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Research Article

EVALUATION OF PROTECTIVE EFFECT OF *BASSIA MALABARICA* LEAVES AGAINST CISPLATIN-INDUCED NEPHROTOXICITY AND DOXORUBICIN-INDUCED CARDIOTOXICITY IN RATS

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ABSTRACT

Objective: The objective of the current investigation is to study the effect of ethanolic extract of *Bassia malabarica* leaves (EBML) against cisplatin-induced nephrotoxicity and doxorubicin (DOX)-induced cardiotoxicity in healthy adult male Wistar rats.

Methods: Nephrotoxicity was induced by cisplatin (7 mg/kg, *i.p*) and cardiotoxicity was induced by DOX (15 mg/kg, *i.p*). In both the models, EBML (150 mg/kg and 300 mg/kg, *p.o*) was administered for 15 days to assess the prophylactic and curative effect. Urinary parameters, biochemical parameters, and *in vivo* antioxidants were monitored for nephroprotective effect. For assessing cardioprotective effect serum parameters, cardiac ATPases and *in vivo* antioxidants were measured. A statistical significance was set at $p<0.05$ which was analyzed by one-way analysis of variance followed by Tukey's multiple comparison test.

Results: The study results show that the EBML has significantly ($p<0.05$) restored the urinary parameters, serum parameters of cisplatin-induced nephrotoxic rats, and serum parameters of DOX -induced cardiotoxic rats. A significant decrease ($p<0.05$) in levels of malondialdehyde and increase in reduced glutathione and catalase were seen in both nephrotoxic and cardiotoxic rats. Ca^{+2} ATPase was significantly decreased and Na^{+} K^{+} ATPase was significantly increased ($p<0.05$) in the treatment groups when compared to DOX disease control group.

Conclusion: EBML showed a protective effect against cisplatin-induced nephrotoxicity and DOX -induced cardiotoxicity.

Keywords: *Bassia malabarica*, Cisplatin, Doxorubicin, *In vitro* antioxidants, *In vivo* antioxidants, Cardiac ATPases.

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INTRODUCTION

Cancer is a disease that kills more globally than tuberculosis, acquired immune deficiency syndrome, and malaria [1]. By 2030, 21.4 million new cancer cases are expected to occur globally with 13.2 million cancer deaths. The most prevalent cancers in men are prostate and lung, and in females, it includes breast, cervical, and colorectal (as per the National cancer registers). The chemotherapy of most cancers is a combination of two or more drugs. Since most of these anticancer drugs and its metabolites affect cells of vital organs (such as kidney, heart, bladder, and lungs) leading to toxicity to vital organs, search for therapeutic aid for alleviating these toxicities from natural sources like medicinal plants has become more important. Recent trends in chemotherapy also emphasize on adjuvant therapy to reduce damage to the vital organs. This prompted us to study the cardioprotective and nephroprotective activity of the selected plants simultaneously.

Medicinal plants play a significant role in ancient traditional systems of medication in many countries. In India, thousands of plant species are known to have medicinal values, and the use of different parts of several medicinal plants to cure specific ailments has been in vogue since ancient time [2].

The genus Madhuca (Sapotaceae) comprises economically important plants and is well known for their wide variety of uses. Plant *Bassia malabarica* (Family - Sapotaceae) flowers are used in renal diseases, fruit in rheumatism, asthma, cough [3], heart diseases, burning sensation, and ear complaints [4,5]. Seed oil was used for cooking, growth of hair, and soap making [6-8].

The review of literature reported that the bark of *B. malabarica* had nephron protective effect [9] and its oil decreased serum cholesterol (CH) and triglyceride (TG) levels of rats [10]. Review revealed that so far no studies have been undertaken on the protective effect of *B. malabarica* leaves (BML) against cisplatin-induced nephrotoxicity and doxorubicin (DOX)-induced cardiotoxicity. Thus, the aim of the present study was to evaluate the protective effect of ethanolic extract of BML (EBML) against cisplatin-induced nephrotoxicity and DOX-induced cardiotoxicity.

