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Protective effect of *Sida cordata* leaf extract against CCl_4 induced acute liver toxicity in rats

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ABSTRACT

Objective: To investigate the hepatoprotective potential of *Sida cordata* (Malvaceae) (*S. cordata*) in experimental rats to validate its traditional claim. **Methods:** Wister albino rats were divided into 6 groups: Group Ⅰ served as control; Group Ⅱ served as hepatotoxic (CCl_4 treated) group; Group Ⅲ, Ⅳ and Ⅴ served as (100, 200 and 400 mg/kg b.w.) *S. cordata* leaf extract (SCLE) treated groups; Group Ⅵ served as positive control (Silymarin) treated group. Liver marker enzymes serum glutamate oxyloacetic transaminase, serum glutamic pyruvic transaminase, pancreatic enzymatic antioxidants superoxide dismutase (SOD), lipid peroxidation, catalase (CAT), reduced glutathione (GSH) were measured and compared along with histopathological studies. **Results:** Obtained results show that the treatment with SCLE significantly ($P<0.05-<0.001$) and dose-dependently reduced CCl_4 induced elevated serum level of hepatic enzymes. Furthermore, SCLE significantly (up to $P<0.001$) reduced the lipid peroxidation in the liver tissue and restored activities of defence antioxidant enzymes GSH, SOD and CAT towards normal levels, which was confirmed by the histopathological studies. **Conclusions:** The results of this study strongly indicate the protective effect of SCLE against CCl_4 induced acute liver toxicity in rats and thereby scientifically support its traditional use.

1. Introduction

Liver is the most important organ, which plays a pivotal role in regulating various physiological processes in the body. It is involved in several vital functions, such as metabolism, secretion and storage. It has great capacity to detoxicate toxic substances and synthesize useful principles. Therefore, damage to the liver inflicted by hepatotoxic agents is of grave consequences[1]. Conventional or synthetic drugs used in the treatment of liver diseases are sometimes inadequate and can have serious adverse effects. On the other hand, Ayurveda, an indigenous system of medicine in India, has a long tradition of treating liver disorders with plant drugs[2].

Sida cordata (Burn. F.) Borss. (syn: Sida vernicifolia Lam.), Family: malvaceae (*S. cordata)*, commonly known as Bhumibala (Heartleaf fanpetal); is a procumbent, diffuse, much branched hairy herb with a very short main stem and long slender trailing branches that occasionally root at places of contact with the soil, found throughout India, mostly in dry places as weed on road sides; leaves long-petioled, cordate to roundish with stellate hairs; flowers yellow, solitary or in pairs in the axils; fruits schizocarp located within the persistent calyx; seeds brownish, glabrous[3]. The species of *Sida* has been mentioned in Charak Samhita as brmhaniya-a bulk-promoting herb and as balya-tonic and prajasthapana-which promote reproduction[4]. The drug is useful in neurological disorders like hemiplegia, facial paralysis and sciatica, general debility, headache, opthalmia, dysuria, leucorrhoea, tuberculosis, diabetes, fever, rheumatism and uterine disorders[5,6]. To best of our knowledge there was lack of scientific reports available in support of traditional claim of its hepatoprotective potential. On the basis of leads available from folklore usage, a systematic research was undertaken to evaluate the possible effect of *S. cordata*

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leaf extract (SCLE) on the hepatotoxicity induced by CCl_4 in experimental animals.

2. Materials and methods

2.1. Chemicals

Silymarin (Microlabs, Mumbai), CCl_4, Liquid paraffin (Qualigen's, Mumbai), estimation of marker enzymes for liver functions such as SGOT, SGPT, ALP, total bilirubin, total protein were performed by using kits provided by Agappe Diagnostics Pvt. Ltd, Kerala, Semi-autoanalyser (MERCK Microlabs-300) was used as instrument for parameter testing. All other chemicals were purchased from SD fine chemicals, Mumbai and were of analytical grade.

2.2. Collection and preparation of plant extract

S. cordata was collected from rural belt of Raipur district in Chhattisgarh, India in July 2010. The plant was identified and authenticated by Dr. MS Mondal, Additional Director, Central National Herbarium, Govt. of India, Howarh (India). The voucher (number is CNH/Ⅰ-304/2010/Tech.Ⅱ/360) was deposited in the institutional herbarium. The fresh leaves were washed under running tap water, air dried and powdered. Coarsely powdered sample (500 g) was defatted with petroleum ether (60-80 ℃) and then extracted with 1 L of 95% (v/v) ethanol and water mixture by hot percolation method. The extract was concentrated under vacuum to the solvent free residues (yield 17.06% w/w). Preliminary phytochemical analysis such as phenolic group, alkaloids, flavonoids, tannins, steroids and triterpenoids were calculated by the standard protocols[7].

