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Antioxidant Potential of Stem Bark Extract of *Shorea roxburghii* against CCl_4 induced Liver Damage in Wistar Rats

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Abstract The aim of the present study was to evaluate the antioxidant potential of the stem bark extract of *Shorea roxburghii* (*S. roxburghii*) on CCl_4 induced liver toxicity. Stem bark extract of *Shorea roxburghii* (SRE) was prepared using ethyl acetate. Administration of *S. roxburghii* inhibited the elevation marker enzymes such as aminotransferase (AST), alkaline phosphatase (ALP) and alanine aminotransferase (ALT) and liver lipid peroxides in CCl_4-treated Wistar rats. The natural antioxidant enzymes such catalase (CAT), superoxide dismutase (SOD) and glutathione peroxidase (GPx) and lipid peroxidation were significantly improved after the treatment of *S.roxburghii.* In this study, the results indicate that *S.roxburghii* can inhibit lipid peroxidation and improve the activities of antioxidant enzymes. The quantitative analysis of biochemical parameters, marker enzymes, antioxidant activities and histological study suggest the administration of the stem bark extract of *S.roxburghii* protecting the liver from CCl_4 toxicity.

Keywords: *antioxidant activity, Shorea roxburghii, liver, liver markers, CCl_4 toxicity*

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1. Introduction

The free radicals influence causes oxidative stress, which collapse the equilibrium between enzymes and the antioxidant defense system present in the human body. The in equilibrium resulted in severe damage to cellular macromolecules such as proteins, lipids and DNA, and ultimately cell necrosis [1]. Liver considered as one of the vital organs that functions as a center for metabolism of nutrients such as carbohydrates, proteins, lipids and excretion of Xenobiotics from the body thereby providing the protection against foreign substances by detoxification and elimination process [2,3,4]. Liver can be easily affected by toxic metabolites and free radical mediated disorders, which causes serious health consequences [5]. Liver damage is always associated with cellular necrosis, increase in tissue liquid peroxidation, and depletion in the glutathione levels in tissues. In addition, serum levels of many biochemical markers such as AST, ALT, ALP, and billirubin are elevated [6]. Drugs that are used for the treatment of hepatic injury have limited therapeutic actions and occasionally unfavorable effects [7]. In this perspective, plant extracts and biomolecules isolated from plants have been reported as potent hepatoprotective agents against chemically induced liver injury [8].

Polyphenols are plant secondary metabolites extensively studied for their ability to neutralize ROS, thereby preventing the oxidative damage [9]. Plants are used to extract pure compounds and development of new drugs, has a supreme frankness of chemical diversity. Natural products derived from plant extract fractions are novel therapeutic agents for various infectious as well as degenerative diseases [10]. People of developed countries have turned back their attention towards botanicals as medical care, but countries like Pakistan, China and India seek help from botanical healers since centuries to till date because they grant them substitutive health care services based on botanicals as an accessible and economical source in comparison to synthetic medicines [11]. Hence, medicinal plants are considered as therapeutic agents against various diseases. Silymarin is a widely used hepatoprotective drug and has been used clinically for the treatment of acute and chronic hepatitis, alcoholic liver disease and toxin-induced hepatitis [12]. Pharmacological studies have shown that silymarin exerts hepatoprotective and antioxidant properties [13]. Hence, protecting the liver from the disease is very essential. Development of protective drug from the medicinal plant is important. Therefore the aim of the study is to evaluate the antioxidant potential of stem bark extract of *S. roxburghii* against CCl_4 induced liver toxicity in Wistar rats.

2. Experimental Methods

2.1. Reagents and Preparation of Extract

Organic solvents such as hexane and ethyl acetate were purchased from Loba Chemie, Merck and Molychem. The stem bark of *S. roxburghii* was collected from Alagar Hills, Madurai, Tamilnadu. The bark was cut into small pieces and dried in shade. The dried material was crushed to coarse powder. The powdered plant material (50 g) was extracted with 200 ml of ethyl acetate. The material was repetitively extracted with ethyl acetate. The excess solvent was evaporated at room temperature using a hot air oven. Then the crude extract was thoroughly washed with hexane to remove fatty materials.

2.2. Experimental Animals

Healthy male and female Wistar albino rats weighing between 180 and 200 g were used in this study. Animals were purchased from the animal house, Department of Biotechnology, KSR College of Technology, Namakkal. The animals were maintained at 22°C (±3°C). All the animal experiments were performed after obtaining necessary approval from the Institutional Animal Ethical Committee of KSR college of Technology governed by the guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India (KSRCT/BT/IAEC/201614).

