Original Article

Ethanolic Leaf Extract of *Ipomoea aquatica* Forsk Abrogates Cisplatin-induced Hepatotoxicity in Albino Rats

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Abstract

Context: Hepatotoxicity is a therapeutic predicament that affects the clinical use of cisplatin (CPT). *Ipomoea aquatica* is traditionally used for the treatment of some diseases. This study examined the protective effect of the ethanolic leaf extract of *Ipomoea aquatica* (EEIA) against CPT-induced hepatotoxicity in albino rats. **Materials and Methods:** Fifty-four adult male albino rats randomized into nine groups (six rats in each group) were treated orally with EEIA (100, 200, and 400 mg/kg) daily for 7 days and CPT (6 mg/kg) intraperitoneally on day 5 and 7, respectively. On day 8, the rats were anesthetized; blood samples were collected and evaluated for plasma liver function markers. Liver samples were harvested and evaluated for biochemical parameters and histology. **Statistical Analysis:** Data are presented as mean ± standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance (ANOVA) and Tukey's test. **Results:** CPT-induced hepatotoxicity was characterized by significant ($P < 0.001$) elevations in liver and plasma levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, gamma-glutamyl transferase, total bilirubin, and conjugated bilirubin when compared to control. The alterations in liver redox status of CPT-treated rats were marked by significant ($P < 0.001$) decreases in superoxide dismutase, catalase, glutathione, and glutathione peroxidase levels with significant ($P < 0.001$) increases in malondialdehyde levels when compared to control. The liver of CPT-treated rat was characterized by hepatocyte necrosis. The hepatotoxic effect of CPT was significantly abrogated in a dose-dependent fashion in rats pretreated with EEIA 100 mg/kg ($P < 0.05$), 200 mg/kg ($P < 0.01$), and 400 mg/kg ($P < 0.001$) when compared to CPT-treated rats. **Conclusion:** EEIA has potential as treatment for CPT-induced hepatotoxicity.

Keywords: *Cisplatin, Ipomoea aquatic, liver, prevention, rat, toxicity*

Introduction

The rapid demise of cancer cells on exposure to chemotherapy has successful reduced cancer-associated mortality.[1] Cisplatin (CPT) is one of the most clinically used drugs for cancer chemotherapy. It has shown good therapeutic outcome against many solid organ malignancies such as brain, neck, testicular, ovarian, and pulmonary cancers.[2] Its mode of action has been linked to its ability to structurally impair purine bases on deoxyribonucleic acid (DNA). This interferes with DNA repair mechanisms, causing DNA damage, and subsequently inducing apoptosis in cancer cells.[3] However, its significant anticancer activity is often affected by numerous toxicities including hepatotoxicity.[4,5] Hepatotoxicity associated with CPT could be predicated on it biotransformation by the liver. Studies have shown that at higher doses; it can be rapidly absorbed and stored by liver hepatocytes leading to hepatocytes perturbation and dysfunction.[6] Clinically, hepatic perturbations caused by CPT are often characterized by hepatocyte necrosis, steatosis central vein congestion, sinusoidal dilatation, and cell apoptosis.[7,8] The precise mechanism by which CPT causes hepatotoxicity is not clear, but multiple studies have speculated hepatic oxidative stress (OS) through the generation of free radicals.[9] Also, alterations in hepatic redox status through CPT-glutathione (GSH) adduct formation causing decreases in liver antioxidants have been speculated.[10]

It is estimated that 80% of the world population presently use medicinal plants for the treatment of some diseases. Medicinal plants are important sources of new chemical substances with potential therapeutic effects.[11] *Ipomoea aquatica* (IPA) is a medicinal plant that belongs to the Convolvulaceae family. It grows in the forest and is also cultivated throughout South East Asia. It is generally consumed as vegetable in different regions of the world. Due

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to its rapid growth, it is common in rice paddies, fish ponds, and drainage canals.[12] IPA is an effective natural herb used traditionally for the treatment of some ailments[13] including liver disease.[14,15] Its traditional use can be supported by some pharmacologic activities reported in *in-vivo* and *in-vitro* studies.[16] Furthermore, studies have reported the presence of essential and active phytochemicals in IPA which can also attest to its traditional use for the treatments of some ailments.[17] This study explore whether the ethanolic leaf extract of *Ipomoea aquatica* (EEIA) contains essential phytochemicals that can abrogate CPT-induced hepatotoxicity in a rat model.

