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Abstract

The present study was conducted to evaluate the nephroprotective effect of a medicinal herb *Costus pictus* against doxorubicin-induced toxicity. Rats were divided into six groups and treated with doxorubicin and ethanol extract of the *C. pictus*. Doxorubicin was administered intraperitoneally with a single dose (4 mg/kg) per week for three weeks. The extract (200 or 400 mg/kg) was administered orally for 4 weeks to two doxorubicin groups. Significant changes of the serum kidney markers, albumin, urea, uric acid and creatinine, and glutathione peroxidase, glutathione-S-transferase, catalase, superoxide dismutase, reduced glutathione and lipid peroxides in the kidney of doxorubicin-treated rat were observed. Histological features were also severely affected. However, biochemical and histological changes in the extract-treated rat were non-significant, showing that the herb is nephroprotective. The effects were comparable to the anti-oxidant vitamin E.

Introduction

Doxorubicin, an anthracycline glycosidic antibiotic is one of the commonly used anti-cancer drugs against a variety of malignancies such as sarcomas, carcinomas and hematological cancers (Young et al., 1981). However, due to its severe toxicity to non-tumor organs such as the heart, kidney and liver (Silber and Barber, 1995), its use as a therapeutic agent has been limited. Though the heart is the major target of doxorubicin-induced toxicity, concern has been expressed over the adverse effects on kidney. The kidney is an important site for xenobiotic metabolism and major eliminating pathways for antineoplastic drugs and their metabolites (Cummings and Schnellmann, 2013). Due to high rate of blood supply, about 25% of cardiac output and delayed drug excretion, the kidney is more prone to renal impairment (Lameire, 2014) during chemotherapy.

Toxicity of doxorubicin has been attributed to excess generation of free radicals and oxidative stress. Doxorubicin reduction to semiquinone radicals and formation of iron anthracycline complexes are highly reactive

to membrane lipids, proteins and DNA, which ultimately cause severe nephrotoxicity (Saad et al., 2001). Doxorubicin also causes an imbalance between free radicals and endogenous antioxidants, resulting in injury to membrane and cellular components (Balli et al., 2004).

Administration of chemotherapeutic agents with anti-oxidant action or supplementing with natural anti-oxidants may augment the efficacy of chemotherapeutics (Rashid et al., 2013) besides reducing the oxidative stress damages. Plants such as *Allium cepa* (Pradeep and Srinivasan, 2018), *Allium sativum* (Anusuya et al., 2013), *Berberis baluchistanica* (Pervez et al., 2018), *Berberis lyceum* (Anwar et al., 2018), *Cestrum nocturnum* (Saleem et al., 2017), *Curcuma longa* (Sharma et al., 2006), *Mentha piperita* (Ullah et al., 2014), *Olea europaea* (Al-Attar and Alsalmi et al., 2017), *Petroselinum crispum* (Combest et al., 2005), *Punica granatum*, and *Trigonella foenum-graecum* (Pradeep and Srinivasan, 2018) are nephroprotective.

In the present study, *Costus pictus* a popular medicinal



herb with rich antioxidants has been selected to assess the antioxidant mediated nephroprotective effect against doxorubicin toxicity. *C. pictus*, also known as spiral ginger and insulin plant, has been reported to have antioxidant activity (Jayasri et al., 2009) and is also used as infusion in renal disorders (Meléndez-Camargo et al., 2006). It is also a rich source of ascorbic acid, alpha-tocopherol, beta-carotene, terpenoids, steroids, and flavonoids (Shankarappa et al., 2011). *C. pictus* is also reported to have anti-cancer activity against colon and lung cancer cells (Sathuvan et al., 2012).

Materials and Methods

Preparation of extract

C. pictus leaves collected from the SASTRA University herbal garden were shade dried. The dried leaves were pulverized to coarse powder and extracted with ethanol using soxhlet apparatus. The extract was concentrated using rotary vacuum evaporator and stored. The plant was identified and authenticated in the Centre for Advanced Research in Indian System of Medicine, SASTRA University, Thanjavur. A voucher specimen was submitted for future reference (CARISM-102/SASTRA).

Chemicals

Doxorubicin, with a commercial name Oncodox was purchased from the Cipla Ltd, India. Crest Biosystems diagnostic kits were purchased from the Diagnostic Suppliers Goa, India. All other reagents used were of analytical grades purchased from the Himedia Laboratories Ltd, India.

