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Original Article

Hepatoprotective Potential of Ethanolic Extract of *Capparis zeylanica* Root on Paracetamol-induced Hepatotoxicity in Rats

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ABSTRACT

Background: *Capparis zeylanica* (Capparaceae), a climbing shrub find its distribution throughout the different parts of India. Traditionally, it is used in the treatment of snake bite, small pox, stomach ulcers, piles, cholera, hepatitis, as liver tonics, rheumatism and inflammation. In the present investigation the hepatoprotective potential of plant was evaluated in paracetamol-induced (750 mg/kg) hepatotoxicity rats. **Methods:** The animals were treated with 200 and 300 mg/kg of ethanolic extract of *C. zeylanica* root using silymarin (100 mg/kg) as reference. The liver function enzymes were determined. The estimation of malondialdehyde, superoxide dismutage, catalase and glutathione were performed in liver tissue homogenate. The excised liver was also subjected to histological study. **Results:** The noticeable declined in aspartate aminotransferase, alanine transaminase, alkaline phosphate, bilirunin and cholesterol and elevating the level of albumin, globulin and protein were observed at 300 mg/kg of drug as compared to 200 mg/kg. The significant decrease in malondialdehyde and increase in superoxide dismutage, catalase and glutathion were noticed in treated group. The periportal hypertrophy, deterioration of hepatic parenchyma, dilation of sinusoidal capillary, central vein and portal vein noticed in hepatotoxicity rats were decreased after administration of extract. **Conclusion:** The hepatoprotective potential of *C. zeylanica* root could be assumed due to the synergistic activities of carbohydrates, alkaloids, phenols, flavonoids, steroids and the strong antioxidant activity by flavonoids, phenolics, β-carotene and rutin.

Keywords: *Capparis zeylanica*, Paracetamol, *In-vivo* antioxidant, Histopathology.

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INTRODUCTION

The liver is a vital organ which is essential for the control of various biochemical and physiological processes, such as the maintenance of homeostasis, the manufacture of energy, the supply of nutrients and the detoxification of drugs and other xenobiotics. Hepatotoxic agents are therefore very likely to cause damage to the liver.[1] Hepatitis, cirrhosis, fibrosis, hepatic steatosis (fatty liver), and alcoholic liver disease are caused by free radicals, alcohol, xenobiotics, food additives, and pollutants.[2] Hepatotoxic chemicals bind covalently with tissue lipid and leads to hepatic injuries by releasing reactive species. The inbuilt protective mechanisms combat with these free radicals. Often, excessive chemical exposure can lead to high levels of free radicals, which overpower the body's natural defensive system and cause damage to the liver.[3] The drug paracetamol is considered safe when taken in therapeutic doses but the overdose may cause hepatic injuries such as hepatic necrosis, nephrotoxicity, extrahepatic lesions, and even death.[4] More than 10% of the world's population is affected by it. Worldwide, liver diseases account for significant morbidity and mortality, particularly in developing countries. Diseases of the liver are imperative to treat, and must be treated properly and extensively. The conventional drug used to treat hepatic disorder may activate the liver function and thus protect or regenerate the hepatic cells.[5] Though, new drugs such as rimonabant, propylthiouracil, corticosteroids, are often used to treat liver disease, but they were associated with several side effects (insomnia, vomiting, constipation, and depression). It is therefore essential to conduct more research on natural derived phytoconstituents which can replace chemical-based drugs, since many medicinal plants show hepatoprotective properties.[1] In order to evaluate natural compounds as alternatives, it is necessary to evaluate their effectiveness.