Materials and Methods

Drug and plant material

CPT injection used for this study was manufactured by Sun Pharmaceutical, Industries Ltd, Mumbai, India. Fresh leaves of IPA were obtained from Niger Delta University, Nigeria. The leaves were washed thoroughly in water and the surface water was removed by air drying. The leaves were subsequently dried in a hot air oven at 48°C for 36 hr and powdered with the aid of a mechanical grinder. For the preparation of ethanolic extract, 350 g of IPA powder was added to 1000 mL of ethanol and macerated for 24 h and filtered. The extract was filtered through Whatman No. 1 paper and evaporated under reduced pressure using a rotary evaporator to a dry extract. The extract was analyzed for carbohydrate, protein, tannins, saponins, steroids, flavonoids, terpenoids, alkaloids, and glycosides according to Harborne[18] and Trease and Evans.[19]

Ethical issues

This study was approved by the Research Ethics Committee of the Department of Pharmacology and Toxicology, Faculty of Pharmacy, Niger Delta University, Bayelsa State, Nigeria. The rats were handled according to the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Science.

Experimental protocol and biochemical analyses

Fifty-four adult male albino rats (200–220 g) sourced from the animal breeding facility of the Faculty of Pharmacy, Niger Delta University, Bayelsa State, Nigeria were kept in an environment controlled at 23°C ± 2°C with a 12 h light/dark periods. The rats had access to standard rodent chow and water *ad libitum* and were allowed for 1 week to acclimatize to laboratory conditions prior to the experiment. Group A (solvent control) (n = 6) and Group B (placebo control) (n = 6) were orally treated with normal saline (0.2 mL) and corn oil (0.2 mL) daily for 7 days, respectively. Groups C–E (n = 6/group) were orally treated with EEIA (100, 200, and 400 mg/kg)[20] daily for 7 days, respectively. Group F (n = 6) was treated once with CPT (6 mg/kg) intraperitoneally (i.p.)[21] on day 5 and 7. Groups G–I (n = 6/group) were pretreated orally with EEIA (100, 200, and 400 mg/kg) daily for 7 days, respectively, whereas CPT (6 mg/kg) was administered i.p. on day 5 and 7. After the completion of treatment, the albino rats were sacrificed under inhalational diethyl ether. Blood samples were collected, centrifuged (3000*g* for 15 min), and plasma samples were separated for biochemical evaluations. Liver samples were excised, rinsed in cold normal saline, and homogenized in 0.1 M Tris-HCl solution buffered (pH 7.4). The homogenates were centrifuged at 1500g for 30 min and the supernatants were collected and assessed for biochemical indices. Plasma and liver alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), conjugated bilirubin (CB), and total bilirubin (TB) were evaluated using commercial laboratory test kits (Randox Laboratories, Crumlin, UK). Liver total protein was analyzed according to Gornall *et al*.[22] whereas malondialdehyde (MDA) was analyzed according to Buege and Aust.[23] Reduced glutathione (GSH) was measured as reported by Sedlak and Lindsay.[24] The method of Sun and Zigman[25] was used for the evaluation of superoxide dismutase (SOD), whereas the method of Aebi[26] was used to assay catalase (CAT). Glutathione peroxidase (GPx) was measured as described by Rotruck *et al*.[27]

Histological evaluation

Liver sections were taken immediately, and fixed in 10% buffered neutral formalin for 24hr. Liver samples were dehydration in increasing concentrations of ethyl alcohol, and embedded in paraffin blocks. The paraffin blocks were sectioned (5–7 µm thick) and stained with hematoxylin and eosin. The sections were examined for the histological changes with the aid of a light microscope.

Statistical analysis

Data are presented as mean ± standard error of the mean (SEM). Data were analyzed using Graph Pad Prism (Version 5.0, Graph Pad Software Inc., La Jolla, California, USA). One-way analysis of variance (ANOVA) was used for comparison among means followed by Tukey's *post hoc* tests. Significance was set at $P < 0.05$, 0.01, and 0.001.