Experimental animals

Male Wistar rats (*Rattus norvegicus*) with body weight between 150 and 200 g were procured from the Central Animal Facility, SASTRA University. The rats were fed with standard rodent feed and water *ad libitum*. About 30 healthy rats were divided into 5 groups with 6 rats each. Group I was control, administered with vehicle (ground nut oil). Group II was administered with doxorubicin (4 mg/kg/week for three weeks i.p.). Group III received doxorubicin (4 mg/kg/week for three weeks i.p.) and *C. pictus* extract 200 mg/kg was administered daily for four weeks orally. Group IV was administered with doxorubicin (4 mg/kg/week for three weeks i.p.) and *C. pictus* extract (400 mg/kg) daily orally for four weeks. Group V was administered with doxorubicin (4 mg/kg/week for three weeks i.p.) and vitamin E (200 mg/kg daily orally for four weeks).

Box 1: Histopathology techniques

Principle

Good quality sections of tissue (human/animal) in either spontaneous or induced diseases to examine the change(s) using a light microscope

Requirements

Automatic slide stainer, automatic tissue processor (Carism/EQP/CAF002), glass slide, hot plate, isopropyl alcohol, kidney tissue, paraplast wax, rotary microtome, slide holder, slide rack, tissue cassette, warm water tub, xylene

Procedure

Step 1 (Tissue fixation): Kidney tissue was fixed in formaldehyde buffer. Trimming the kidney to get and proper orientation. Trimmed kidney tissues were placed in tissue cassette for dehydration and wax infiltration.

Step 2 (Dehydration, cleaning and wax infiltration): Tissue jar was fitted with the processor and time was set. Dehydration with increasing concentration of isopropyl alcohol (70, 80, 90, 96 and 100%) each for an hour. Cleaning alcohol with xylene twice. Wax infiltration with paraplast wax for an hour.

Step 3 (Embedding tissue in wax): Wax infiltrated tissue was removed from tissue jar and plastic tissue cassette for embedding in wax.

Step 4 (Metal base mold was filled with molten wax): Kidney tissue was embedded inside the wax in proper orientation. The cassette was placed on the metal mold before cooling wax which serve as the base of the block for sectioning.

Tissue block was removed from the metal mold and cooled on ice plate.

Wax blocks were trimmed for sectioning

Step 5 (Sectioning): Tissue block was fixed in the rotary microtome and cut the sections. Rotate the microtome at normal speed for ribbon formation. Thickness of the tissue section was set at 6 µm. Tissue ribbon was placed on warm water tub for spreading. Pick up the section on the slide carefully. Label the slide and dry in a slide rack.

Fix the section on the slide by warming on a hot plate.

Step 6 (Staining): Slide was placed in a slide holder for staining with hematoxyline and eosin.

Step 7 (Dewaxing and rehydration): a) Dewaxing using xylene, b) rehydration of the section in ethanol in decreasing concentrations (100, 90, 80, 70 and distilled water), c) hematoxyline, d) distilled water, e) eosin, f) water, g) dehydration using increasing concentration of ethanol (80, 90 and 100%), h) xylene rinsing

Step 8 (Cover slip mounting): Wipe the surface under the slide while keeping the tissue section covered with the clearing agent. Apply two drops of mounting medium (e.g. Eukitt). Place a cover slip on the slide and avoid the formation of bubbles.

Step 9 (Observation):

Step 10 (photography):

Reference

Pervez et al., 2018; Zaware et al., 2018

After 4 weeks of treatment period, rats were anesthetized by CO₂ asphyxiation and blood samples were collected by retro-orbital bleeding for serum separation. Kidneys were excised carefully after biopsy, washed with cold physiological saline and frozen for biochemical studies.

Biochemical studies

Kidney function markers albumin, urea, uric acid and creatinine were estimated in serum using Crest Biosystems diagnostic kits in a UV-Visual spectrophotometer. Kidney tissue homogenate was prepared in 0.1M Tris-HCL buffer and used for the estimation of lipid peroxidation, reduced glutathione, glutathione peroxidase, glutathione-S-transferase, catalase and superoxide dismutase.