2.3. Animals

Healthy adult Wistar albino rats weighing (150-180 g) and Swiss albino mice (25-30 g) of either sex were procured from the animal house, Gayatri College of Pharmacy, Sambalpur (Reg. No. 1339/ac/10/CPCSEA). The animals were housed in spacious cages. The animals were maintained for 12 h in light and dark cycle at (28±2) ℃ in a well-ventilated animal house under natural conditions in large polypropylene cages and they were acclimatized to laboratory conditions for 10 days prior to the commencement of the experiment. The animals were fed with standard pelleted diet supplied by Anjali foods, Indore, India and provided with water *ad libitum*. All animal experiments were performed according to the ethical guidelines suggested by the Institutional animal ethics committee (IAEC, CPCSEA, India).

2.4. Acute oral toxicity studies

Acute toxicity study was performed according to Organisation for Economic Co-operation and Development guideline No. 423[8]. Swiss albino mice (25-30 g) of either sex were divided into six groups with six animals in each group. SCLE was administered orally as a single dose to mice at different dose levels of 250, 500, 1 000, 1 500 and 2 000 mg/kg b.w. Animals were observed periodically for the symptoms of toxicity and death within 24 h and then daily for 14 days.

2.5. Induction of hepatotoxicity and drug administration schedule

Hepatoprotective activity was carried out using adult Wistar albino rats (150-180 g). The animals were grouped into 6 (six) groups of 6 (six) animals each group, maintained on standard diet and the food was withdrawn 18-24 h before the experiment though water was given *ad libitum*.

Normal group Ⅰ: Serve as normal control, 4% w/v gum acacia 1.0 mL/kg/b.w. orally for 5 days with 1.0 mL liquid paraffin given subcutaneously on 2nd and 3rd day; Positive control group Ⅱ: Serve as toxicant receiving 4% w/v gum acacia 1.0 mL/kg/b.w. orally for 5 days with 1:1 v/v, CCl_4 in liquid paraffin,1.0 mL/kg/b.w. subcutaneously on 2nd and 3rd day; Test group Ⅲ: Received SCLE in (1 %, w/v, CMC) at 100 mg/kg/b.w. orally for 5 days with 1:1 v/v, CCl_4 in liquid paraffin, 1.0 mL/kg/b.w. subcutaneously on 2nd and 3rd day; Test group Ⅳ: Received SCLE in (1 %, w/v, CMC) at 200 mg/kg/b.w. orally for 5 days with 1:1 v/v, CCl_4 in liquid paraffin, 1.0 mL/kg/b.w. subcutaneously on 2nd and 3rd day; Test group Ⅴ: Received SCLE in (1 %, w/v, CMC) at 400 mg/kg/b.w. orally for 5 days with 1:1 v/v, CCl_4 in liquid paraffin, 1.0 mL/kg/b.w. subcutaneously on 2nd and 3rd day; Test standard group Ⅵ: Serve as standard receiving Silymarin 100 mg/kg/b.w. orally for 5 days with 1:1v/v, CCl_4 in liquid paraffin, 1.0 mL/kg/b.w. subcutaneously on 2nd and 3rd day.

Rats were anesthetized with anesthetic ether on 6th day and blood was collected from retro-orbital plexus and then sacrificed by cervical dislocation. The liver was carefully isolated and preserved in 10% formalin. The weight of each liver was recorded and then subjected to histopathological studies[9].

2.6. Estimation of biochemical parameters

The collected blood was allowed to clot and serum was separated at 2500 rpm for 15 min. The serum was collected and then diluted in the ratio of 1:10 with saline. Aliquot of the diluted serum was used for estimation of serum enzymes like serum glutamic pyruvic transaminase (SGPT), serum glutamate oxyloacetic transaminase (SGOT), alkaline phosphatase (ALP) and bilirubin. The enzyme levels were assayed using standard kits obtained from Agappe Diagnostics Pvt. Ltd, Kerala[10-13]. The liver homogenate was prepared and the clear supernatant was used for the estimation of lipid peroxidation (LPO)[14,15], total protein[16], reduced glutathione (GSH)[17,18] and antioxidant enzymes *viz*. catalase (CAT)[19] and superoxide dismutase (SOD)

levels[17,18].

