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Research Article

Evaluation of Liver Protective Activity of Some Indigenous Plants Against Acute Paracetamol Toxicity in Rodents

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ABSTRACT

Aim: The aim of the present study was to evaluate the liver protective activity of some indigenous plants against acute paracetamol toxicity in rodents. Liver intoxication was induced by paracetamol drug at a dose level of 500 mg/kg b.w, p.o for 9 days. To conduct this study the hydroalcholic extract of *Prunus persica, Calotropis procera* and *Canscora decussate* were taken as test compounds. Methods: Rats (180-200 g) were used for all the study and they were divided into 9 groups containing 6 animals each. Rats in Group I served as normal control (distilled water) group, Group II served as toxic control (Paracetamol treated) group, Group III served as standard (Silymarin) group. The rats of groups IV, V, VI, VII, VIII and IX served as test control groups. Group IV, V received the hydroalcoholic extract of *Prunus persica* at the dose of 200 and 400 mg/kg b.w, p.o respectively for 9 days. Group VI, VII received the hydroalcoholic extract of *Calotropis procera* at the dose of 200 and 400 mg/kg b.w, p.o respectively for 9 days. Group VIII and IX received the hydroalcoholic extract of *Canscora decussate* at the dose of 200 and 400 mg/kg b.w, p.o respectively for 9 days. The degree of protection was measured by using biochemical parameters such as serum glutamate oxalate transaminase (SGOT) and serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), bilirubin and total protein and albumin. Results: Results of this study showed that the treatment of the toxic effect of the paracetamol were significantly controlled in the hydroalcoholic extract of plants treated groups. The hydroalcholic extract of plants at 400 mg/kg b.w, showed significant reduction in elevated serum enzyme levels compared to paracetamol induced toxic group. The hydroalcoholic extract of *Calotropis procera* at a dose of 400 mg/kg, b.w showed the most significant hepatoprotective activity among all the test groups. Conclusion: From the results it was concluded that the all the test plants extract possess significant Hepatoprotective activity which was manifested by restoration of serum biochemical parameters to nearer the normal values. On the basis of results obtained, it can also be concluded that the hydroalcoholic extract of Plants seems to have hepatoprotective activity which may be due to the presence of flavonoids.

Keywords: *Prunus persica*, *Calotropis procera*, *Canscora decussate*, Hepatoprotective activity, Serum enzymes, Silymarin.

INTRODUCTION

Liver is the major organ which plays a key roles in processing critical biochemical and physiological phenomena including metabolism and Detoxification of endogen and exogenous compounds such as drugs and xenobiotics, homeostasis, growth, energy and nutrient supply[1,2]. The toxicity of liver is a damage or injury to liver which is caused by various drugs, chemicals and other agents. Severity of liver damage or injury depends on degree of exposure, mild liver damage cause dysfunction but severe liver damage result in liver failure[3]. However we do not have satisfactory liver protective drugs in allopathic medical practice for serious liver disorders. Nature has bestowed mankind with several plants which contains natural substances which cure diseases and promote health[4]. Herbal drugs play a role in the management of various liver disorders most of which speed up the natural healing processes of the liver. Numerous medicinal plants and their formulations are used for liver disorders in ethnomedical practice as well as traditional system of medicine in India. More than fifteen of these plants are evaluated for their hepatoprotective activities in light of modern medicine[5]. *Prunus persica*, *Calotropis procera* and *Canscora decussata* were taken as test compounds to conduct this study.