Results

Phytochemical analyses and serum liver function parameters

The evaluation of EEIA shows the presence of flavonoids, glycosides, carbohydrate, alkaloids tannins, saponins, and protein. The plasma levels of AST, ALT, ALP, LDH, GGT, CB and TB were normal (p>0.05) in rats treated with EEIA when compared to control [Table 1]. On the other hand, treatment with CPT significantly increased ($P < 0.001$) plasma AST (258.6%), ALT (347.8%), ALP (289.5%) LDH (388.0%), GGT (462.3%), CB (213.6%), and TB (346.3%) levels when compared to control [Table 1]. On the contrary, the plasma levels of AST, ALT, ALP, LDH, GGT, CB, and TB were significantly decreased in a dose-dependent fashion in EEIA 100 mg/kg ($P < 0.05$), 200 mg/kg ($P < 0.01$), and 400 mg/kg ($P < 0.001$) pretreated rats when compared to CPT-treated rats [Table 1].

Effects on liver tissue biochemical indices

Treatment with EEIA did not produce significant (p>0.05) effects on liver AST, ALT, ALP, LDH, and GGT levels when compared to control [Table 2]. On the other hand, the liver levels of AST, ALT,

Table 1: Effect of *Ipomoea aquatica* leaf extract on liver function parameters of cisplatin-treated rats

Dose (mg/kg)	ALT (U/L)	AST (U/L)	ALP (U/L)	LDH (U/L)	GGT(U/L)	TB (g/dL)	CB (g/dL)
Control	60.3 ± 6.21	81.0 ± 7.24	65.6 ± 5.00	53.9 ± 5.36	0.53 ± 0.09	8.00 ± 0.95	3.89 ± 0.75
EEIA 100	59.6 ± 5.40	79.9 ± 6.61	63.6 ± 5.31	53.0 ± 4.49	0.52 ± 0.05	7.95 ± 0.60	3.72 ± 0.63
EEIA 200	57.1 ± 3.61	78.0 ± 6.20	63.0 ± 4.20	52.3 ± 5.00	0.50 ± 0.03	7.75 ± 0.53	3.65 ± 0.54
EEIA 400	55.9 ± 4.32	76.3 ± 3.11	61.0 ± 6.41	50.2 ± 4.62	0.49 ± 0.07	7.63 ± 0.69	3.58 ± 0.32
CPT 6	270.0 ± 13.4[a]	290.5 ± 14.2[a]	255.5 ± 13.0[a]	263.0 ± 13.5[a]	2.98 ± 0.12[a]	35.7 ± 3.07[a]	12.2 ± 1.17[a]
EEIA 100 + CPT6	200.0 ± 11.5[b]	210.2 ± 12.9[b]	200.1 ± 11.9[b]	210.8 ± 10.8[b]	1.85 ± 0.09[b]	24.0 ± 2.90[b]	8.27 ± 1.76[b]
EEIA 200 + CPT6	130.8 ± 12.4[c]	141.4 ± 10.52[c]	130.3 ± 10.2[c]	131.5 ± 8.32[c]	1.00 ± 0.07[c]	16.4 ± 1.54[c]	5.10 ± 0.72[c]
EEIA 400 + CPT6	82.5 ± 7.00[d]	90.7 ± 6.55[d]	70.3 ± 5.63[d]	60.4 ± 6.32[d]	0.67 ± 0.03[d]	8.55 ± 0.71[d]	3.00 ± 0.56[d]

EEIA = ethanolic leaf extract of *Ipomoea aquatic*, CPT= cisplatin, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase, ALP = alkaline phosphatase, CB = conjugated bilirubin, TB = total bilirubin
Data are expressed as mean ± standard error of the mean (SEM), $n = 6$
[a]Differ significantly ($P < 0.001$) when compared to control
[b]Differ significantly ($P < 0.05$) when compared to CPT
[c]Differ significantly ($P < 0.01$) when compared to CPT
[d]Differ significantly ($P < 0.001$) when compared to CPT

Table 2: Effect of *Ipomoea aquatica* leaf extract on liver tissue biochemical indices of cisplatin-treated rats