Lipid peroxidation end product malondialdehyde was measured as an index for lipid peroxidation (Ohkawa et al., 1979) and expressed as n moles of malondialdehyde released/mg of protein. The reduced glutathione content was measured following Ellman method (1959) and expressed the amount of glutathione as µg/mg protein. Superoxide dismutase was measured as specific activity of the enzyme required for 50% inhibition of nitro blue tetrazolium and expressed as µmoles/min/mg of protein (Kakkar et al., 1984). Catalase activity was determined by decomposition of H₂O₂ and expressed as µmoles of H₂O₂ decomposed/min/mg of protein (Aebi, 1974). Glutathione peroxidase was measured following Rotruck et al. (1973) method and expressed as µmol of glutathione consumed/mg of protein. Glutathione-S-transferase activity was measured as the catalytic reaction of 1-chloro-2,4-dinitrobenzene (CDNB) with reduced glutathione. (Habig et al., 1974). The enzyme activity is defined as the amount of enzyme required to convert 1 µmol of substrate CDNB in 1 min per mL reaction mixture under assay condition (µmol/min/mL).

Statistical analysis

Statistical analysis of the results was done by one-way analysis of variance (ANOVA) using GraphPad prism 5 software, followed by Dunnet's comparison test for significance.

Results

The present study revealed significant alterations of kidney function markers in doxorubicin-treated groups (Table I). Serum albumin level was significantly ($p < 0.05$) reduced in rats treated with doxorubicin when compared to control group rats. On the other hand, serum urea, uric acid and creatinine levels were significantly ($p < 0.05$) increased by doxorubicin-treatment. However, the levels of albumin in both the *C. pictus* extract-treated groups were only moderately altered without significant variation from the control levels. Similarly, serum levels of urea, uric acid and creatinine in the extract-treated rats were found to be close to the control levels, without significant alterations. The levels of serum albumin, urea, uric acid and creatinine in both dose levels (200 and 400 mg/kg) of *C. pictus* extract were comparable to the levels observed in vitamin E treated groups.

Doxorubicin administration also resulted in drastic alterations of kidney tissue antioxidants (Table II). Significant ($p < 0.05$) elevation of lipid peroxidation end product malondialdehyde was observed in doxorubicin group, indicating enhanced free radical mediated lipid peroxidation. On the other hand, extract-treated groups exhibited no significant changes of malondialdehyde content when compared to the control level, and was comparable to the vitamin E group, showing protective effect of the extract. The reduced glutathione, a non-enzymatic antioxidant was significantly lowered in the doxorubicin-treated groups. The reduced glutathione reduction was accompanied by significant ($p < 0.05$) reduction of kidney antioxidant enzymes glutathione-S-transferase, glutathione peroxidase, catalase and superoxide dismutase in the doxorubicin-treated groups when compared to control group rats. CPE treatment, however, showed significant protection against doxorubicin toxicity as evident from non-significant change of antioxidant enzymes when compared to the control group and vitamin E groups.

Histological observations

Experimental groups	Albumin (g/dL)	Urea (U/L)	Uric acid (mg/dL)	Creatinine (mg/dL)
Control	4.2 ± 0.1	42.6 ± 0.8	2.3 ± 0.3	1.4 ± 0.6
Doxorubicin	2.3 ± 0.1 ^a	58.9 ± 0.3 ^a	7.7 ± 0.1 ^a	3.8 ± 0.7 ^a
Doxorubicin + <i>C. pictus</i> extract (200 mg/kg)	3.6 ± 0.2 ^b	46.3 ± 0.8 ^b	4.1 ± 0.2 ^b	2.2 ± 0.5
Doxorubicin + <i>C. pictus</i> extract (400 mg/kg)	3.8 ± 0.2	44.1 ± 0.2	3.1 ± 0.4	1.1 ± 0.3
Doxorubicin + Vitamin E (200 mg/kg)	3.4 ± 0.1 ^b	43.3 ± 0.9	3.8 ± 0.7 ^b	0.8 ± 0.1

Data are mean ± SE of six observations; Significant from control values at ^a $p < 0.01$; ^b $p < 0.05$

Table II

Shows the level of lipid peroxides, glutathione and anti-oxidant enzymes in the kidney

