group – V (Paracetamol [2 g/kg p.o.] + MECT [400mg/kg])
Group – VI (Paracetamol [2 g/kg p.o.] + MECT [600mg/kg])
Group – VII (Paracetamol [2 g/kg p.o.] + PECT [200mg/kg])
Group – VIII (Paracetamol [2 g/kg p.o.] + PECT [400mg/kg])
Group – IX (Paracetamol [2 g/kg p.o.] + PECT [600mg/kg])

**II) Effect of MECT and PECT on Thioacetamide Induced Hepatotoxicity:**

**1 Physical Parameters**

**a) Wet Liver Weight and Wet Liver Volume:**

Thioacetamide treatment in rats resulted in enlargement of liver which was evident by increase in the wet liver weight and volume. The groups were treated with Silymarin and MECT and PECT showed significant restoration of wet liver weight and wet liver volume nearer to normal. The results are summarized in Table No.5 and graphically depicted in Figure. No.8 and 9.

**Table No. 5: Effect of MECT and PECT on Wet Liver Weight & Wet Liver Volumes in Thioacetamide Induced Hepatotoxic Rats.**

| Groups | Treatment | Wet Liver weight (gm/100gm) (Mean ± SEM) | Wet Liver volumes (ml/100gm) (Mean ±SEM) |
|---|---|---|---|
| Group I | Negative Control (1ml distilled water) | 3.358 ± 0.173 | 3.473 ± 0.148 |
| Group II | Positive Control Thioacetamide (100 mg/kg s.c.) | 4.637 ± 0.160 | 4.823 ± 0.103 |
| Group III | Thioacetamide + Standard (Silymarin) (100 mg/kg s.c.+ 100 mg/kg p.o.) | 3.397 ± 0.112*** | 3.523 ± 145*** |
| Group IV | Thioacetamide + MECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 3.895 ± 0.087*** | 3.972 ± 0.105*** |
| Group V | Thioacetamide + MECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 3.652 ± 0.085*** | 3.842 ± 0.094*** |
| Group VI | Thioacetamide + MECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 3.425 ± 0.097*** | 3.535 ± 0.94*** |
| Group VII | Thioacetamide + PECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 4.035 ± 0.097$^{ns}$ | 4.205 ± 0.108** |
| Group VIII | Thioacetamide + PECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 3.853 ± 0.093*** | 4.008 ± 0.071*** |
| Group IX | Thioacetamide + PECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 3.618 ± 0.061*** | 3.727 ± 0.088*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to thioacetamide treated group. MECT-Methanolic extract of Cassia tora, PECT: Petroleum ether extract of Cassia tora

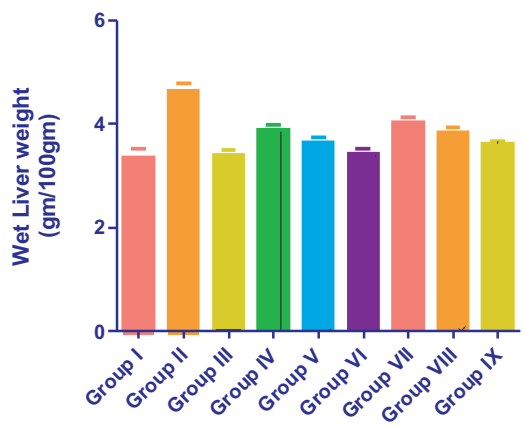



**Figure No. 8: Effect of MECT and PECT on Wet Liver Weight in Thioacetamide Induced Hepatotoxic Rats.**

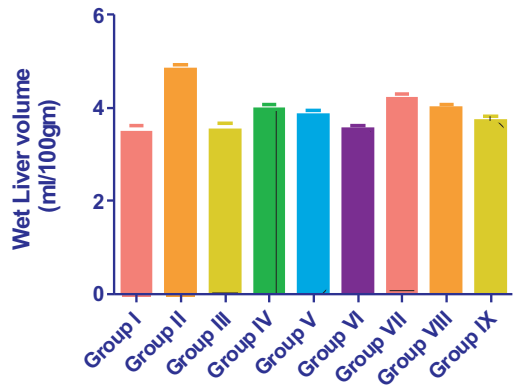



**Figure No. 9: Effect of MECT and PECT on Wet Liver Volumes in Thioacetamide Induced Hepatotoxic Rats.**

**2 Biochemical Parameters**

**1 Effect on Serum Marker Enzymes:**

There is a marked increase in SGPT levels observed in thioacetamide treated group. However the SGPT levels were decreased by MECT and PECT dose dependently. In addition the standard silymarin has restored the SGPT levels significantly.