Prunus Persica

Prunus persica L. (Peach) named as Amygdalus persica is a perennial and deciduous tree of the subfamily Prunoideae of the family Rosaceae. The leaves are insecticidal, sedative, diuretic, demulcent, expectorant, vermicidal and are used in leucoderma, and in piles[6]. Leaf paste is used to kill worms in wounds, and fungal infections. The treatment of gastritis, whooping cough, and chronic bronchitis is carried out internally with leaves[7]. Peach has an 86-89%

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Figure: *Prunus persica*

Figure: *Calotropis procera*

Figure: *Canscora decussata*

Table 1: Phytoconstituents present in hydroalcoholic extracts of *Prunus persica*, *Calotropis procera* and *Canscora decussata*

S. No.	Chemical Constituents	Tests	*Prunus persica*	*Calotropis procera*	*Canscora decussata*
1.	Alkaloids	Mayer's test	+	+	+
		Dragendorff's test	+	+	+
		Wagner's test	+	+	+
		Hager's test	+	+	+
2.	Carbohydrates	Molisch's test	-	-	+
		Benedict's test	+	-	+
		Fehling's test	-	-	+
3.	Glycosides	Modified borntrager's	+	+	-
		Legal test	+	+	+
4.	Saponins	Foam test	-	+	+
		Froth test	+	+	+
5.	Phytosterols	Salkowski's test	-	+	+
		LibermannBurchard test	+	+	-
6.	Resins	Acetone-Water test	-	+	-
7.	Fixed oils	Filter Paper	-	-	-
8.	Phenols	Ferric Chloride test	+	+	+
9.	Tannins	Gelatin test	+	-	-
10.	Flavonoids	Alk. Reagent test	+	+	+
		Lead acetate	+	+	+
		Zn-HCl acid reduction	+	+	-
		Shinoda test	+	+	+
11.	Proteins	Xanthoproteic test	-	-	+
		Ninhydrin test	+	-	+
		Biuret test	+	-	+

Note: '+' sign indicates presence and '—' sign indicates absence

water content, a 7.5-8.5% sugar content (mainly sacarose, glucose and fructose), a 0.6-1.2% protein content, a 0.3% fat content, a 1.2-1.4% fibre content (mainly cellulose, pectins and hemicelluloses), a 0.63% acid content, a 0.8% mineral content (potassium being the main constituent), several vitamins (mainly from group B and C) and a 0.20-0.80% carotenoid content (mainly β- carotene). Table 1 shows the main components found in peaches. Total acids present in peaches are malic acid and, in a smaller proportion, citric and quinic acid. It also contains phenolic compounds, catequins and leucoanthocyanins. The presence of carotenoids and their derivatives is significant and more important than in other fruits. In particular, β-cryptoxantine, β-carotene and α-carotene (vitamin A precursors) have been detected, together with zeaxanthine, lycopene and xanthophyll, that gives peaches their characteristic colour.

Calotropis procera

Calotropis procera is a wild growing plant of family Asclepiadaceae. It is well known for its medicinal properties. A number of ethanomedicinal uses of the drug are reported. Whole plant was used either alone or with other herbs for the treatment of common diseases such as fever, rheumatism, indigestion, cold, eczema and diarrohea, paste of root bark was locally applied in the treatment of elephantiasis and Root bark powder was used to treat diarrhea and dysentery and it is an excellent substitute for ipecac. Traditionally it was used to treat cholera, extracting guinea worms and indigestion[8].

The leaves of Calotropis procera contain mainly a-amyrin, aamyrin acetate, ß-sitosterol, urosolic acid, cardenolides, calotropin, calotropagenin[9].

Canscora decussate

Canscora decussata is popularly known as "Shankhpushpi" and found throughout India, up to an altitude of 1300 m. It is also found to contain triterpines, alkaloids and

Table 2: Effect of hydroalcholic leaves extract of some plants of Northern India against acute Paracetamol toxicity on Biochemical parameters.