Capparis zeylanica (Capparaceae), a climbing shrub commonly known as 'Asadua' in Oriya is widely distributed throughout the different parts of India.[6-7] Various phytoconstituents such as α-amyrin, fixed oil, glucocapparin and n-tricontane were reported in leaves and seeds.[8] Several other constituents such as alkaloid, phytosterol, mucilage, L-stachydrine, rutin and β-sitosterol were reported in plant.[6] The plant also reported with saponin, p-hydroxybenzoic, syringic, vanillic, ferulic and p-coumanic acid compounds.[9] The leave was reported to contain β-Carotene.[10] Traditionally it is used to various diseases such as snake bite, small pox, swelling of testicles, anthelmintic, sedative, stomachic, stomach ulcers, antihidrotic, piles, cholera, hernias, hepatitis, liver tonics, anti-rheumatic and anti-inflammatory.[8,11-12] In Unani medicine, the bark of root is prescribed to cure de-obstruent to liver and spleen.[13] Besides the folklore claim plant is also reported as antibacterial,[14] antimicrobial,[15] anti-ulcer,[16] and antibacterial[17] activities. No scientific evident on hepatoprotective effect of this plant was reported in literature. Thus, the present work was under taken to examine the hepatoprotective efficacy of *C. zeylanica* root on paracetamol-induced hepatotoxicity animals.

MATERIALS AND METHODS

Collection and Identification of Plant Material

The root of the *C. zeylanica* was collected in the month of July-August from the surrounding area of Barpali. The collected materials were authenticated by Botanist Dr. Surya Kumar and the voucher specimen (TPC/COL/21/013) was kept in the department of pharmacology for further use.

Extraction

The roots were thoroughly washed to remove the earthy materials and dried. The materials were subjected to powdering and stored in air tight container. The petroleum ether (60-80°C) and ethanol were used for the successive extraction of 100g of powdered root materials in soxhlet apparatus. The solvents were distilled out and dried. The percentage of extract was calculated and subjected to the preliminary phytochemical screening for the identification of different phytoconstituents.[18] For the experimental purpose the ethanolic extract of *C. zeylanica* (ECZ) was taken.

Experimental Animals

Wistar albino rats of either sex (160-190g) were procured and placed in animal cage and; acclimatized to the laboratory condition. They were provided standard pellet diets and water ad-libitum. The temperature was maintained at 22 ± 30°C with 12 hr of day and night cycle for 7 days. During this period proper hygienic condition was maintained. The experimental protocol was approved by Animal Ethics Committee (1376/PO/Re/S/ 10/CPCSEA).

Effect of Ethanolic Extract of *C. zeylanica* on Paracetamol-induced Hepatotoxicity in Rats

The effect of ECZ on paracetamol-induced hepatotoxicity in rats was studied by taking five groups, each having six animals.[19] Group-I taken carboxy methyl cellulose (1 % w/v, 2 ml/kg) and considered as normal control; Group-II taken 750 mg/kg of paracetamol and considered as negative control; Group-III taken silymarin (100 mg/kg) and considered as positive control; Group-IV and Group-V taken 200 and 300 mg/kg of ECZ respectively for 7 days. The suspension of paracetamol was administered to all groups except Group-I on day 7.

Serum Biochemical Investigation

The blood samples were collected from the experimental rats after scarification and subjected to the centrifugation at 1000 rpm for 10 min. The resultant serum was taken for the estimation of aspartate aminotransferase (AST), alanine transaminase (ALT), alkaline phosphate (ALP), total bilirubin (TB), total protein, Albumin (ALB), globulin and cholesterol.[20-21]

Assay of *in vivo* Antioxidant Enzymes

The excised hepatic tissues were homogenized using ice-cold phosphate buffered (50 mM, pH 7.4) and the resultant mixture was centrifuged by 800 rpm (10 min) at 4°C. The obtained supernatant liquid was taken for the estimation of lipid peroxidation (LPO), catalase (CAT), super oxide dismutase (SOD) and reduced glutathione (GSH) activities. Malondialdehyde (MDA), a well-known marker of lipid peroxidation was determined (532 nm) against the blank and expressed as nmol of thiobarbituric acid reactive substances (TBARS) per mg of protein. Utilizing hydrogen peroxide as a substrate, catalase (CAT) enzyme activity was measured at 240 nm in UV-VIS spectrophotometer. Units of catalase activity per mg of protein were used to express the activity of catalase.[22] The superoxide dismutase (SOD) was measured at 420 nm against a blank in UV-VIS spectrophotometer. The result was expressed in units per mg of protein.[23] The reduced glutathione (GSH) was also determined in UV-VIS spectrophotometer at absorbance 412 nm and expressed as nmol/mg of protein.[24]