METHODS

Plant material and extraction

The leaves of *B. malabarica* grown in the forests of Tirumala region have been identified taxonomically and authenticated by Dr. S. Madhavachetty, Department of Botany, SVU, Tirupathi, Andhra Pradesh. Voucher specimen of the plant was deposited in CMR College of Pharmacy, Hyderabad (voucher no- CMRCP/2014/07). Freshly collected leaves were shade dried and made into a coarse powder (Sieve No: 40). The powder was defatted with petroleum ether initially and later successively extracted with different solvents in increasing order of polarity, i.e., chloroform, ethyl acetate, and ethanol using Soxhlet apparatus for 6 h. The extracts were dried under reduced pressure using a rotary vacuum evaporator and stored at 4°C for further use.

Phytochemical screening

The extracts were screened for various phytoconstituents such as alkaloids, glycosides, flavonoids, tannins, and steroids by employing standard phytochemical tests [11].

Drugs and chemicals

Cisplatin injection available as cytoplatin (50 mg/50 ml) was procured from Cipla and DOX injection available as Adrim (2 mg/ml) was procured from Fresenius Kabi Oncology Ltd.;

chemicals such as 1, 1-diphenyl-2-picrylhydrazyl (DPPH), 2, 2'-azino-bis (3-ethyl benzothiazoline-6-sulfonic acid) (ABTS), and ethylenediaminetetraacetic acid were procured from Sigma Chemical Co. India. Adenosine triphosphate (ATP) was procured from HiMedia, and the other chemicals used were of analytical grade from EMerck and SD fine. The biochemical kits used in this study were purchased from Excel, Span, and Coral Diagnostics.

Experimental animals

Healthy adult male albino rats of Wistar strain weighing 150–200 g were procured from Teena labs, Hyderabad (CPCSEA Regd. No: 177/99/CPCSEA). The rats were acclimatized to the laboratory conditions for 10 days at room temperature (27±3°C) and relative humidity (65±10%). All the rats were fed with commercially available pellet diet obtained from Amruth Foods, Pranav Agro Industries, Sangli, India, and water was given *ad libitum.* Rats used in this study were treated and cared for in accordance with the guidelines recommended by CPCSEA (Reg. No: 1657/PO/a/12/CPCSEA). The study was approved by the Institutional Animal Ethics Committee of CMR College of Pharmacy, Hyderabad (CPCSEA/1657/IAEC/CMRCP/PhD14-31).

Acute toxicity studies

The acute oral toxicity study of EBML was carried in healthy adult female rats of Wistar strain. This method was done according to OECD guideline 423, acute toxic class method [12].

Preparation of solution for administration to animals

Since the EBML was water insoluble, it was suspended in 1% carboxymethyl cellulose (CMC) solution (75 mg/ml). The suspension was prepared freshly just before administration to the animals.

Treatment schedule to evaluate cisplatin-induced nephrotoxicity

Animals were divided into seven groups (n=8):

- Group I: Rats were administered with 1% CMC (p.o) once daily for 15 days and sacrificed on the 16th day, served as normal.
- Group II: Rats received a single dose of cisplatin (7 mg/kg, i.p) to induce nephrotoxicity onthe day 1 and were sacrificed on the 6th day, served as cisplatin disease control.
- Groups III and IV: Rats were treated with EBML 150 mg/kg and 300 mg/kg for 15 days. On the 16th day, rats were administered with a single dose of cisplatin (7 mg/kg, i.p) and were sacrificed on the 21st day, served as prophylactic groups at two doses of 150 and 300 mg/kg, respectively.
- Groups V and VI: Rats were administered with a single dose of cisplatin (7 mg/kg, i.p) on the 1st day and then treated with EBML 150 mg/kg and 300 mg/kg for 15 days (i.e., 6th to 20th day). They served as curative groups at two doses of 150 and 300 mg/kg, respectively, and sacrificed on the 21st day.
- Group VII: Rats were treated with 300 mg/kg of EBML for 15 days and sacrificed on the 16th day, served as EBML control group [13].