Parameters	Normal Control	Toxic Control	Silymarin (100 mg/kg)	*Prunus persica* Extract (200 mg/kg)	*Prunus persica* Extract (400 mg/kg)	*Calotropis procera* Extract (200 mg/kg)	*Calotropis procera* Extract (400 mg/kg)	*Canscora decussate* Extract (200 mg/kg)	*Canscora decussate* Extract (400 mg/kg)
SGOT (IU/L)	79.61±3.12	298.64±4.32##	98.04±7.52*	196.5±6.13**	174.5±4.34**	143.3±4.13**	122.7±2.86**	173.9±2.43**	165.3±4.02**
SGPT (IU/L)	71.23±5.66	201.63±4.44##	82.52±3.32*	184.7±4.21**	125.4±3.40**	132.8±6.33**	97.81±4.50**	167.6±5.55**	100.5±5.45**
SALP (IU/L)	129.44±5.34	318.21±6.34##	138.11±4.17**	197.4±6.22**	173.6±2.1**	153.3±5.32**	146.42±7.12**	178.23±2.22**	158.43±7.17**
Sr. Bilirubin (mg/dl)	0.34±0.21	5.22±0.11##	0.73±0.12*	1.82±0.03**	1.21±0.12**	1.10±0.11**	0.92±0.06**	1.43±0.12**	1.19±0.22**
Sr. Albumin (g/dl)	7.88±0.31	1.23±0.16##	5.68±0.13**	2.45±0.07**	4.53±0.03*	3.03±0.14**	4.98±0.24*	2.85±0.21**	4.57±0.12*
Sr. Total Protein (g/dl)	9.22±0.21	3.78±0.19##	7.28±0.27**	4.13±0.22**	6.28±0.15**	5.88±0.22**	7.01±0.12**	4.32±0.33**	6..58±0.17**

All values represent Mean ± S.E.M. of n=6/group; ## $p<0.01$ when compared with normal control and *$p<0.05$, **$p<0.01$ as compared with toxic control group.

xanthones. It is also a natural source of pentaoxygenated, hexaoxygenated and dimeric xanthones.

This plant contains bitter substances, oleoresin triterpenes, alkaloids and xanthones such as mangiferin. The leaves of Canscora decussata has been reported in the literature with beneficial effects in inflammation hypertension, tuberculosis, nervous disorders and viral infections etc.

MATERIALS AND METHODS

Chemicals

All chemicals used were of analytical grade. Silymarin was purchased from local medical store (Silybon-140, Micro Labs Ltd, H.P. India). The kits for biochemical estimation were purchased from Merk Ltd, Kalyan Badlapur Road, Ambernath (India). Paracetamol (API) was obtained from Cipla Ltd, Vill Juddikalan, Baddi, H.P. The solvents and other chemicals were obtained from local dealers.

Plants Collection and Authentication

The leaves of *Prunus persica* and *Calotropis procera* were collected from the garden of Aman Vihar Colony, Krishna Nagar, Roorkee Road Meerut and leaves of *Canscora decussate* were purchased from Khari Baoli street, Chandni chowk, New Delhi in the month of July and then authenticated by Dr. R.S. Saxena, Reader and Head Botany Department, Meerut College, Meerut (U.P.) 250001, deposited to T.I.P.E.R. for future reference.

Preparation of Leaves Extract

The coarsely powdered leaves (500 g) were extracted with soxhlet apparatus using petroleum ether for about 24 hrs. After defatting, the marc was dried in hot air oven at 50^0C, packed in soxhlet apparatus, and further extracted with 1 L of 95% (V/V) ethanol and water mixture by percolation method. The solvent were removed from the extracts under reduced pressure by using rotary vacuum evaporator[10].

Phytochemical Screening

The hydroalcholic extract of plants were screened for the presence of various phytoconstituents by adopting standard procedures[11,12,13].

Animals

After prior approval from the Institutional Animal Ethical Committee (IAEC approval No. IAEC/Ph-16/TIPER/057), the rats were obtained from animal house facility of T.I.P.E.R. for evaluation of hepatoprotective activity of *Calotropis procera*, *Canscora decussate* and *Prunus persica* against paracetamol induced hepatic injury in rats. The healthy albino rats of Wistar strain of either sex weighing about 170-200 gm were kept at temperature 23±2 ºC and humidity (50-55 %) with 12 hrs light and dark cycles. They were caged with a maximum of three animals in each polypropylene cage and were fed with standard pellet diet and water *ad libitum*.