Dose (mg/kg)	ALT(U/L)	AST(U/L)	ALP(U/L)	GGT(U/L)	LDH (U/L)
Control	250.9 ± 19.5	270.8 ± 12.5	210.1 ± 14.7	250.9 ± 11.7	25.0 ± 3.17
EEIA 100	245.0 ± 15.6	262.3 ± 13.6	205.0 ± 15.8	247.3 ± 12.0	24.5 ± 2.55
EEIA 200	237.3 ± 10.1	258.9 ± 14.5	200.6 ± 12.4	245.6 ± 10.3	24.0 ± 2.45
EEIA 400	235.2 ± 14.0	252.7 ± 13.6	198.4 ± 15.6	240.8 ± 10.2	22.2 ± 3.00
CPT 6	990.3 ± 20.7[a]	950.5 ± 21.7[a]	992.3 ± 22.9[a]	895.4 ± 15.7[a]	145.7 ± 7.22[a]
EEIA 100 + CPT6	737.7 ± 16.0[b]	725.8 ± 19.8[b]	674.1 ± 20.0[b]	570.7 ± 16.5[b]	100.5 ± 8.42[b]
EEIA 200 + CPT6	500.5 ± 12.9[c]	521.9 ± 17.3[c]	452.4 ± 15.4[c]	351.8 ± 12.4[c]	61. 4 ± 5.00[c]
EEIA 400 + CPT6	370.4 ± 11.8[d]	370.5 ± 13.7[d]	321.0 ± 10.6[d]	265.6 ± 13.8[d]	30.5 ± 4.57[d]

EEIA = ethanolic leaf extract of *Ipomoea aquatic*, CPT = cisplatin, AST = aspartate aminotransferase, GGT = gamma-glutamyl transferase, ALT = alanine aminotransferase, LDH = lactate dehydrogenase, ALP = alkaline phosphatase
Data are expressed as mean ± standard error of the mean (SEM), $n = 6$
[a]Differ significantly ($P < 0.001$) when compared to control
[b]Differ significantly ($P < 0.05$) when compared to CPT
[c]Differ significantly ($P < 0.01$) when compared to CPT
[d]Differ significantly ($P < 0.001$) when compared to CPT

Table 3: Effect of *Ipomoea aquatica* leaf extract on liver oxidative stress markers of cisplatin-treated rats

Dose (mg/kg)	MDA (nmol/mg protein)	CAT (U/mg protein)	SOD (U/mg protein)	GSH (µmole /mg protein)	GPx (U/mg protein)
Control	0.28 ± 0.09	36.0 ± 3.00	20.6 ± 3.52	9.52 ± 0.10	18.6 ± 1.00
EEIA 100	0.27 ± 0.01	36.9 ± 3.17	21.3 ± 2.43	9.70 ± 0.54	18.9 ± 2.32
EEIA 200	0.27 ± 0.05	38.1 ± 2.53	21.9 ± 2.67	10.1 ± 0.63	19.0 ± 1.20
EEIA 400	0.25 ± 0.04	39.2 ± 3.11	22.7 ± 3.00	10.9 ± 0.44	20.3 ± 3.12
CPT 6	1.23 ± 0.07[a]	8.59 ± 0.67[a]	5.25 ± 0.73[a]	2.56 ± 0.32[a]	5.05 ± 0.26[a]
EEIA 100 + CPT6	0.80 ± 0.09[b]	15.9 ± 1.91[b]	8.34 ± 0.66[b]	4.60 ± 0.53[b]	7.27 ± 1.38[b]
EEIA 200 + CPT6	0.58 ± 0.06[c]	22.5 ± 2.33[c]	13.7 ± 1.12[c]	6.71 ± 0.22[c]	11.0 ± 1.57[c]
EEIA 400 + CPT6	0.30 ± 0.08[d]	35.0 ± 3.22[d]	19.6 ± 2.00[d]	8.96 ± 0.60[d]	17.9 ± 2.44[d]

EEIA = ethanolic leaf extract of *Ipomoea aquatic*, CPT = cisplatin, SOD = superoxide dismutase, MDA = malondialdehyde, GSH = glutathione, GPX = glutathione peroxidase, CAT = catalase
Data are expressed as mean ± standard error of the mean (SEM), $n = 6$
[a]Differ significantly ($P < 0.001$) when compared to control
[b]Differ significantly ($P < 0.05$) when compared to CPT
[c]Differ significantly ($P < 0.01$) when compared to CPT
[d]Differ significantly ($P < 0.001$) when compared to CPT

ALP, LDH, and GGT were significantly ($P < 0.001$) increased in CPT-treated rats when compared to control [Table 2]. The increases observed in the aforementioned parameters represent 251.0%, 294.7%, 372.3%, 482.8%, and 256.9%, respectively. However, the liver levels of AST, ALT, ALP, LDH, and GGT were significantly decreased in a dose-dependent fashion in rats pretreated with EEIA 100 mg/kg ($P < 0.05$), 200 mg/kg ($P < 0.01$), and 400 mg/kg ($P < 0.001$) when compared to CPT-treated rats [Table 2].