2.7. Histopathological studies

For histological studies, the liver tissues were fixed with 10% phosphate buffered neutral formalin, dehydrated in graded (50%-100%) alcohol and embedded in paraffin. Thin sections (5M) were cut and stained with routine hematoxylin and eosin (H&E) stain for photo microscopic assessment. The initial examination was qualitative, with the purpose of determining histopathological lesions in liver tissue.

2.8. Statistical analysis

The values were represented as mean±SEM. for six rats. Analysis of variance (ANOVA) test[20] was followed by individual comparison by Newman-Keuls test using Prism Pad software (Ver 3.0) for the determination of level of significance. The values of $P<0.05$ was considered statistically significant.

3. Results

3.1. Acute toxicity studies

SCLE produces no mortality at 2 000 mg/kg. Therefore, one-tenth of the maximum no mortality dose of extract were selected as therapeutic middle dose (200 mg/kg) and just double as well as half dose of it as highest (400 mg/kg) and lowest dose (100 mg/kg) respectively, in this study.

3.2. Effect of SCLE on SGOT, SGPT, ALP and total bilirubin

The effect of various doses of SCLE were studied on serum marker enzymes and total bilirubin in CCl_4 intoxicated animal. Hepatic injury induced by CCl_4 caused significant changes in marker enzyme as SGOT by 275.10%, SGPT by 397.88%, ALP by 128.29% and total bilirubin by 423.28% compared to control group. The percentage protection in marker enzyme of treated group at 100, 200 mg/kg as SGOT 29.16 ($P<0.01$), 51.55 ($P<0.001$), SGPT 24.24 ($P<0.05$), 53.30 ($P<0.001$), ALP 26.88 ($P<0.01$), 44.29 ($P<0.001$) and total bilirubin 27.27 ($P<0.001$), 50.85 ($P<0.001$) compared to CCl_4 group while maximum percentage protection in marker enzyme at the dose of 400 mg/kg and silymarin (100 mg/kg) as SGOT 67.52 ($P<0.001$), 70.62 ($P<0.001$), SGPT 74.32 ($P<0.001$), 77.49 ($P<0.001$), ALP 53.79 ($P<0.001$), 54.63 ($P<0.001$) and total bilirubin 73.58 ($P<0.001$), 75.28 ($P<0.001$) which is almost comparable to the group treated with silymarin, a potent hepatoprotective drug used as reference standard (Table 1).

3.3. Estimation of LPO, GSH, SOD and CAT

The results in Table 2 showed clear significant percentage change in the levels of LPO in CCl_4 intoxicated rats as 254.05 ($P<0.001$) compared to control group. Treatment with SCLE at the dose of 100, 200, 400 mg/kg significantly prevented this heave in levels and the percentage protection in LPO were 25.95 ($P<0.05$), 48.09 ($P<0.01$) and 63.36 ($P<0.001$), respectively. The GSH, SOD and CAT content had significantly increased in SCLE treated groups whereas CCl_4 intoxicated group had shown significantly decrease in these parameters compared to control group. The percentage

Table 1
Effect of SCLE on SGOT (U/L), SGPT (U/L), ALP (U/L) and total bilirubin level (mg/dL) against CCl_4 induced liver toxicity in rats.

Groups	SGOT	SGPT	ALP	TBL
Control	101.56±19.17	45.92±1011	68.66±59.23	0.73±0.53
CCl_4	380.96±36.25*	228.63±36.73*	156.75±37.71*	3.52±0.75*
SCLE 100	269.89±33.52$^{\#\#}$	173.21±52.27$^{\#}$	114.61±51.78$^{\#\#}$	2.56±0.23$^{\#\#}$
SCLE 200	184.59±23.72$^{\#\#\#}$	106.75±29.67$^{\#\#\#}$	87.33±23.14$^{\#\#\#}$	1.73±0.67$^{\#\#\#}$
SCLE 400	123.73±12.67$^{\#\#\#}$	58.72±42.87$^{\#\#\#}$	72.43±39.26$^{\#\#\#}$	0.93±0.43$^{\#\#\#}$
Silymarin	111.92±18.24$^{\#\#\#}$	51.46±11.21$^{\#\#\#}$	71.11±53.65$^{\#\#\#}$	0.87±0.22$^{\#\#\#}$

Values are mean±SEM. of 6 rats in each group. *$P<0.001$ compared with respective control group Ⅰ; #$P<0.05$, ##$P<0.01$, ###$P<0.001$ compared with group Ⅱ (CCl_4).