Selection of Doses

As per Debjit, B *et al*., 2010, doses were selected on the basis of maximum tolerated safe doses found from toxicity studies. The doses were selected $1/10^{th}$ and $1/5^{th}$of the maximum tolerated safe dose 2000 mg/kg, *i.e.* 200 mg/kg and 400mg/kg respectively and were administered orally once daily for twenty eight days[14].

Induction of Hepatotoxicity

The Paracetamol (PCM) induced hepatotoxicity model described by Parmer *et al*., (2010) was used with slight modifications. Rats were fasted overnight and hepatotoxicity was induced by administration of Paracetamol in pure form (API) in distilled water at the

dose of 500 mg/ kg body weight by gastric gavage once daily for the entire duration of study[15].

Acute Model for Hepatoprotective Activity

Animals were randomly divided into nine groups of six

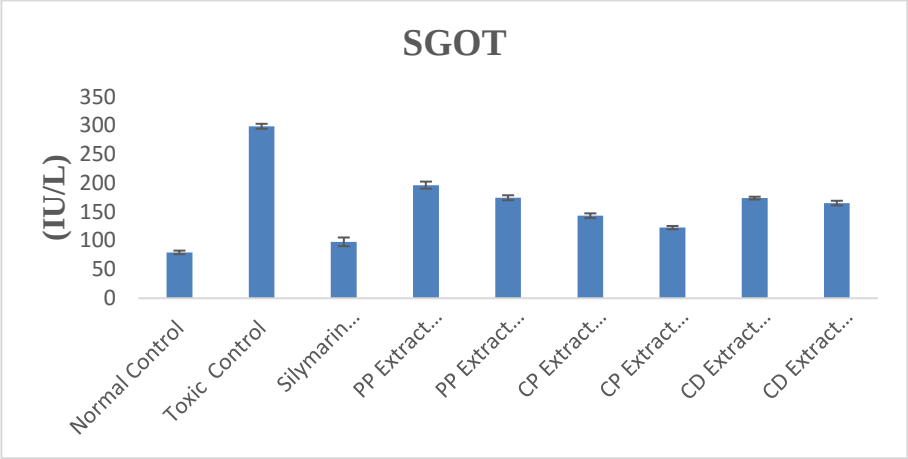

Figure 4: Effect of hydroalcoholic extracts pretreatment on SGOT level in PCM induced Acute liver injury in rats.

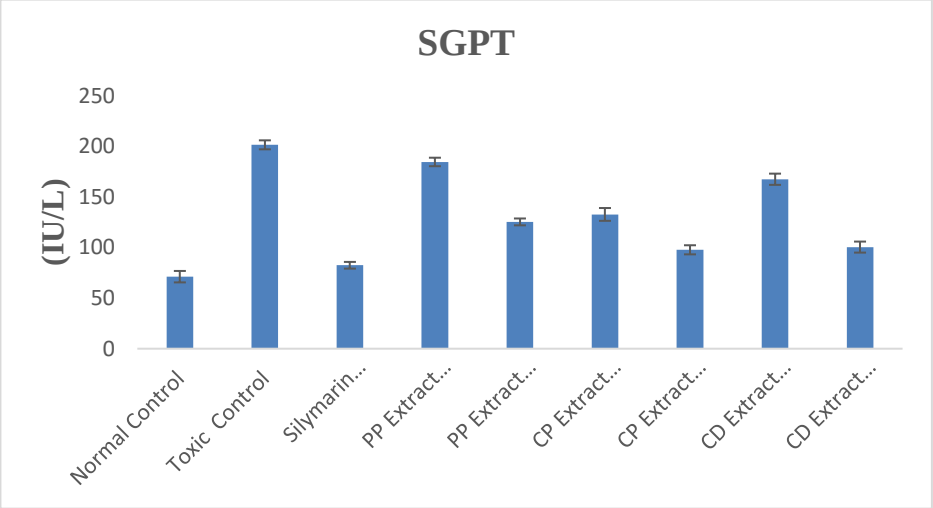

Figure 5: Effect of hydroalcoholic extracts pretreatment on SGPT level in PCM induced Acute liver injury in rats