Treatment groups	Lipid peroxidation	Reduced glutathione	Glutathione peroxidase	Glutathione-S-transferase	Catalase	Superoxide dismutase
Control	16.6 ± 1.5	26.1 ± 1.4	19.0 ± 1.2	7.2 ± 1.0	18.0 ± 1.8	26.0 ± 1.8
Doxorubicin	38.0 ± 2.0 ^a	14.7 ± 1.8 ^a	9.0 ± 1.8 ^a	2.5 ± 1.6 ^b	7.4 ± 1.4 ^a	12.1 ± 1.4 ^a
Doxorubicin + <i>C. pictus</i> extract (200 mg/kg)	21.5 ± 1.5	18.2 ± 1.3 ^b	12.1 ± 1.0 ^b	5.3 ± 1.3	11.9 ± 1.8 ^b	18.7 ± 1.5 ^b
Doxorubicin + <i>C. pictus</i> extract (400 mg/kg)	19.7 ± 1.2	21.2 ± 1.6	17.6 ± 1.6	6.7 ± 1.5	16.1 ± 1.1	22.7 ± 1.2
Doxorubicin + Vitamin E (200 mg/kg)	17.2 ± 1.0	23.6 ± 1.4	16.3 ± 1.1	6.4 ± 0.6	14.2 ± 1.0	21.3 ± 1.9

Data are mean ± SE of six observations; lipid peroxidation is expressed as nmol of MDA released/mg of protein; reduced glutathione is expressed as µg/mg protein; glutathione peroxidase is expressed as nmol of reduced glutathione oxidized/min/mg protein; glutathione-S-transferase is expressed as µmol/min/mL; catalase is expressed as µmol of H₂O₂ consumed/min/mg protein; superoxide dismutase is expressed as µmol/min/mg protein; Significant from control values at ^ap<0.01; ^bp<0.05

Histological observation of the kidney exhibited normal architecture in control rats. Glomerulus and Bowman's capsule appeared normal among the proximal and distal convoluted tubules. Proximal tubules are with columnar cells with deeply stained acidophilic cytoplasm. Distal tubules are shorter and narrower and lined with low cuboidal cells with less acidophilic cytoplasm with a central nucleus. Tubules are interspersed with minute capillaries.

Kidney of doxorubicin group rats were extensively damaged by doxorubicin. The kidney exhibited increased glomerular space, congestion of Bowman's capsule, tubular cell degeneration and vacuolation. Desquamation of epithelial cells and pyknotic nuclei were also noted. Localized mononuclear cell infiltration was also noted. Collecting tubules showed extensive cytoplasmic vacuolation and degeneration. Rats administered with CPE showed only mild degeneration of kidney tubular cells and glomerular congestion. Vitamin E treated group rats exhibited mild focal necrosis of the tubular cells. In general, histological observations of the of the CPE groups showed only mild alterations, indicating protection by the herb *C. pictus* (Figure 1).

Discussion

Kidney, a complex and dynamic organ helps elimination of wastes, regulates total homeostasis, and controls acid base balance (Perazella, 2009). Toxicological insult to kidneys would affect any or all of these functions. The observations of the present study substantiate these facts that kidney is more vulnerable to doxorubicin generated free radicals. Doxorubicin administration to rats caused significant reduction of serum albumin and elevations of urea, uric acid and creatinine when compared to the control levels. Plasma proteins include a heterogeneous group with albumin constituting the major portion. Though albumin is manufactured in the liver, when the kidneys are damaged they become leaky, allowing albumin to be excreted in the urine.

This causes reduced serum concentration. Elevations of serum urea, uric acid and creatinine show poor clearance by kidney indicating doxorubicin-induced damage to the renal tissues. Doxorubicin-induced reduction of serum albumin, and increased uric acid, urea and creatinine have been reported (Monsour et al., 1999). The levels of serum albumin, urea, uric acid and creatinine in the CPE treated groups were found to be not affected significantly. This shows that herbal compounds of *C. pictus* offered considerable protection to the kidney tissues. Similar nephroprotective effect of herbal plants against gentamicin toxicity have been reported (Pervez et al., 2018).

In addition to the changes of the renal function markers, antioxidant status of the kidneys in doxorubicin treated rats was drastically altered. Significantly elevated lipid peroxidation end products malondialdehyde in doxorubicin group of rats indicates accelerated lipid peroxidation by the free radicals. This can be attributed to doxorubicin caused free radical formation, oxidative damages of biological molecules, membrane lipid peroxidation and protein oxidation (Liu et al., 2007). Significant reduction in the levels of reduced glutathione and, antioxidant enzymes glutathione peroxidase, glutathione S-transferase, superoxide dismutase and catalase in the doxorubicin group rats indicate severe free radical mediated nephrotoxicity.