Serum SGOT levels have been also elevated in the thioacetamide treated groups. Treatment with standard silymarin has brought back the SGOT levels to the near normal levels. However treatment with the MECT and PECT has decreases the SGOT levels in a dose dependent manner, which statistically significant.

In case of total and direct bilirubin there is a noticeable rise in serum levels on thioacetamide treatment observed. Treatment with MECT and PECT has reversed the total and a direct bilirubin serum level by dose dependent manner, which is statistically significant when compared with thioacetamide treated group.

Rise in ALP serum levels observed in thioacetamide treated group and was remarkable decreased significantly by the MECT and PECT by dose dependent manner and standard silymarin treatment. The results are summarized in Table No.6 and graphically depicted in Figure. No. 10 and 11.

**Table No. 6: Effect of MECT and PECT on SGPT, SGOT, ALP, Direct Bilirubin, Total Bilirubin levels in Thioacetamide Induced Hepatotoxic Rats**

| Groups | Treatment | SGPT Levels ( U/L) (Mean± SEM) | SGOT Levels ( U/L ) (Mean± SEM) | Total Bilirubin Levels (mg/dl) (Mean ±SEM) | Direct Bilirubin Levels (mg/dl) (Mean ±SEM) | ALP Levels ( U/L ) (Mean± SEM) |
|---|---|---|---|---|---|---|
| Group I | Negative Control (1ml distilled water) | 69.27 ± 2.196 | 94.21 ± 4.208 | 0.792 ± 0.047 | 0.286 ± 0.038 | 123.6 ± 4.153 |
| Group II | Positive Control Thioacetamide (100 mg/kg s.c.) | 294.3 ± 8.375 | 402.6 ± 7.320 | 3.872 ± 0.254 | 1.063± 0.146 | 264.2 ± 7.236 |
| Group III | Thioacetamide + Standard (Silymarin) (100 mg/kg s.c.+ 100 mg/kg p.o.) | 72.13 ± 4.108*** | 113.2 ± 4.653*** | 0.985 ± 0.086*** | 0.325 ± 0.027*** | 109.3 ± 4.567*** |
| Group IV | Thioacetamide + MECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 183.4± 6.274*** | 232.1 ± 6.173*** | 1.823 ± 0.215*** | 0.697 ± 0.045*** | 172.3 ± 5.673*** |
| Group V | Thioacetamide + MECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 103.5 ± 4.122*** | 154.9 ± 5.046*** | 1.421 ± 0.159*** | 0.504 ± 0.031*** | 122.6± 5.117*** |
| Group VI | Thioacetamide + MECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 83.72 ± 4.578*** | 131.6 ± 4.853*** | 1.103 ± 0.162*** | 0.339 ± 0.028*** | 112.5 ± 3.761*** |
| Group VII | Thioacetamide + PECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 202.5 ± 6.983*** | 243.4 ± 6.520*** | 2.152 ± 0.340*** | 0.758 ± 0.042*** | 192.8 ± 5.168*** |
| Group VIII | Thioacetamide + PECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 134.7 ± 5.276*** | 179.1 ± 4.980*** | 1.691 ± 0.274*** | 0.638 ± 0.033*** | 143.3 ± 4.337*** |
| Group IX | Thioacetamide + PECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 92.07 ± 5.634*** | 139.7 ± 4.183*** | 1.308 ± 0.233*** | 0.451 ± 0.026*** | 132.7 ± 4.189*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to thioacetamide treated group. MECT-Methanolic extract of Cassia tora, PECT: Petroleum ether extract of Cassia tora.