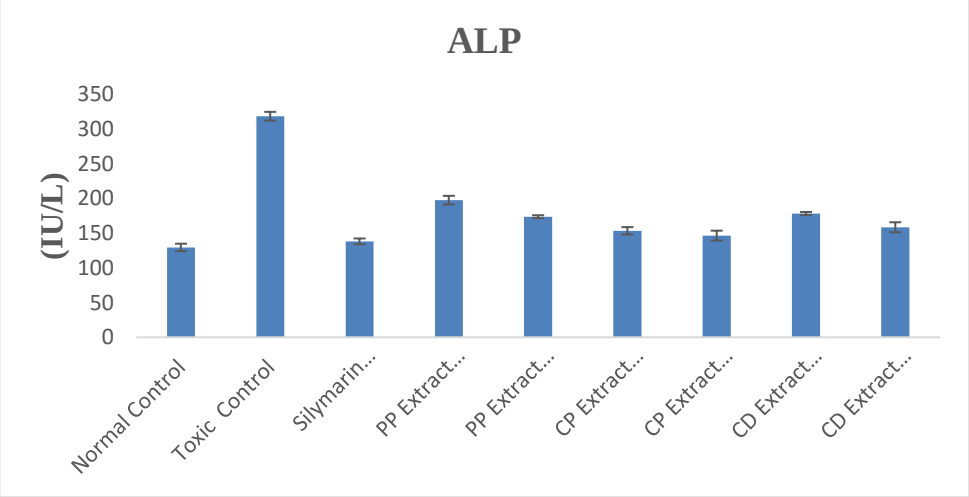

Figure 6: Effect of hydroalcoholic extracts pretreatment on ALP level in PCM induced Acute liver injury in rats

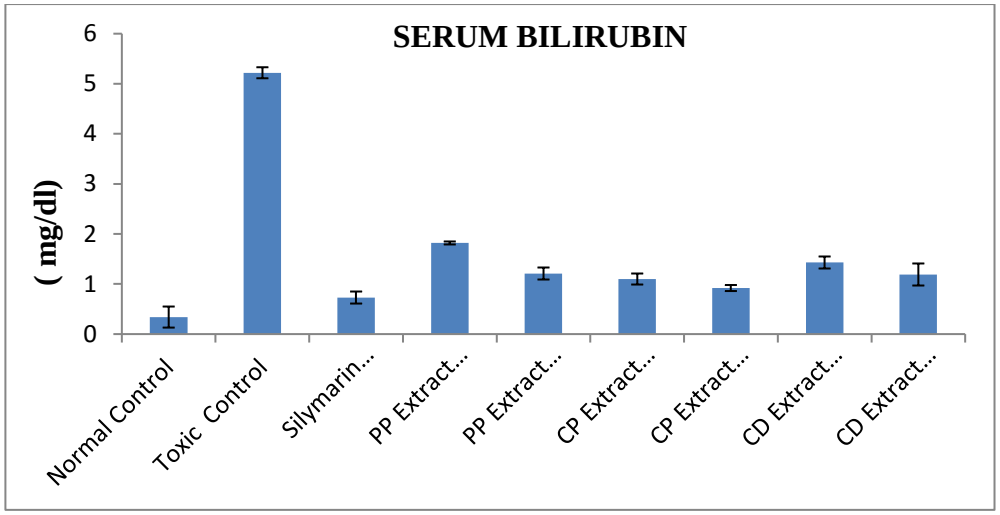

Figure 7: Effect of hydroalcoholic extracts pretreatment on Bilirubin level in PCM induced Acute liver injury in rats