2.3. Animal Model

Animals were divided into four of six rats each. Group I animals was served as control. Group II animals received CCl_4 + Olive Oil at the dose 2 ml CCl_4/kg body weight. Group III oral administration of animals was received CCl_4+Olive oil+ stem bark extract of *S. roxburghii*. Group IV received in addition to CCl_4 suspension, Silymarin (100 mg/kg body weight) daily. The quantity of extract and standard used to treat the animals was 200 mg. The animal was kept starved overnight of the 30th day of the experiment. On the next day the animals were sacrificed by decapitation and the blood was collected by cutting the jugular vein. The liver in each case was dissected out, blotted off the blood. Washed in saline and stored a freezer. Liver and serum were used for various biochemical estimations.

2.4. Preparation of Liver Homogenate

1 g of the liver, sliced into small pieces, was homogenized into a 2 ml ice-cold tris-buffered saline (TBS), pH 7.4. The mixtures were homogenized for 15 min, then filtered and centrifuged. Supernatants were collected and stored at -20°C and the resultant supernatant was used for the determination of antioxidant activities.

2.5. Biochemical Assays

2.5.1. Estimation of Catalase Activity

The activity of catalase was determined according to the procedure described in the literature [14]. Briefly, 1ml of tissue homogenate was added to 4 ml of 0.2 M hydrogen peroxide and 5 ml of phosphate buffer and mixed thoroughly. From the above mixture, 1 ml of the solution was taken and mixed with the dichromate acetic acid reagent and allowed to incubate for 30 min at room temperature. The absorbance was read at 570 nm using spectrophotometer. The activity of catalase was expressed as micromole of H_2O_2 consumed/min/mg protein.

2.5.2. Estimation of Glutathione Peroxidase

Tissue homogenate, 0.1 ml was mixed with 0.2 ml of EDTA, sodium azide, hydrogen peroxidase. To this, 0.4 ml of phosphate buffer was added and allowed to incubate at room temperature. The reaction was detained by the addition of 0.5 ml of trichloroacetic acid (TCA). The reaction mixture was centrifuged at 3000 rpm followed by the collection of the supernatant. The supernatant, 0.5 ml was added to 4 ml of disodium hydrogen phosphate and 0.5 ml of DTNB. The color developed was read immediately at 420 nm. The activity of glutathione peroxidase was expressed as micromole of glutathione oxidized/min/mg [15].

2.5.3. Estimation of Superoxide Dismutase

Briefly, 0.5 ml of the homogenate was mixed with 1.5 ml of carbonate buffer and 0.5 ml of 0.1 mM EDTA and mixed. The above mixture, 0.4 ml of adrenaline was added and the optical density read at 480 nm. The antioxidant activity of SOD enzyme was expressed as units/min/mg protein [16].

2.5.4. Glutathione-S-transferase Assay

Glutathione-S-transferase activity was measured according to the method of Habig et al. [17]. The reaction mixture consisted of 1.475 ml phosphate buffer (0.1 mol, pH 6.5), 0.2 ml reduced glutathione (1 mM), 0.025 ml (CDNB) (1 mM) and 0.3 ml of homogenate in a total volume of 2.0 ml. The changes in the absorbance were recorded at 340 nm and enzyme activity was calculated as nM CDNB conjugate formed/min/mg protein using a molar extinction coefficient of $9.6 \times 103\ M^{-1}\ cm^{-1}$.

2.5.5. Estimation of Lipid Peroxidation

To 0.1 ml of tissue homogenate, 2 ml of TBA-TCA-HCL reagent ratio of 1:1:1) was added and mixed and kept in a water bath for 15 min. Afterwards the solution was cooled and the supernatant was removed and absorbance was measured at 535 nm against reference blank. The level of lipid peroxidation was given as moles of MDA formed/mg protein [18].

2.5.6. Estimation of Serum Markers and Protein

Aspartate aminotransferase, alanine aminotransferase and alkaline phosphatase were determined according the procedure cited in the literature [19,20]. Protein content, creatinine and uric acid liver samples were determined according to Lowry et al [21].

2.6. Histopathological Study of Tissues

The liver tissues were removed from the animals and immediately fixed in 10% formalin. Subsequent processing

included dehydrating in increasing ethanol solutions, clearing in xylene and embedding in paraffin. Sections (4–5 µm) were prepared and then stained with Eosin dye for microscopic observation. The section was examined for the pathological finding of hepatoxicity and structural morphology of vein and portal tract of liver tissues.

2.7. Statistical Analysis

All results were expressed as mean ± SEM. Data was subjected to ANOVA followed by a Tukey post hoc test. $p < 0.05$ was considered statistically significant.

3. Results and Discussion

3.1. Hepatoprotective Activity of *S. roxburghii*

The biochemical parameter such as TP, AST, ALT, ALP, creatinine and uric acid were estimated from the serum samples are presented in Table 1. Intraperitoneal administration of CCl_4 suspended in olive oil induced significant ($p<0.05$) liver damage.