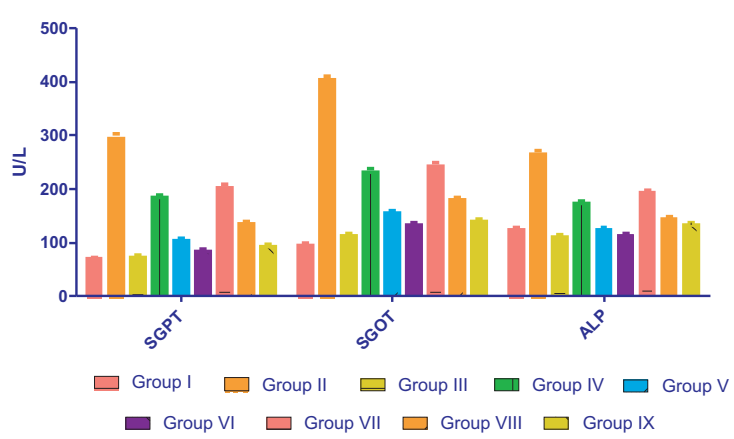



**Figure No. 10: Effect of MECT and PECT on SGPT, SGOT, ALP, levels in Thioacetamide Induced Hepatotoxic Rats**

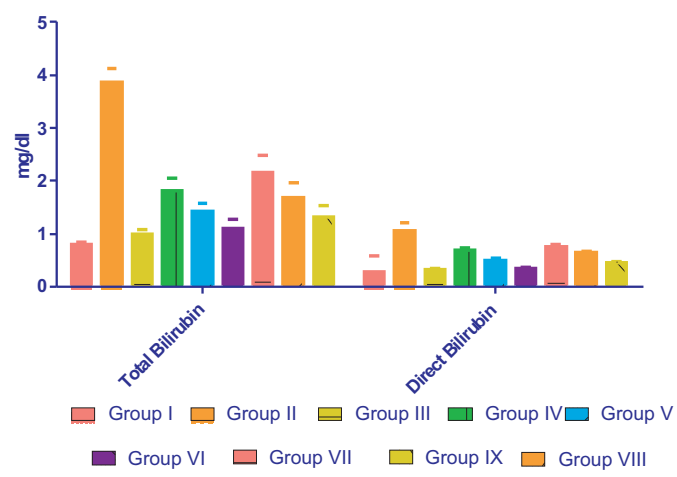



**Figure No. 11: Effect of MECT and PECT on Direct Bilirubin, Total Bilirubin levels in Thioacetamide Induced Hepatotoxic Rats**

**2 Serum Total Protein**

Thioacetamide treatment considerably reduced serum total protein levels. Pretreatment with Silymarin and MECT and PECT showed a significant increase in total protein levels as compared with toxicant control group. The results are summarized in Table No.7 and graphically depicted in Figure No. 12.

**Table No. 7: Effect of MECT and PECT on Serum Total Protein Levels in Thioacetamide Induced Hepatotoxic Rats**

| Groups | Treatment | Total Protein levels (gm/dl ) (Mean±SEM) |
|---|---|---|
| Group I | Negative Control (1ml distilled water) | 6.768 ± 0.271 |
| Group II | Positive Control Thioacetamide (100 mg/kg s.c.) | 2.813 ± 0.146 |
| Group III | Thioacetamide + Standard (Silymarin) (100 mg/kg s.c.+ 100 mg/kg p.o.) | 6.603 ± 0.279*** |
| Group IV | Thioacetamide + MECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 5.167 ± 0.245*** |
| Group V | Thioacetamide + MECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 5.960 ± 0.209*** |
| Group VI | Thioacetamide + MECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 6.482 ± 0.156*** |
| Group VII | Thioacetamide + PECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 4.920 ± 0.215*** |
| Group VIII | Thioacetamide + PECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 5.675 ± 0.140*** |
| Group IX | Thioacetamide + PECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 6.178 ± 0.256*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to thioacetamide treated group. MECT-Methanolic extract of Cassia tora, PECT: Petroleum ether extract of Cassia tora