The reduced glutathione is the major non-enzymatic antioxidant for regulating intra cellular radical concentration (Chanson et al., 2007). The reduced glutathione scavenges hydroxyl radical and singlet oxygen directly, detoxifying hydrogen peroxides and lipid peroxides by the catalytic action of glutathione peroxidase. Glutathione is also a co-factor of detoxifying enzymes of oxidative stress such as glutathione peroxidase and glutathione-S-transferase. Glutathione-S-transferase exerts protection by catalyzing the conjugation of reduced glutathione with oxidation end products and defends against the highly toxic spectrum of substances

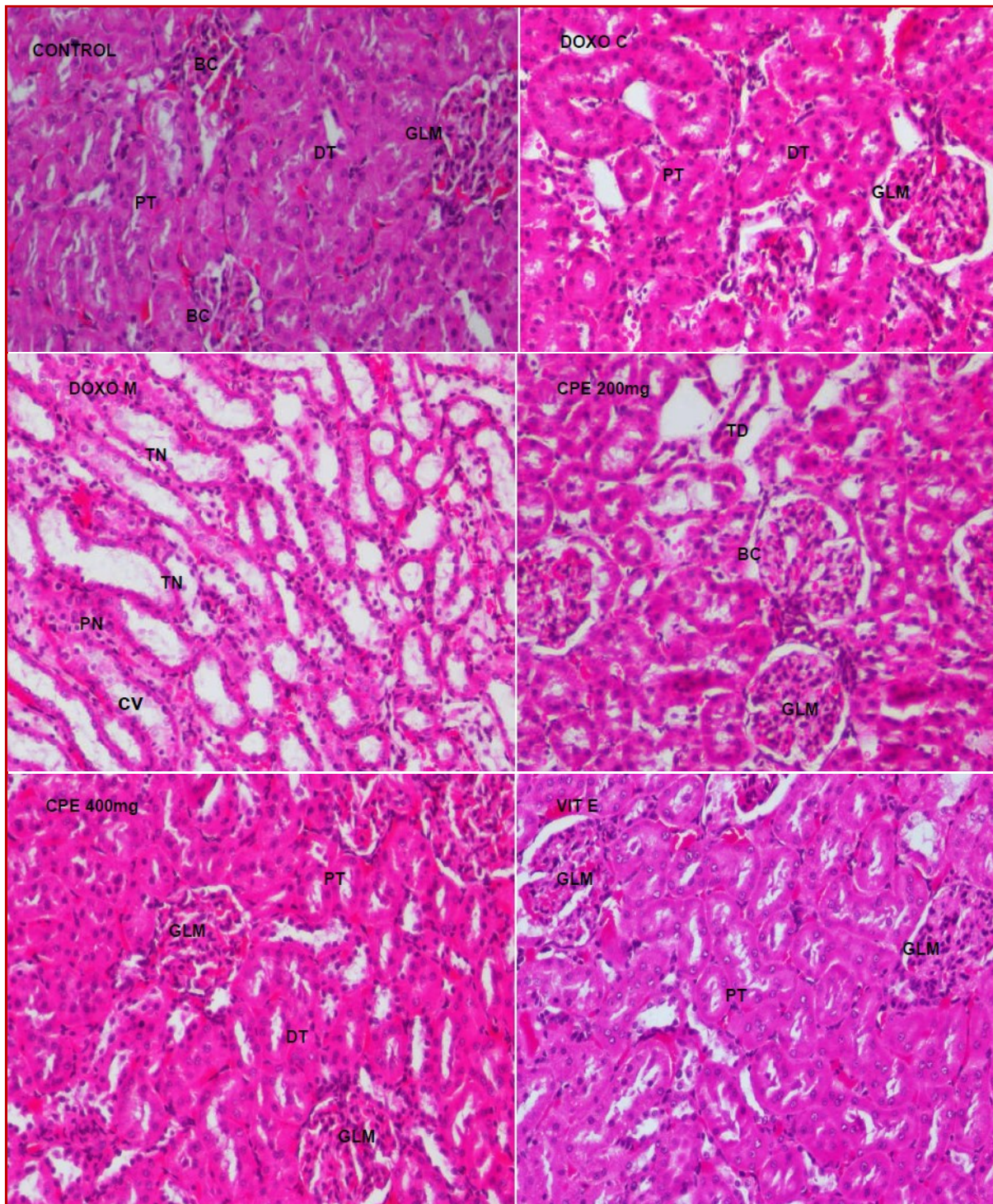


Figure 1: Shows the histological changes observed in the kidney of rats in the different treatment groups