Collection of urine for cisplatin-treated rats

After completion of the treatment schedule, the rats (Groups I–VII) were kept in metabolic cages for 24 h for urine collection. The urine collected was measured in volume (Vol, ml/24 h) and was used to calculate creatinine clearance (Cr Cl). Cr Cl is expressed as ml/hr and estimated using the following formula:

Cr Cl = [Urine Cr. (mg/dl)×Urine vol. (ml/h)]/[S. Cr.(mg/dl)]×100

Treatment schedule to evaluate DOX-induced cardiotoxicity

Animals were divided into seven groups (n=8)

- Group I: Rats were administered with 1% CMC (*p.o*) once daily for 15 days and sacrificed on the 16th day, served as normal.
- Group II: Rats received a single dose of DOX (15 mg/kg, i.p) to induce cardiotoxicity on the day 1 and sacrificed on the 4th day, served as DOX disease control.
- Groups III and IV: Rats were treated with EBML 150 mg/kg and 300 mg/kg for 15 days. On the 16th day, rats were administered with a single dose of DOX (15 mg/kg, i.p) and sacrificed on the 19th day, served as prophylactic groups at two doses of 150 and 300 mg/kg, respectively.
- Groups V and VI: Rats were administered with single dose of DOX (15 mg/kg, i.p) on the 1st day and then treated with EBML 150 mg/kg and 300 mg/kg for 15 days (i.e., 4th–18th day) and were sacrificed on the 19th day, served as curative groups at two doses 150 and 300 mg/kg, respectively.
- Group VII: Rats were treated with 300 mg/kg of EBML for 15 days and sacrificed on the 16th day, served as EBML control group [14].

Calculation of percentage change in body weight (wt)

Individual wt of rats was recorded on the day 1 and at the end of the treatment schedule before sacrificing the animal. Percentage change in body wt was calculated using the following formula:

% change in body wt = (Initial body wt–Final body wt)/(Final body wt)×100

Collection of blood

Blood was collected by retro-orbital puncture before sacrificing the rats and allowed to clot for 20 min. It was then centrifuged in a cooling centrifuge at 3000 g for 10 min at 4°C initially and later at 5000 g for 10 min. The supernatant serum obtained was collected and stored at −20°C until used for the estimation of serum parameters of kidney and heart using biochemical kits by recording the values using semi-auto analyzer (Inkarp ES-100).

Biochemical parameters of the kidney and heart to be evaluated

The serum parameters used to evaluate nephroprotective activity include serum creatinine (S.Cr, mg/dl), total protein (g/dl), serum urea (S. urea, mg/dl), serum uric acid (S. uric acid, mg/dl), and blood urea nitrogen (BUN mg/dl).

The serum parameters used to assess cardioprotective activity are creatine kinase-myocardium (CK-MB, IU/L), lactate dehydrogenase (LDH, IU/L), (TG, mg/dl), (CH, mg/dl), low-density lipoproteins (LDLs, mg/dl), and high-density lipoproteins (HDLs, mg/dl). After collection of blood, rats were sacrificed by cervical dislocation method. Kidney and heart tissues were rapidly excised, trimmed of connective tissue, and washed with ice-cold normal saline, and wet wt was noted to calculate organ wt (mg/100 g).

Quantification of phytochemical constituents of the plant extracts

Total flavonoid content was determined according to a modified colorimetric method [15] and the amount of total phenol was determined according to the Folin–Ciocalteu procedure [16].

Antioxidant ability assays

ABTS radical scavenging activity [17,18], DPPH radical scavenging assay [19], metal chelating assay [20], total antioxidant activity [21], and reducing power assay [22] were done to know the potential of antioxidant activity of the plant extracts.

***In vivo* antioxidant studies**

10 % post-mitochondrial supernatant was prepared according to Naveen *et al*. [23] for the assay of *in vivo* antioxidants such as malondialdehyde (MDA) content [24], reduced glutathione (GSH) [25], and catalase (CAT) [26].