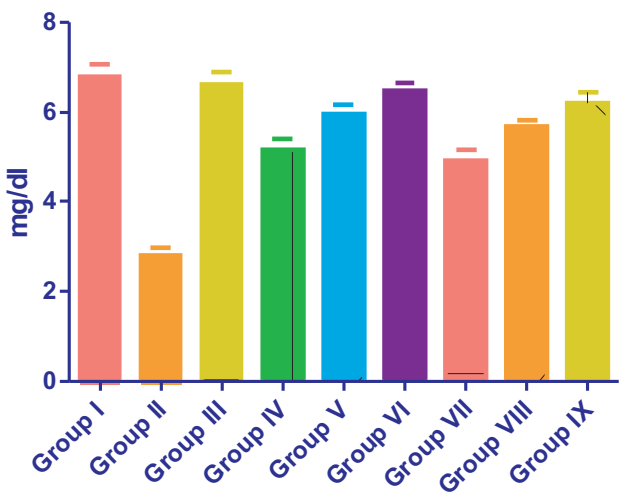



**Figure No.12: Effect of MECT and PECT on Serum Total Protein Levels in Thioacetamide Induced Hepatotoxic Rats**

### 3 Serum Lipid Profile

The lipid profile was evaluated by estimating triglycerides (TG), total cholesterol (TC), HDL-Cholesterol (HDL-C), LDL-Cholesterol (HDL-C), VLDCholesterol (VLDL-C) in normal and thioacetamide induced hepatotoxic rats. The thioacetamide induced hepatotoxic rats showed a significant increased in the TG, TC, LDL-C and VLDL-C levels and suppression of HDL-C levels compared to control group (Table No. 8 and Figure No. 13). But after treatment with the 200mg/kg, 400mg/kg, 600mg/kg p.o dose of MECT and PECT and silymarin thioacetamide induced hepatotoxic rats showed decrease in the TG, TC, LDL-C and VLDL-C levels and increase in the HDL-C levels compared to untreated thioacetamide induced hepatotoxic rats.

**Table No. 8: Effect of MECT and PECT on Lipid Profile Levels in Thioacetamide Induced Hepatotoxic Rats**

| Groups | Treatment | Serum Lipid Profile mg/dl | | | | |
|---|---|---|---|---|---|---|
| | | TC | TG | HDL-C | LDL-C | VLDL-C |
| Group I | Negative Control (1ml distilled water) | 125.2 ± 4.064 | 132.3 ± 3.178 | 33.54 ± 2.214 | 65.20 ± 1.214 | 26.46± 0.635 |
| Group II | Positive Control Thioacetamide (100 mg/kg s.c.) | 242.4 ± 6.750 | 221.7 ± 6.533 | 19.70 ± 2.160 | 178.3 ± 3.283 | 44.34 ± 1.306 |
| Group III | Thioacetamide + Standard (Silymarin) (100 mg/kg s.c.+ 100 mg/kg p.o.) | 131.6 ± 5.127*** | 143.4 ± 4.028*** | 32.72 ± 1.544*** | 70.20 ± 2.777*** | 28.68 ± 0.805*** |
| Group IV | Thioacetamide + MECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 167.4 ± 5.638*** | 178.5 ± 5.650*** | 27.57 ± 1.529*** | 104.1 ± 2.979*** | 35.70 ± 1.130*** |
| Group V | Thioacetamide + MECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 149.3 ± 5.114*** | 156.3 ± 4.176*** | 29.33 ± 1.182*** | 88.71 ± 3.096*** | 31.26 ± 0.835*** |
| Group VI | Thioacetamide + MECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 133.7 ± 4.068*** | 145.1 ± 3.247*** | 31.69 ± 1.423*** | 72.99 ± 1.995*** | 29.02 ± 0.649*** |
| Group VII | Thioacetamide + PECT (100 mg/kg s.c.+ 200 mg/kg p.o.) | 195.3 ± 5.273*** | 180.9 ±5.631*** | 23.02 ± 1.622$^{ns}$ | 136.1 ± 2.524*** | 36.18 ± 1.126** |
| Group VIII | Thioacetamide + PECT (100 mg/kg s.c.+ 400 mg/kg p.o.) | 161.5 ± 4.206*** | 166.2 ±4.385*** | 27.19 ± 1.271*** | 101.0 ± 2.058*** | 33.24 ± 0.877*** |
| Group IX | Thioacetamide + PECT (100 mg/kg s.c.+ 600 mg/kg p.o.) | 143.9 ± 4.006*** | 157.6 ± 3.125*** | 30.76 ± 1.076*** | 81.52 ± 2.305*** | 31.52± 0.625*** |