Histopathological Examination of Liver

The excised liver from the experimental animals was taken and fixed in neutral buffered formalin (10%) for 24 hr followed by treatment with xylene. Then it was kept in paraffin wax box and subjected to sectioning of 4 µm thicknesses in microtome. Hematoxylin and eosin were used as staining agent. The photo images were taken by digital camera under light microscope.[19]

Statistical Analysis

The data generated from the result were statistically analyzed by One-way ANOVA (Analysis of variance), *post hoc* Tukey HSD test and expressed as mean ± S.E.M (standard error mean). The statistical significant was considered by $p < 0.05$.

RESULTS

Examination of Biochemical Parameters

The noticeable elevations in AST, ALT and ALP in Group-II rat were observed in paracetamol treated rats (Figure 1). The significant increase in DBL, TBL and cholesterol and; decrease in ALB, globulin and TP were noticed in Group-II animals in contrast to normal healthy rats (Table 1). These altered biochemical parameters were significantly balance when administered with ECZ at 200 and 300 mg/kg. However, silymarin treated group exhibited significant improved in the serum biochemical enzyme parameters.

Effect of Ethanolic Extract of *C. zeylanica* on Antioxidant Enzyme

Negative control group was noticed with significant elevation in MDA content in contrast Group-I animals. The increase in MDA content was significantly counteracted by the administration of ECZ (200 and

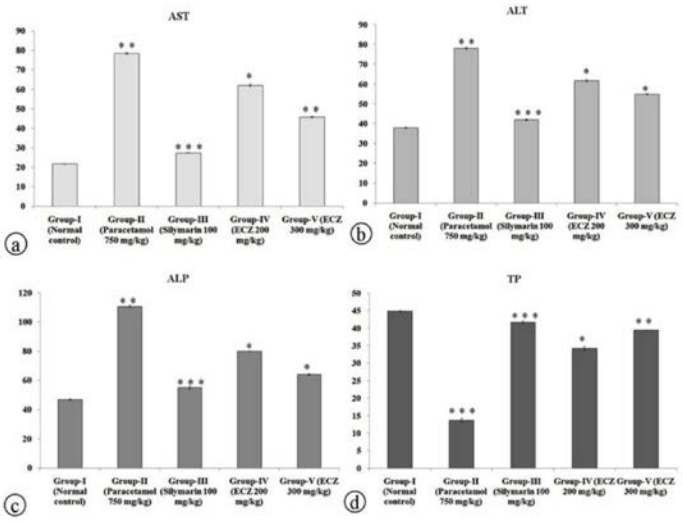

Figure 1: Effect of ethanolic extract of *C. zeylanica* root on liver function enzymes in paracetamol induced hepatotoxicity in rats.
Values are expressed as mean ± SEM, *n*=6 and was estimated using one-way ANOVA followed by *post hoc* Tukey HSD test. Comparisons are made between i) Group-I Vs Group-II, ii) Group-II Vs Group-III, IV and V. **p*<0.05, ***p*<0.01, ****p*<0.001 considered as significant

Table 1: Effects of ethanolic extract of *C. zeylanica* root on some liver function indices in paracetamol induced hepatotoxic rats.