Table 2
Effect of SCLE on liver LPO (MDA nmole/min/mg of protein), GSH (nmole/mg of protein), SOD (unit/mg of protein) and CAT (unit/mg of protein) against CCl_4 induced liver toxicity in rats.

Groups	LPO	GSH	SOD	CAT
Control	0.37±0.23	0.92±0.11	26.67±3.54	57.67±6.82
CCl_4	1.31±0.31^{a}	0.41±0.06^{a}	8.89±2.72^{a}	34.78±2.73^{a}
SCLE 100	0.97±0.56^{a}	0.57±0.15^{n}	13.55±1.76	40.57±3.67
SCLE 200	0.68±0.43^{b}	0.71±0.04^{b}	18.11±2.34^{a}	47.34±4.11^{a}
SCLE 400	0.48±0.22^{c}	0.82±0.23^{c}	22.67±3.67^{c}	54.41±2.45^{b}
Silymarin	0.41±0.54^{c}	0.88±0.05^{c}	23.61±2.53^{c}	55.44±1.43^{b}

Values are mean±SEM. of 6 rats in each group. *$P<0.001$ compared with respective control group Ⅰ; #$P<0.05$, ##$P<0.01$, ###$P<0.001$ compared with group Ⅱ (CCl_4).

changed of GSH, SOD and CAT in CCl_4 intoxicated group were as 55.43 (P<0.001), 66.67 (P<0.001) and 39.69 (P<0.001) respectively. The percentage protection in GSH as 39.02 (ns), 73.17 (P<0.01), 100.00 (P<0.001) and SOD 52.42 (ns), 103.71 (P<0.05), 155.00 (P<0.001) while in CAT 16.65 (ns), 36.12 (P<0.05), 56.44 (P<0.01) at the dose levels 100, 200 and 400 mg/kg, respectively. In different doses level of SCLE, 400 mg/kg has shown maximum protections which were almost comparable to those of the normal control and silymarin.

3.4. Histopathological observations

The histological observations (Figure 1) basically support the results obtained from serum enzyme assays. The histopathological examination of the liver control group showed normal hepatocytes with portal triad (A). The liver section of CCl_4 treated rats showed typical centribular hepatocytic steatosis (both macrovesicular and microvesicular) and necrosis, limiting plate necrosis, apoptosis especially in the periportal hepatocytes and portal triaditis (B). This could be due to the formation of highly reactive free radicles because of oxidative stress caused by CCl_4. Simultaneous administration of SCLE along with CCl_4 prevented these effects (C and D). The animals administered SCLE; 400 mg/kg showed a significant protection almost comparable to the control and silymarin treated groups (E and F).

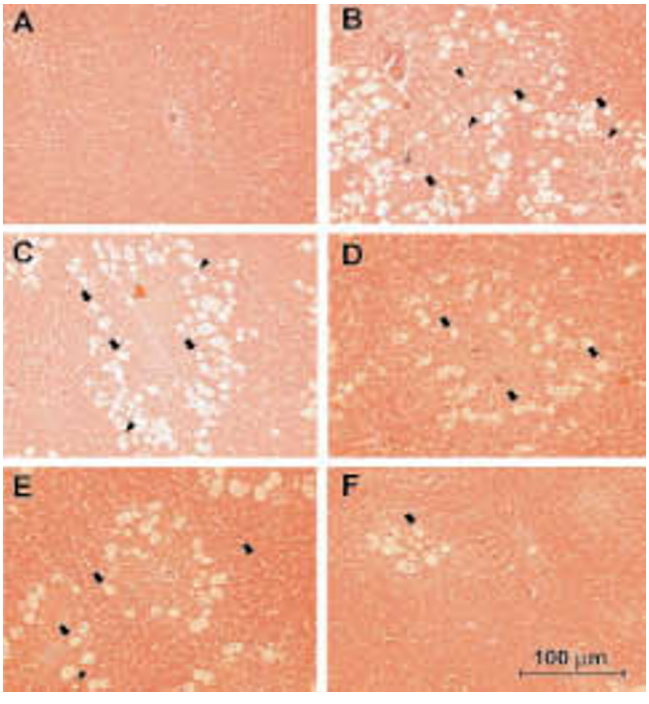

Figure 1. Liver sections stained with haematoxylin and eosin.
(A) Control group; (B) CCl_4 treated rats; (C) 100 mg/kg b.w. of SCLE treated rats; (D) 200 mg/kg b.w. of SCLE treated rats; (E) 400 mg/kg b.w. SCLE treated rats; (F) Silymarin treated rats(100 mg/kg b.w.).