Values are Mean ± SEM (n=6) one way ANOVA followed by Tukey-Karmer's test. Where, *** P<0.001, ** P<0.01, * P<0.05 and ns represents Not significant. All the values are compared to thioacetamide treated group. MECT- Methanolic extract of Cassia tora, PECT: Petroleum ether extract of Cassia tora.

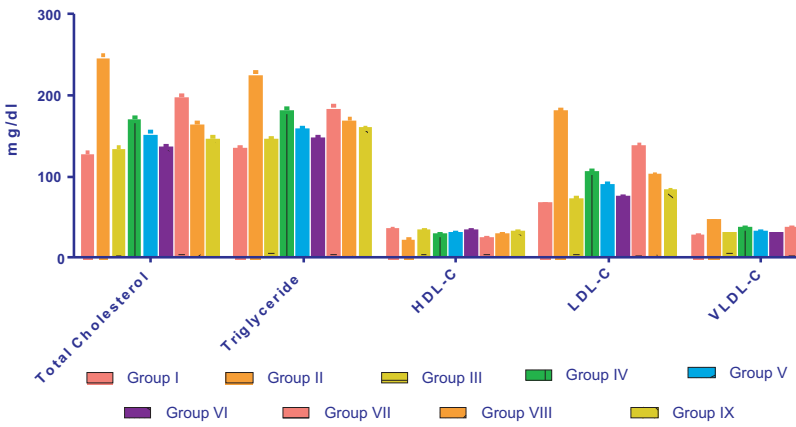
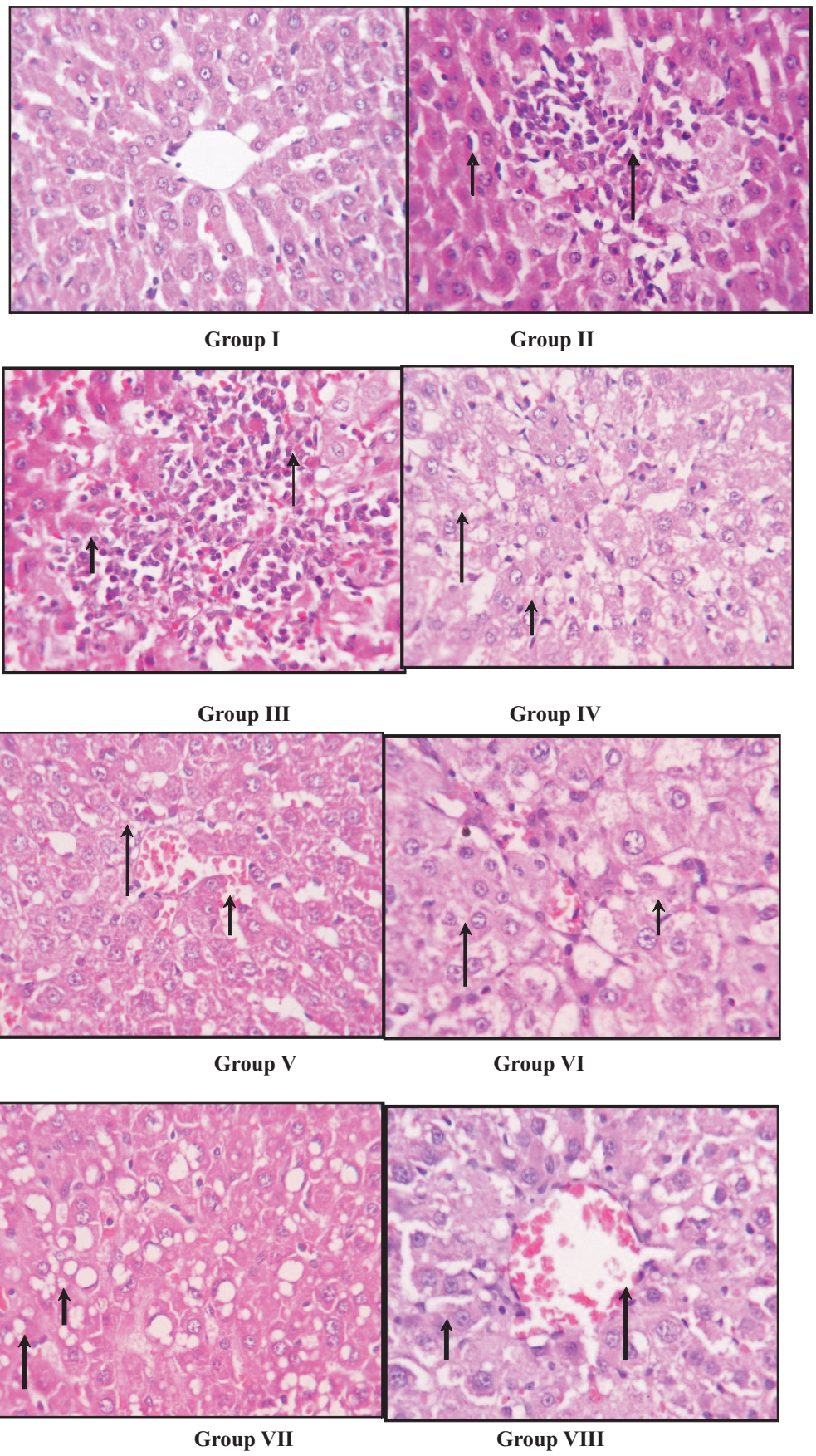
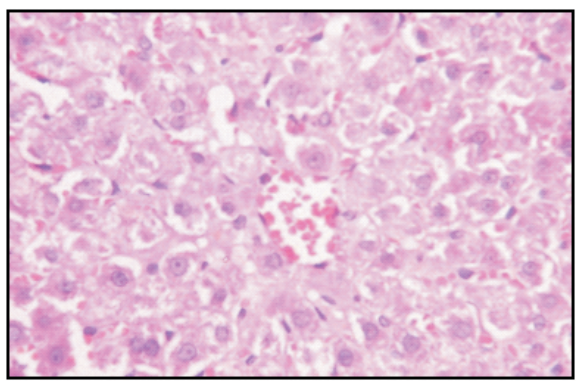