Treatment	ALB	DBL	TBL	Globulin	Cholesterol
Group-I (Normal control)	35.11±0.09	16.66±0.98	15.09±0.23	14.88±0.90	15.09±0.32
Group-II (Negative control)	12.09± 0.56**	54.12±0.06**	48.90±0.89**	7.98±0.34**	43.87±0.45**
Group-III (Positive control)	32.67±0.65***	28.67±0.32***	18.09±0.65**	13.76±0.87**	19.65±0.22***
Group-IV (200 mg/kg)	21.89±0.45*	43.04±0.11*	36.75±0.09*	9.88±0.54*	36.11±0.34*
Group-V (300 mg/kg)	28.55±0.33**	34.90±0.54**	25.11±0.63*	11.07±0.11*	27.88±0.34***

ALB:Albumin; DBL:Direct bilirubin; TBL: Total bilirubin

Values are expressed as mean ± SEM, n=6 and was estimated using one-way ANOVA followed by *pos thoc* Tukey HSD test. Comparisons are made between i) Group-I Vs Group-II, ii) Group-II Vs Group-III, IV and V. *p<0.05, **p<0.01, ***p<0.001 considered as significant.

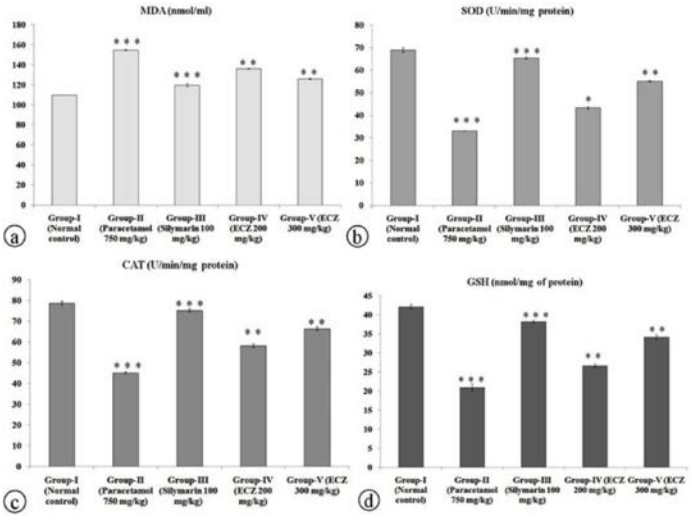

Figure 2: Effects of ethanolic extract of *C. zeylanica* root on antioxidant enzymes activity and liver malonaldehyde content of paracetamol treated rats. Values are expressed as mean ± SEM, n=6 and was estimated using one-way ANOVA followed by *post hoc* Tukey HSD test. Comparisons are made between i) Group-I Vs Group-II, ii) Group-II Vs Group-III, IV and V. *p<0.05, **p<0.01, ***p<0.001 considered as significant