Effects on liver oxidative stress markers and histology

Treatment with EEIA had no significant ($p>0.05$) effects on liver CAT, SOD, GSH, GPx and MDA levels when compared to control [Table 3]. However, treatment with CPT produced significant ($P < 0.001$) decreases in liver CAT, SOD, GSH, and GPx levels with significant ($P < 0.001$) increase in MDA level when compared to control [Table 3]. On the contrary, MDA levels were significantly decreased whereas CAT, SOD, GSH, and GPx levels were significantly increased in a dose-dependent fashion in rats pretreated with EEIA 100 mg/kg ($P < 0.05$), 200 mg/kg ($P < 0.01$), and 400 mg/kg ($P < 0.001$) when compared to CPT-treated rats [Table 3]. The liver of the control rats showed normal hepatocytes [Figure 1A]. Also, the liver of rats treated with EEA (100, 200, and 400 mg/kg) showed normal hepatocytes, respectively [Figure 1B–D]. However, the liver of rats treated with CPT (6mg/kg) showed hepatocyte necrosis [Figure 1E]. On the contrary, the liver of rats pretreated with EEIA (100, 200, and 400 mg/kg) showed normal hepatocytes, respectively [Figure 1F–H].

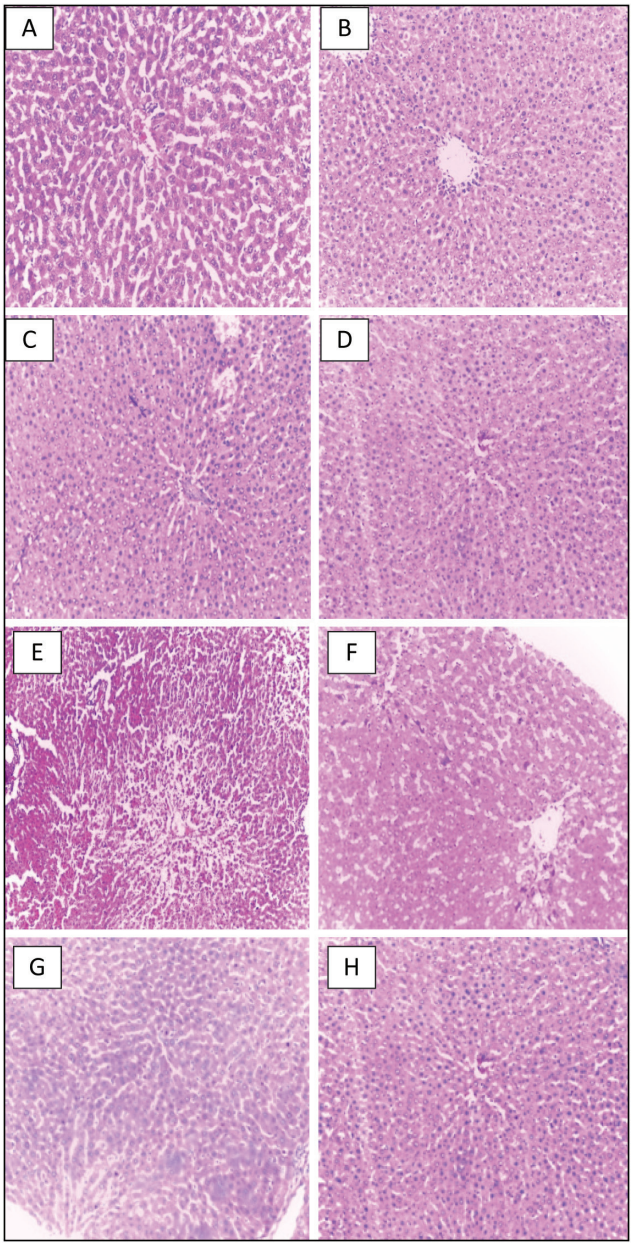

Figure 1: (A) Liver of control rat showing normal hepatocytes. (B–D) Liver of rat treated with ethanolic leaf extract of *Ipomoea aquatica* (100, 200, and 400 mg/kg) showing normal hepatocytes. (E) Liver of rat treated with 6 mg/kg of cisplatin showing hepatocyte necrosis. (F–H) Liver of rats pretreated with ethanolic leaf extract of *Ipomoea aquatica* (100, 200, and 400 mg/kg) prior to the administration of cisplatin (6 mg/kg) showing normal hepatocytes (Hand E X100)