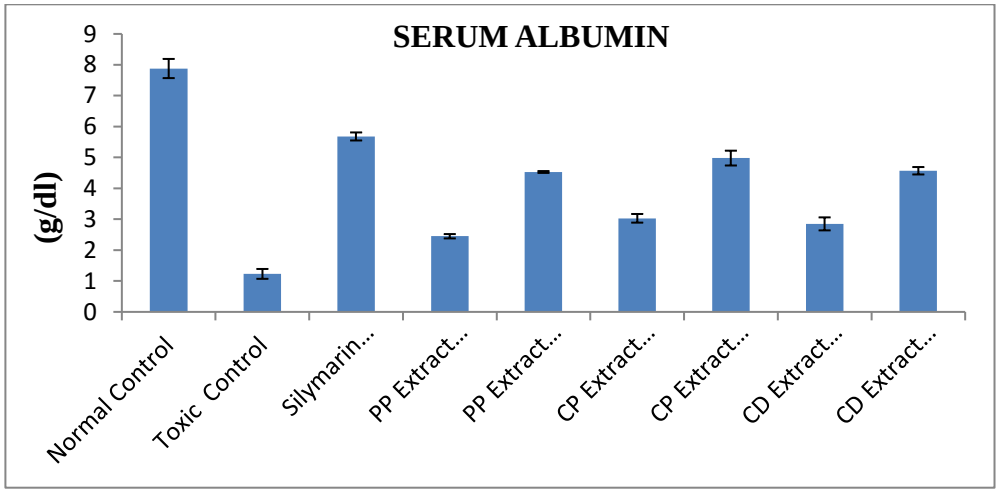

Figure 8: Effect of hydroalcoholic extracts pretreatment on Serum albumin level in PCM induced Acute liver injury in rats

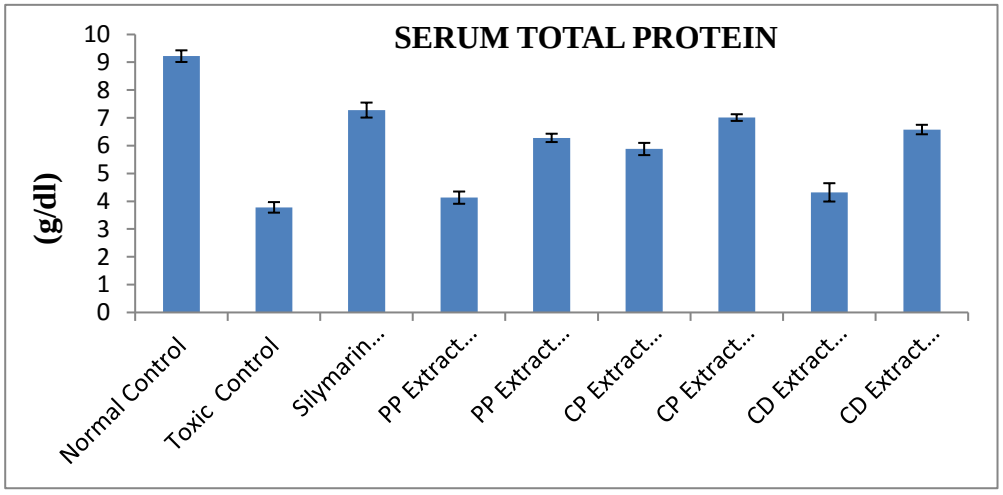

Figure 9: Effect of hydroalcoholic extracts pretreatment on Serum total protein level in PCM induced Acute liver injury in rats