The elevated levels of ALT, AST, ALP, creatinine and uric acid levels in CCl_4 treated rats indicate the liver damage (Table 1). Administration of *S. roxburghii* extract significantly reduced the elevated level of marker enzymes. It also reduced total protein, creatinine and uric acid, moderately. The treatment of *S. roxburghii* at 200 mg/kg body weight exhibited significant antioxidant property comparable to the standard drug silymarin (100 mg/kg).

3.2. Lipid Peroxidation

The change in liver levels in MDA means of lipid peroxidation in control and in experimental rats is shown in Table 2. The present findings showed a significant increase of MDA content in the ethyl acetate extract of *S.roxburghii* treated animals. The LPO activity of *S.roxburghii* treated liver showed much improved activity as compared to that of the standard, Silymarin treated rats.

3.3. In Vivo Antioxidant Activity *S. roxburghii*

The effect of the stem bark extract of *S.roxburghii* on antioxidant enzymes in the liver was examined using CCl_4 induced damage in Wistar rats.

It is observed that the CCl_4 significantly decreased the activities of antioxidant enzymes in the CCl_4 induced group compared to the control group (Table 2). The levels of SOD, CAT, GST and GPx were significantly increased in the *S.roxburghii* treated group compared to the CCl_4 group. Furthermore, ethyl acetate extract of *S. roxburghii* found to be potential extract with antioxidant activities in the liver homogenate which is comparable to the standard drug.

3.4. Histopathological Study

Figure 1 shows the histopathology section of liver samples. Histopathological sections of CCl_4 model group showed remarkable damages like necrosis, inflammatory infiltration and vacuole formation with feathery degeneration.

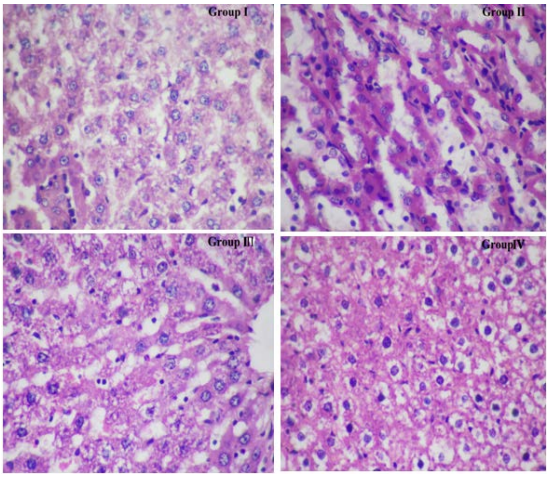

Figure 1. Microscopic study of liver sections (Group I showing normal hepatic architecture of control; Gruop II showing significant sinusoids congestion, ballooning of hepatocytes with enlargement of nuclei and infiltration in the portal triads and sinusoids; Group III & IV treated *S. roxburghii* and Silymarin show improvement in the structure

Table 1. Liver functions markers in serum

Treatment	Control	C+CCl_4	CCl_4+Extract	CCl_4+Std
TP*	7.073±0.040	8.38±0.147	7.76±0.097	8.253±0.320
AST*	134.5±5.604	173.4±0.458**	128.7±5.9**	150.9±35.123**
ALT*	93.4±3.459	125.23±0.493**	86.53±26.45	77.333±16.25**
ALP*	192.36±0.493	251.36±28.73	184.8±125.38	203.3±21.67**
Creatinine*	0.52±0.0458	0.636±0.097	0.58±0.09	0.563±0.104
Uric acid*	4.13±0.351	6.3±0.4000	5.30±0.50	5.233±2.203

Results expressed as mean ± SEM. (n=6); ALP (U/l); AST (U/l); ALT (U/l); creatinine (mmoles/l); uric acid (mmoles/l) and protein (g/l) levels in serum; p<05; *** indicate p<0.05.

Table 2. Enzymatic antioxidants estimated in liver homogenate

Treatment	Control	C+CCl_4	CCl_4+Extract	CCl_4+Std
GST	0.447±0.016	0.658±0.025	0.471±0.046	0.635±0.145
CAT	0.135±0.045	0.464±0.068	0.145±0.035	0.124±0.033
LPO	0.340±0.040	0.502±0.041	0.426±0.014	0.482±0.014
SOD	0.573±0.018	0.812±0.018	0.586±0.006	0.562±0.030
GPx	0.278±0.003	0.498±0.014	0.359±0.013	0.333±0.004