**Figure No.13: Effect of MECT and PECT on Lipid Profile Levels in Thioacetamide Induced Hepatotoxic Rats**


Group I
Group II
Group III
Group IV
Group V
Group VI
Group VII
Group VIII



**Group IX**

**Figure No. 14: Histopathological Studies of the Rat Liver in Thioacetamide Induced Hepatotoxicity**

Group –I(Negative Control - Saline)
Group –II (Positive Control Thioacetamide [100 mg/kg s.c.])
Group –III (Thioacetamide [100 mg/kg s.c.]+ Silymarin [100mg/kg])
Group – IV (Thioacetamide [100 mg/kg s.c.]+ MECT [200mg/kg])
Group – V (Thioacetamide [100 mg/kg s.c.]+ MECT [400mg/kg])
Group – VI (Thioacetamide [100 mg/kg s.c.]+ MECT [600mg/kg])
Group – VII (Thioacetamide [100 mg/kg s.c.]+ PECT [200mg/kg])
Group – VII (Thioacetamide [100 mg/kg s.c.]+ PECT [400mg/kg])
Group – IX (Thioacetamide [100 mg/kg s.c.]+ PECT [600mg/kg])

**DISCUSSION**

Treatment with MECT and PECT significantly reduced the wet liver weight and wet liver volumes of animals and hence it possesses statistically significant hepatoprotective activity. Treatment with MECT and PECT reversed the elevated levels of all the biochemical markers to the near normal levels in this model also. The histopathological parameters of PCM induced hepatotoxicity were normalized by the treatment MECT and PECT. These observations indicate that the MECT and PECT possess hepatoprotective activity against PCM induced hepatotoxicity.