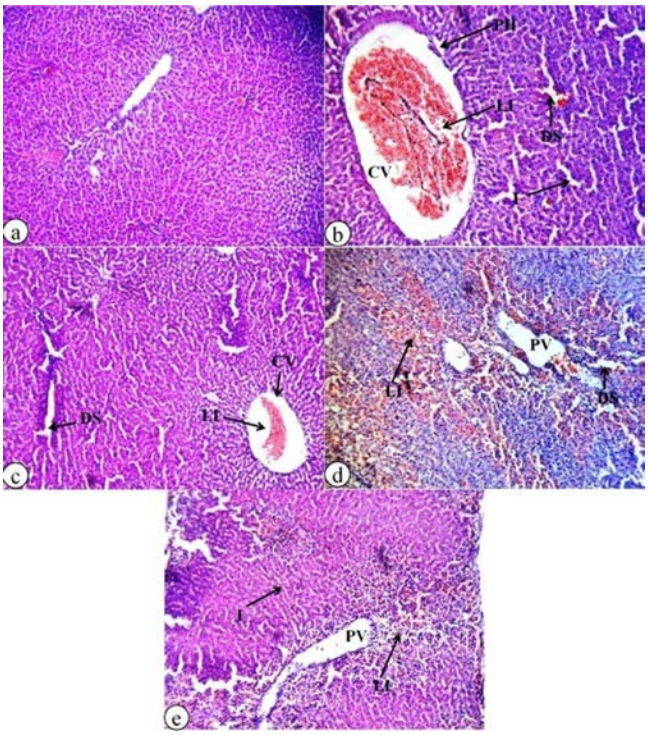

Figure 3: Effects of ethanolic extract of *C. zeylanica* root on histopathological study of liver; (a) Normal control; (b) paracetamol hepatotoxic control; (c) paracetamol hepatotoxic treated with silymarin (100 mg/kg); (d) paracetamol hepatotoxic treated with 200 mg/kg b.w ECZ; (e) paracetamol hepatotoxic treated with 300 mg/kg b.w ECZ.

Abbreviations: I: Inflammation; PH: Periportal hypertrophy; D: Deterioration of hepatic parenchyma; DS: Dilation of sinusoidal capillary; LI: Leucocytary infiltration; CV: Central vein; PV: Portal vein, St: Steatosis.

300 mg/kg) and thus decrease the MDA content. Group treated with standard also noticed with significant reduction in MDA concentration in contrast to Group-II animals. Paracetamol-induced hepatotoxicity also caused significant reduction in SOD, CAT and GSH as compared to normal control group. However, after administration of 200 and 300 mg/kg of ECZ lead to remarkable increase in these parameters as compared to negative control group (Figure 2).

Histopathological Examination

The histological section of liver of Group-I rats showed normal cytoplasm, nuclei and sinusoidal space (Figure 3a). Group-II rats marked with sever inflammation, periportal hypertrophy, deterioration of hepatic parenchyma, dilation of sinusoidal capillary, central vein and portal vein (Figure 3b). Positive control group marked with steatosis, inflammation and central vein (Figure 3c). Group treated with ECZ 200 mg/kg noticed with periportal hypertrophy, steatosis, portal vein and central vein (Figure 3d). Group treated with ECZ 300 mg/kg observed with central vein, leucocytary infiltration, steatosis and portal vein (Figure 3e).

DISCUSSION

In the present study, the ECZ root was found as potential hepatoprotective in paracetamol-induced hepatotoxicity rat model. The paracetamol at doses of 150-250 mg/kg in adults can cause liver damage.[25] The liver is the major organ affected by paracetamol poisoning, causing acute centrilobular hepatic necrosis. Oversaturated and excess paracetamol are oxidatively metabolized to N-acetyl-p-benzoquinone imine (NAPQI) by the hepatic cytochrome p-450 (CYP450) system. In normal conditions, NAPQI is detoxified by glutathione (GSH), which is a nonprotein thiol with oxidant scavenger and redox-regulation functions.[26] The toxic dose of paracetamol decreased GSH levels, leading to an agglomeration of NAPQI that covalently binds with cysteinyl sulfhydryl groups of cellular proteins and forming NAPQI-protein adducts. The binding of excess amount of NAPQI to liver cell protein and DNA causes mitochondrial dysfunction and lead to acute hepatic injury, which result in formation of reactive oxygen species (ROS), hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), and hydroxyl (OH^-) radical that affect the cellular membrane and induce lipid peroxidation.[25-26]

The endogenous antioxidant enzymes superoxide dismutase (SOD), catalase (CAT), and glutathione (GSH) protect the cells from reactive oxygen species. Superoxide radicals are converted into hydrogen peroxide by the defense of SOD enzyme. The catalase enzyme present in peroxisomes of eukaryotic cells is responsible for converting hydrogen peroxide into water and oxygen. The declined in GSH level in paracetamol-induced toxicity group could be attributed by the conjugation of glutathione with NAPQI to form mercapturicacid.[27] The elevated level of MDA in the liver implies the increase in lipid peroxidation which damages tissues and causes a failure of antioxidant defense mechanisms to arrest the over loaded free radicals.[2] In the present study the reduction in glutathione, SOD and catalase enzyme activity was indicative of hepatotoxicity by paracetamol which was strongly counteracted by ECZ (300 mg/kg).