The results expressed as ± SED. (n=6); GST (mm of glutathione oxidized/min/mg; CAT (mm of H_2O_2 consumed/min/mg protein); SOD (units/min/mg protein); LPO (moles of MDA formed/mg protein); GPx (CDNB conjugate formed/min/mg protein using a molar extinction coefficient of 9.6 × 103 M^{-1} cm^{-1}); p<0.05

Microscopic examination of tissues showed that pretreatment with extracts and silymarin provides protection to hepatic cells from CCl_4 induced toxicities. Experimental group pretreated with *S.roxburghii* showed moderate damage to hepatic morphology compared to the CCl_4 treated group. Furthermore, very less hepatic injury was observed in the *S.roxburghii* treated groups which are comparable to the standard silymarin drug. Histopathological examination of the liver also provided supporting evidence for our study. Rats treated with *S.roxburghii* reduced damage caused by CCl_4 administration. The central veins, sinusoids appear and the portal triads appeared normal in the extracted animals. This clearly showed the membrane stabilizing effect of *S.roxburghii* by scavenging free radicals and preserving the integrity of the membranes. The overall results of our study confirm the protective effect of *S.roxburghii* in CCl_4-induced toxicity in rats by its ability to stabilize cell membranes, scavenge free radicals and antioxidant properties. The present investigation has confirmed the effectiveness of *S.roxburghii* as an effective natural protecting agent.

4. Discussions

It is known that the hepatotoxicity of CCl_4 is the consequence of reductive dehalogenation, which generates unstable trichloromethyl (CCl_3) and trichloromethyl (CCl_3O_2) radicals [22]. Both radicals having the capacity to bind with the proteins or lipids and initiate the lipid peroxidation. It is proved that the biomolecules present in the medicinal plants exhibited strong antioxidant activity that could act against CCl_4 induced liver damage [2,23]. The results obtained our study prove that *S.roxburghii* has a favorable effect against CCl_4 induced liver damage. It is understood that the injury occurs due to the formation of free radicals, which reduced the activity of antioxidants [24]. It is also known that the damage of the hepatocytes is also caused by the lipid perixodation [25]. The elevated levels of MDA and the decreased GSH level and also SOD, GPx, GR, and CAT activities suggests the lipid peroxidation mainly significant to toxicity in the liver tissues. The natural antioxidant enzymes such as SOD, CAT and GPx are control the superoxide ion, hydrogen peroxide and other. The use of antioxidant is shown to reduce oxidative stress either by scavenging the free radicals or by rectifying the activity of antioxidant defense system [26]. In the present study, it is observed that *S.roxburghii* rejuvenate the CCl_4 induced liver disruption by normalizing the SOD activity. The ethyl acetate extract of *S.roxburghii* increase the GSH, SOD, GPx and CAT activities in the tissues of CCl_4 induced rats. Hence, the protective effect of *S.roxburghii* on may be due to its antioxidant property. Our findings indicate significant alterations in the levels of oxidative parameters in the liver caused by *S.roxburghii*. SRE administration inverted the reduction of the antioxidant enzyme activities. SER increased the GSH level and SOD, and CAT activities in liver tissue.

Accordingly the assessment of the level of enzyme markers, AST, SGPT, ALP are more specific to the liver and are better parameters for detecting liver injury [28,29]. *S. roxburghii* extracts reduced activities of superoxide dismutase, catalase, glutathione, and increased lipid peroxidation in the CCl_4-treated group animal. The ethyl acetate extract of *S. roxburghii* treated model showed significant increased level of superoxide dismutase, catalase, and reduced lipid peroxidation, which may be due to its free radical scavenging activity of extract.

The antioxidant activity of the *S. roxburghii* extracts have been further confirmed by the histopathological analysis of liver tissues. In the CCl_4 model group, the hepatic injury, including membrane infiltration and fibrosis were observed in the histopathological sections. The *S. roxburghii* administered groups exhibited lesser destruction in the cellular structure. It revealed the regenerative capacity of the *S. roxburghii* extract in CCl_4 induced liver after damage. This study also confirms the preventive effect of stem bark extract of *S. roxburghii* which causes regeneration of hepatic cells and decreased necrosis. The phytochemical investigations of stem bark extract of *S.roxburghii* revealed about the phenolic compounds present in this plant. These phenolic compounds present in the stem bark extract of *S. roxburghii* might be responsible for the free radical scavenging activity and inhibition of lipid peroxidation.

5. Conclusions

It has concluded that, the *S. roxburghii* stem bark collected from Alagar Hills, Tamil Nadu in India has proved to have enzymatic antioxidant activity against carbon tetrachloride induced liver damage in Wistar rats. The supplementation of stem bark extract of *S. roxburghii* provided significant protection against CCl_4 induced liver damage, biochemical changes and histopathological damages. Therefore, the stem bark extract of *S. roxburghii* could be used as a natural antioxidant.

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