CONTROL: The kidney shows normal architecture with intact glomerulus (GLM) and Bowman's capsule (BC). Proximal tubules (PT) and Distal tubules (DT) appear normal with tubular cells intact. Nuclei of the tubular cells are normal. **DOXO C:** Glomerular congestion, increased Bowman's space, tubular necrosis and lymphocytic infiltration were noted in the cortical region. **DOXO M:** Medullary region shows tubular degeneration (TD), tubular necrosis (TN), cytoplasmic vacuolation (CV) and pyknotic nuclei (PN). **CPE200 mg:** Mild to moderate degeneration of the tubular cells. Glomerular congestion is mild. **CPE 400 mg:** Glomerulus appear normal with reduced space. Proximal and distal tubules exhibit normal histology. Mild tubular degeneration at focal areas is noted. **VIT E:** Glomerulus and Bowman's capsule appear normal. Tubular cells are normal. Mild focal necrosis of the tubular cells is evident.

produced by ROS. Both glutathione peroxidase and glutathione-S-transferase activities can eventually reduce the level of intracellular reduced glutathione (Masella et al., 2005). Reduction in the reduced glutathione level may also be due to reduced glutathione consumption in the interaction of doxorubicin-induced free radicals with biomembranes and lipid peroxides. Reduced glutathione deficiency could be the possible reason for increased lipid peroxidation and reduction of glutathione peroxidase and glutathione-S-transferase (Elberry et al., 2010).

Antioxidant enzymes superoxide dismutase is the major enzyme acting against superoxide radicals, and catalase, and glutathione peroxidase catalyzes dismutation of superoxide anion into hydrogen peroxide, and converting H_2O_2 into water providing protection against ROS (Vasquez-Garzon et al., 2009). The reduction of antioxidant enzymes observed in the present study can be explained on the basis of their exhaustion in combating the oxidative stress caused by the doxorubicin-induced free radicals. The observations of the study shows that CPE treatment prevented lipid peroxidation, associated with normalization of the reduced glutathione and antioxidant enzymes, indicating that the plant has significant anti-peroxidation and antioxidant activities.

The biochemical changes observed in doxorubicin-treated rats were well corroborated with the histological changes noted in the kidney. The damages observed in the kidney following doxorubicin treatment could be attributed to increased free radicals associated with diminished antioxidant enzymes that culminate to loss of cell membrane integrity and function. The possible reasons for the altered kidney markers and antioxidant enzymes might be due to epithelial cell damages and hemodynamic changes in glomeruli caused by doxorubicin (Mohajeri and Sahebkar, 2018).

Mild histological alterations associated with non-significant changes in the level of biochemical markers and antioxidant enzymes in the extract-treated group rats are indications of protection by the antioxidant compounds in *C. pictus*. Doxorubicin caused glomerular and tubular damages were protected by madecassoside triterpenoid of *Centalla asiatica* herb (Su et al., 2015). Normalization of the renal function markers and antioxidant enzymes by *Murraya konigii* in cyclophosphamide induced renal toxicity (Mahipal and Pawar, 2017) and *Psidium guajava* on doxorubicin-induced nephrotoxicity (Mohan et al., 2014) reveal that plants are effective in protecting kidney from the adverse effect of anti-cancer drugs. Protective activity of *Eclipta prostrata* against gentamicin nephrotoxicity has been attributed to its phytochemicals and antioxidant activity (Ahmad et al., 2018). Nephroprotective activity of the plants is attributed to the diverse phytochemicals with multiple functions (Sundararajan et al., 2014).

Review by Javaid et al. (2012) also showed that the antioxidant herbal drugs were effective for renal disorders. All these substantiate that herbs are promising sources of nephroprotective compounds. The protective effect of *C. pictus* extract against the doxorubicin caused nephrotoxicity can be attributed to the rich phytochemicals, particularly antioxidant compounds. This plant with its nephroprotective and anti-cancer effects can be used as preventive medicine against the adverse effects of chemotherapeutic agents.

Conclusion

Ethanol extract of *C. pictus* herb is effective in protecting kidney from free radical mediated doxorubicin toxicity.

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Ethical Issue

Rats were procured from the Central Animal Facility, SASTRA University and maintained in an optimum condition as per the guidelines of Committee for the Purpose of Control and Supervision of Experiments on Animals. The study was approved by the institutions ethical committee(CPCSEA:149/SASTRA/IAEC/RAP).

Conflict of Interest

Authors declare no conflict of interest

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