animals each.
Group I- served as normal control and received distilled water (5 ml/kg) for 9 days.
Group II- served as toxic control and received Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group III- served as standard group and received silymarin (100 mg/kg) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group IV- treated with hydroalcholic extract of *Prunus persica* leaves (200 mg/kg/day) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group V- administered with hydroalcholic extract of *Prunus persica* leaves (400 mg/kg/day) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group VI- treated with hydroalcholic extract of *Calotropis procera* leaves (200 mg/kg/day) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group VII- administered with hydroalcholic extract of *Calotropis procera* leaves (400 mg/kg/day) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group VIII- treated with hydroalcholic extract of *Canscora decussate* leaves (200 mg/kg/day) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.
Group IX- administered with hydroalcholic extract of *Canscora decussate* leaves (400 mg/kg/day) and Paracetamol in distilled water (500 mg/ kg body weight) for 9 days.

Analysis of liver biomarkers

After 24 hours of Paracetamol administration (on 10th day) blood samples were collected separately into sterilized dry centrifuge tubes by retro-orbital plexus puncture under mild ether anesthesia. The collected blood was allowed to clot at room temperature and serum was separated by centrifugation at 2500 rpm for 15 min. Then serum was used for the estimation of biomarkers such as serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), total bilirubin (TB) and total protein (TP).The biochemical parameters were estimated as per the standard procedure prescribed by manufacturer's instruction manual provided in the standard kit using autoanalyser[16].

Statistical analysis

All the data are expressed as mean ± SEM of six animals from each group. One-way analysis of variance (ANOVA) was used for statistical analysis of data followed by using Graph Pad Prism software. A probability of less than 5% ($p<0.05$) was considered statistically significant.

RESULTS AND DISCUSSION

The preliminary phytochemical screening confirmed the presence of alkaloids, glycosides, saponins, flavonoids, phenols and proteins in the hydroalcholic leaves extract of *Prunus persica*. After phytochemical screening of the hydroalcoholic extract of *calotropis procera*, it was found that the extract contain alkaloids, glycosides, saponins, phytosterols, flavonoids and the hydroalcoholic extract of

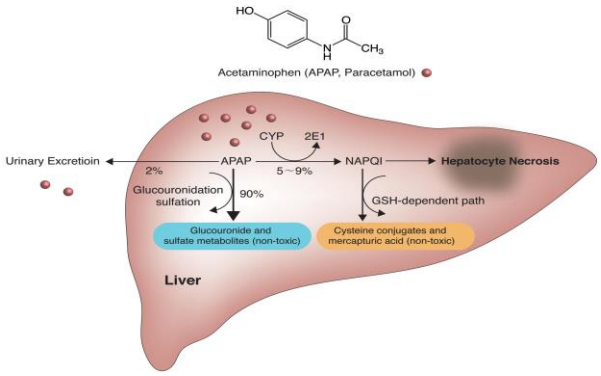

Figure 10: Mechanism of Paracetamol induced liver injury.

Canscora decussate showed the presence of alkaloids, carbohydrates, glycosides, saponins, flavonoids, phenols and proteins.

The results of Hepatoprotective effects of hydroalcoholic extracts of some indigenous plants of Northern India against paracetamol toxicity in rats were shown in table 2. The levels of SGOT [(298.64±4.32) IU/L], SGPT [(201.63±4.44) IU/L], ALP [(318.21±6.34) IU/L] and bilirubin [(5.22±0.11) mg/dl] were significantly increased in toxic control group (Group II) when compared with normal control group but the levels of albumin [(1.23±0.16) g/dl] and total protein [(3.78±0.19) g/dl] were significantly decreased. Rats pre-treated with *Prunus persica* and *Canscora decussata* leaves extracts at dose 400 mg/kg showed significant reduction in the levels of SGOT, SGPT, ALP and bilirubin when compared with toxic control group. But the maximum reduction of SGOT, SGPT, ALP and bilirubin were observed in the rats of VI and VII groups, pretreated with hydroalcoholic extract of *calotropis procera* at the doses 200 and 400 mg/kg respectively.