Discussion

This study shows the presence of flavonoids, glycosides, carbohydrate, alkaloids tannins, saponins, and protein in EEIA. This finding is consistent with previous report.[28] The liver contains AST, ALT, ALP, GGT, and LDH in higher concentrations than the serum. Injury to the liver can lead to the leakage of the aforementioned parameters into the serum causing increased serum concentrations.[29] This study observed the leaching of AST, ALT, ALP, GGT, LDH, CB, and TB into systemic circulation confirmed by high plasma levels in CPT-treated rats. This observation is in agreement with previous findings.[30] The observed high levels of AST, ALT, ALP, GGT, LDH, CB, and TB in systemic circulation are clear evidence of the destruction of hepatocyte membrane in CPT-treated rats.[20] However, the functionality of hepatocyte membrane was restored in EEIA-pretreated rats in a dose-dependent fashion as shown by low plasma levels of the aforementioned parameters. OS is a condition that occurs when the steady-state balance of prooxidants to antioxidants is shifted in the direction of the former, causing damage to lipids, proteins, and DNA. Antioxidants including SOD, CAT, GSH and GPx protect biomolecules from OS-induced damage caused by prooxidants such as free radicals. Substantial evidence has shown that excess OS can decrease antioxidant activities.[31] This study observed decreases in SOD, CAT, GSH, and GPx activities in the liver of CPT-treated rats. This observation has been previously reported.[32] This observation shows that OS is a biochemical process in CPT-induced hepatotoxicity. However, upregulations in the activities of SOD, CAT, GSH, and GPx in a dose-dependent fashion were observed in the liver of EEIA-pretreated rats. Lipid peroxidation (LPO) is a biochemical process that leads to the destruction of polyunsaturated fatty acids (PUFA) in cells, thereby impairing their functions and structures. MDA is one of the most readily assayed end products of both enzymatic and nonenzymatic LPO reactions. High tissue level of MDA is used vividly to establish the oxidative destruction of PUFA.[33] This study observed the destruction of PUFA marked by high

levels of MDA in the liver of CPT-treated rats. This observation is in agreement with previous report.[34] However, there were evident decreases in the levels of MDA in a dose-dependent fashion in the liver of EEIA-pretreated rats. This observation is an evidence of the inhibitory effect of EEIA on CPT-induced destruction of hepatic PUFA. Furthermore, the liver section of CPT-treated rats showed hepatocyte necrosis. This observation is in agreement with previous studies.[35] However, the observed necrosis in the liver of CPT-treated rats was abrogated in EEIA-pretreated rats. Despite the fact that the mechanism of CPT-induced hepatotoxicity is not fully understood, some studies have speculated hepatic OS through the generation of free radicals.[36] Free radicals can damage biological molecules such as lipids, proteins, and DNA and eventually stimulate cell apoptosis.[37] Also, functional and structural mitochondrial injury and the production of pro-inflammatory mediators have been speculated in CPT-induced hepatotoxicity.[38] In this study, the abrogation of CPT-induced hepatotoxicity by EEIA could be attributed to its phytochemical constituents. EEIA contains flavonoids, tannins, and other phytochemical constituents that have antioxidant activities.[39,40] Flavonoids are antioxidants that scavenge and chelate free radicals. Also, tannins act as free radical terminators and are involved in the retardation of oxidative degradation of lipids.[41] The presence of these phytochemical constituents in EEIA might have inhibited, scavenged, or neutralized CPT-induced free radical production in the liver, thereby preventing hepatotoxicity.

Conclusion

Ipomoea aquatica Forsk contains essential phytochemical(s) that may be used as treatment for hepatotoxicity caused by CPT.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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