The hepatic cell injury causes liberation of cellular enzymes into the blood stream, which are measured in the serum. ALT, along with AST and ALP, is an important serum biomarker of liver injuries that is routinely assessed to monitor liver function.[28] ALT it is considered as better parameter for assessing liver injury due to its specific to the liver tissue. The loss of membranous function and cellular leakage causes elevation of AST level in liver. The elevation in AST and ALT leads to conversion of amino acids into keto acids. The levels of serum ALP and bilirubin are associated with liver cell damage. An increase in serum ALP results from increased biliary pressure and thus increase biliary synthesis.[29] The remarkable elevation in ALT, AST, and ALP in group administered with paracetamol (750 mg/kg) was observed as compared to normal control group. The administration of ECZ (200, 300 mg/kg) caused dose-independent reduction of these enzymes. The increase in production or hemolysis or impede bilirubin transport might be responsible for in increasing the concentration of bilirubin in blood.[30] Rats treated with ECZ were found significantly decrease in bilirubin level as compared to induced group.

Since albumin is primarily synthesized in the liver, a decrease in serum albumin and total protein is another sign of liver damage which could be due to the proteinuria produced by high dose of paracetamol.[31] The overdose of paracetamol caused destruction of the hepatic cell and causing hepatic dysfunction; which leads to declined in the level of serum total protein, albumin, and globulin. Paracetamol-induced hepatotoxicity in rats was noticed with significant decrease in total protein, albumin, and globulin levels in contrast to the normal rats. The current investigation demonstrated that the administration of ECZ (200, 300 mg/kg) significantly attenuated these levels. The intoxication of paracetamol seems to affect lipoprotein metabolism, resulting in an altered metabolism of cholesterol, which raises serum cholesterol levels.[19] In the present study, the paracetamol-treated group observed with remarkable increase TC in contrast to normal control rats. Group received with ECZ significantly decreased the serum TC.

The histopathological study revealed severs hepatic necrosis in rats treated with paracetamol. The administration of ECZ (200 and 300 mg/kg) cause declined in periportal hypertrophy, central vein, leucocyte infiltration and steatosis. However, animal treated with silymarin remarkably declined the inflammation and recover the destruction of hepatic parenchyma.

In the current investigation the hepatoprotective efficacy of ECZ could be explained by the presence of carbohydrates, alkaloids, phenols, flavonoids, and steroids which were confirmed from phytochemical screening. Various pharmacological activities of flavonoid have been reported such as; antioxidant,[32] anti-inflammatory,[33] vasoprotective, anti-allergic, antimicrobial, and hepatoprotective.[34] Presence of flavonoids, phenolics, β-carotene,[10] rutin[6] could be beneficial for the antioxidant properties of *C. zeylanica*. There were some studies which revealed the hepatoprotective activity due to the strong antioxidant property.[35] There fore, hepatoprotective activity of *C. zeylanica* could be attributed to antioxidant capacity phytoconstituents.

CONCLUSION

The current investigation, 300 mg/kg of *C. zeylanica* root strongly scavenged the free radicals, checked the alter serum enzyme level and recovered the destruction of hepatic parenchyma by reducing periportal hypertrophy, central vein, leucocyte infiltration and steatosis. Thus, it can be concluded that hepatoprotective efficacy of root of *C. zeylanica* could be attributed to the synergistic activities of carbohydrates, alkaloids, phenols, flavonoids, steroids and the strong antioxidant activity of flavonoids, phenolics, β-carotene and rutin. Further study is to be carried out to understand the molecular mechanism of *C. zeylanica* responsible for hepatoprotective activity.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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