DISCUSSION

The present study involves the evaluation of liver protective activity of some indigenous plants against acute paracetamol toxicity in rodents. Paracetamol or acetaminophen has been used as a tool to induce hepatic injury in the experimental rats. Acetaminophen (APAP) is one of the most frequently used drugs for its analgesic and antipyretic properties[17]. It is safe and effective at recommended doses, whereas overdose may lead to hepatotoxicity and acute liver failure (ALF)[18,19]. Acetaminophen is bioactivated to a toxic reactive metabolite, N-acetyl-p-benzoquinone imine (NAPQI), by cytochrome 2E1 (Cyp2E1) and, to a much lesser extent, Cyp1A2 in the liver. NAPQI depletes glutathione (reduced glutathione [GSH]) and subsequently binds to liver proteins, leading to oxidative stress, mitochondrial dysfunction, and necrotic cell death. Cyp2E1 is critically involved in the bioactivation of APAP to form NAPQI and, thus, APAP hepatotoxicity[20,21]. This study showed that hydroalcoholic extracts of some indigenous plant leaves possess hepatoprotective activity, as evidenced by the

significant reduction in the elevated levels of serum biomarkers which was increased by PCM.

There was an increase in SGOT (↑275.12%), SGPT (↑183.07%), ALP (↑145.83%) and bilirubin (↑1435.2%) level of toxic control group treated with PCM when compared to that of normal control group whereas there was decrease in serum albumin (↓84.39%) and total protein (↓59 %) level. Rats pretreated with standard drug silymarin (100 mg/kg) exhibited decrease in SGOT (↓67.17%), SGPT (↓59.07%), ALP (↓56.5%), bilirubin (↓86.0%) level and increase in serum albumin (↑361.79%) and total protein (↑92.59%) level as compared to that of toxic control group. Further, rats pretreated with hydroalcoholic leaves extract of *Prunus persica* (200 mg/kg and 400 mg/kg) showed decrease in SGOT (↓34.20% and 41.57%), SGPT (↓8.40% and 37.8%), ALP (↓37.9% and 45.4%), bilirubin (↓65.13% and 76.8%) level and increase in serum albumin (↑99.19% and 268.29%) and total protein (↑9.26.7% and 66.14%) level respectively as compared to that of toxic control group. But rats pre administered with hydroalcoholic leaves extract of *Calotropis procera*, 200 and 400 mg/kg (Group VI and VII) for nine days; showed the more decrease in percentage of SGOT (↓52.02% and 58.9%), SGPT (↓34.14% and 51.49%), ALP (↓51.8% and 53.9%), bilirubin (↓78.9% and 82.3%) level and increase in serum albumin (↑146.34% and 304.8%) and total protein (↑55.56% and 85.45%) level respectively when compared to that of toxic control group. Also, the rats pretreated with hydroalcoholic extract of *Canscora decussata* (200 and 400 mg/kg) showed decrease in SGOT (↓41.77% and 44.65%), SGPT (↓16.88% and 50.16%), ALP (↓43.99% and 50.21%), bilirubin (↓72.6% and 77.2%) level and increase in serum albumin (↑131.7% and 271.5%) and total protein (↑14.29% and 74. 07%) level respectively as compared to that of toxic control group.

Thus hydroalcoholic extracts of *Prunus persica*, *Calotropis procera* and *Canscora decussate* leaves possess hepatoprotective properties in the dose dependant manner, against paracetamol intoxication in rats, after nine days pretreatment; at the dose level 200mg/kg and 400 mg/kg.

CONCLUSION

In present investigation it was found that the hydroalcoholic extracts of some indigenous plants of Northern India brought all the parameters affected by Paracetamol toxicity near to normal. Thus, the hydroalcoholic extracts of *Prunus persica*, *Calotropis procera*, *Canscora decussate* has hepatoprotective effect which minimizes the hepatotoxicity induced by Paracetamol. Among all the plants *Calotropis procera* at the dose of 400 mg/kg showed maximum reduction in the level of biomarkers present in the liver.

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