4. Discussion

Herbal medicines derived from plant extracts are being increasingly utilized to treat a wide variety of clinical disease. There is a growing interest in the pharmacological evaluation of various plants used in Indian traditional system of medicine[21]. In the present investigation, SCLE was evaluated for the hepatoprotective activity using CCl_4 induced hepatotoxicity in rat, the hepatotoxic effect of CCl_4 is due to the conversion by the cytochrome −p450 mixed function enzyme in the smooth endoplasmic reticulum of the liver and other organs to the highly reactive $CCl_3^{\bullet}$ molecules[22]. Highly reactive $CCl_3^{\bullet}$ free radicals formation directly attacks the poly unsaturated fatty acids of the endoplasmic reticulum and thus causes over production of SGOT, SGPT, ALP, bilirubin and LDH enzymes[23-26]. The present study revealed a significant increase in the activities of SGOT, SGPT, ALP and serum bilirubin levels on exposure to CCl_4, indicating considerable hepatocellular injury. Administration of SCLE at different doses level (100, 200 and 400 mg/kg) attenuated the increased levels of the serum enzymes, produced by CCl_4 and caused a subsequent recovery towards normalization comparable to the control groups animals. Reduction in the level of SGOT, SGPT and LDH towards the normal value is an indication of the hepatic cell regeneration process. Reduction in the level of ALP with the concurrent depletion with the raised bilirubin level suggests the stability of the biliary function. In CCl_4 intoxicated rats the level of total protein and albumin were significantly reduced, this might be due to the functional failure of the cytochrome −p450 complexes[27].The reduced activities of SOD and catalase observed and point out the hepatic damage in the rats administered with CCl_4 but the treated 100, 200 and 400 mg/kg of SCLE groups showed significant increase in the level of these enzymes, which indicates the antioxidant activity of the *S. cordata*. Furthermore, a decrease in hepatic tissue GSH level was observed in the CCl_4 treated groups. The increase in hepatic GSH level in the rats treated with 100, 200 and 400 mg/kg of SCLE groups may be due de novo GSH synthesis or GSH regeneration. The level of lipid peroxide is a measure of membrane damage and alteration in structure and function of cellular membranes. In the present study, elevation of lipid peroxidation in the liver of rats treated with CCl_4 was observed. The increase in LPO levels in liver suggests enhanced lipid peroxidation leading to tissue damage and failure of antioxidant defense mechanism to prevent the formation of excessive free radicals[28]. Treatment with SCLE significantly reversed all the changes. Hence, it is possible that the mechanism of hepatoprotection of *S. cordata* may be due its antioxidant potential. The hepatoprotective

effect of the SCLE was further accomplished by the histopathological examinations. SCLE at different dose levels offers hepatoprotection, but 400 mg/kg is more effective and comparable with the standard drug silymarin (100 mg/kg). The histopathological examination of the liver sections confirmed that, normal liver cellular architecture was damage with CCl_4 treated rats. However, the liver sections from SCLE treated rats showed that, the reduction in histopathological scores as well as cellular damage and thus further, confirming the hepatoprotective effect of SCLE. On preliminary qualitative phytochemical screening, SCLE revealed the presence of flavonoids, alkaloids, steroids, saponins, phenolic compounds, tannins and musilages are the major chemical constituents. These antioxidant phytochemicals might contribute to the hepatoprotective and antioxidant activities of SCLE. In conclusion, this study provide a lead to initiate detailed exploration of the untapped values of this plant as a traditional medicament offering protection against various liver aliments that were proven by biochemical and histopathological analysis. The SCLE has shown dose dependent activity among which at the dose level of 400 mg/kg, shows greater activity which is comparable with the control and standard groups. However, further investigations have been extended on the isolation and characterization of components that may be responsible for hepatoprotective activity, are in progress.

Conflict of interest statement

We declare that we have no conflict of interest.

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