There are reports that paracetamol induced hepatotoxicity is due to activation of PCM to a toxic electrophile N-acetyl p-benzoquinine amine (NAPQI) by a number of iso-enzyme of CYP-450 namely CYP2E1, CYP1A2, CYP2A6, CYP3A4, CYP2D6. Normally PCM is eliminated from the body as sulphate and glucuronide to the extents of 95% before oxidation. However, 5% of PCM is undergoing bioactivation by above mentioned isoenzymes of CYP to a highly reactive NAPQI36.

After the over dosage of paracetamol, routs of sulphation and glucuronidation saturates. As a consequence oxidation of PCM, CYP-450 iso-enzymes are increased leading to the increased concentration of NAPQI. This NAPQI further loses one electron resulting into the toxic radical. This radical interact covalently with membrane macromolecules and damage the membrane. However this reaction is countered by inbuilt tissue antioxidants systems like GSH. Excessive concentration of NAPQI radical over powers the inbuilt protecting mechanisms thereby damages the cell membrane. This results into the leakage of biochemical markers into the serum. It is apparent from the results that treatment with MECT and PECT prevents the formation of one electron reduced metabolite of NAPQI (which mediates cytotoxic effects of NAPQI) due to its antioxidant property i.e. hydroxyl and superoxide anion scavenging activities. Further, this may be helpful in retaining the membrane GSH contents, reduced lipid peroxidation and prevents the tissue damage37-38.

Subcutaneous thioacetamide (TAA) 100 mg/kg b.w. for one day has induced hepatotoxicity as indicated by the elevation in the biochemical markers SGPT, SGOT, total protein, bilirubin (total and direct triglycerides (TG), total cholesterol (TC), HDL-Cholesterol (HDL-C), LDL-Cholesterol (LDL-C), VLDL-Cholesterol (VLDL-C) and ALP. In addition TAA was found to increase tissue GSH and decrease the lipid peroxidation. Treatment with MECT and PECT (200, 400 and 600mg/kg.p.o.) significantly reduced dose dependently all the biochemical markers enzymes and increased the tissue GSH levels. The MECT and PECT have improved the liver architecture as similar to other models of hepatotoxicity. Hence, it can be informed that the test extract possess hepatoprotective activity in this model also.

TAA is metabolised by the liver CYP4502E1 enzymes reducing sulfonesand sulfoxide derivatives which are

apparently responsible for inactivation of enzymes and proteins39. In addition there is a report that thioacetamide is metabolised by CYP-450 to thioacetamide 5-oxide, which responsible for the change in cell permeability results in increased intracellular concentration in Ca++ nuclear volume, enlargement of nucleoli and inhibits the mitochondrial activity and consequently leads to cellular death. Further there are reports that TAA enhanced the lipid peroxidation and depleted the tissue GSH40.

In the present study TAA has reduced the tissue GSH and increased the lipid peroxidation. Treatment with MELA, PELA, MECT and PECT has reversed the TAA induced elevated lipid peroxidation and decreased tissue GSH.

## CONCLUSION

Treatment with MECT and PECT brought back the elevated levels of SGPT, SGOT, ALP, total protein, total and direct bilirubin, triglycerides (TG), total cholesterol (TC), HDL-Cholesterol (HDL-C), LDL-Cholesterol (LDL-C), VLDL-Cholesterol (VLDL-C) and ALP in Paracetamol and Thioacetamide induced hepatotoxicity in rats near to health levels. Histopathological observation revealed that treatment with GASD has reversed the hepatic damage by Paracetamol and Thioacetamide. Hence, Cassia tora possesses hepatoprotective activity.

Further, the work could be extended to evaluate the effectiveness of the marker compounds for the treatment of liver disorders at its cellular level to elucidate its exact mechanism for the traditional claim.

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**ABBREVIATIONS**

MECT- Methanolic extract of Cassia tora
PECT: Petroleum ether extract of Cassia tora
Serum glutamate pyruvate transaminase (SGPT/ALT)
Serum glutamate oxaloacetate transaminase (SGOT/AST)
Serum alkaline phosphatase (ALP)

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