Assay of cardiac ATPases

The heart tissues were washed with ice-cold 0.9% saline, and homogenate was prepared in 0.1 N Tris-hydrochloric acid buffer (pH 7.4). Tissue homogenate pellet obtained after centrifugation was resuspended in ice-cold Tris buffer (10 mM, pH 7.4) to get a final concentration of 10% and was used for the estimation of $Na^{+}K^{+}$ ATPase [27], Ca^{+2} ATPase [28], and Mg^{+2} ATPase [29].

Statistical analysis

All the results were expressed as mean ± standard error of mean. Data obtained from various groups were subjected to one-way analysis of variance followed by Tukey's multiple comparison test. Significant values were set at $p<0.05$.

RESULTS

Phytochemical screening of EBML revealed the presence of alkaloids, glycosides, flavonoids, phenols, and saponins. Total flavonoid content expressed as µg/mg of quercetin equivalents and total phenol content expressed as µg/mg of gallic acid equivalents was tested for solvents pet ether, chloroform, ethyl acetate and ethanol of *B. malabarica*. The quercetin euivalents and gallic acid euivalents were found to be higher in the ethanolic extract than the other extracts pet ether, choloroform and ethyl acetate *B. malabarica* (Table 1).

The EBML exhibited higher free radical scavenging and reducing power among all the extracts studied in different *in vitro* models (Table 2).

Group II rats of cisplatin treatment group showed a significant decrease in percentage change in body wt, urine volume, and Cr Cl and a significant increase in the kidney wt when compared to Group I. Treatment with EBML prophylactically and curatively has significantly increased the body wt, urine volume, and Cr Cl. and significantly decreased kidney wt when compared to Group II (Table 3).

Animals treated with cisplatin in Group II showed a significant increase in S.Cr, total protein, S. urea, S. uric acid, and BUN levels when compared to normal group. Treatment Groups III to VI treated with EBML have shown a significant decrease in S.Cr, total protein, S. urea, S. uric acid, and BUN levels when compared to Group II (Table 4).

A significant increase in MDA and a significant decrease in reduced GSH and CAT enzymes were observed in Group II rats treated with cisplatin on comparison with Group I. MDA levels were significantly decreased with increase of GSH and CAT in the treatment Groups III, IV, V, and VI on comparison with Group II (Table 5).

A significant decrease in % change in body wt and HDL and a significant increase in heart wt, CK-MB, LDH, CH, and TG levels were observed in DOX-treated Group II rats when compared with Group I rats. Treatment with EBML has significantly increased the HDL levels and significantly decreased the CK-MB, LDH, CH, and TG levels on comparison with Group II (Table 6).

A significant decrease in cardiac ATPases such as Na^+K^+ ATPase and Mg^{2+} ATPase and a significant increase in Ca^{2+} ATPase were seen in Group II when compared to Group I. On treatment with EBML in Groups III–VI, a significant increase in Na^+K^+ ATPase and a significant decrease in Ca^{2+} ATPase levels were observed on comparison with Group II (Table 7).

Group II rats treated with DOX showed a significant increase in MDA and a significant decrease in reduced GSH and CAT levels on comparison with Group I. Animals treated with EBML prophylactically and curatively in Groups III–VI have shown a significant decrease in MDA content with a simultaneous decrease in reduced GSH levels when compared to Group II (Table 8).

Table 1: Quantification of phytochemical constituents of BML

Extracts	Quantification of phytochemical constituents	
	Total flavonoid	Total phenol
	µg/mg QE±SEM	µg/mg GAE±SEM
Ethanol	311.7±03.33	165.0±04.33
EAF	228.3±03.33	154.2±01.67
ChF	225.0±10.89	132.5±01.25
Pet ether	106.7±07.95	108.3±02.21

EAF: Ethyl acetate fraction, ChF: Chloroform fraction, QE: Quercetin equivalents, GAE: Gallic acid equivalents, BML: *Bassia malabarica* leaves, SEM: Standard error of mean

DISCUSSION

Many plants contain antioxidant compounds, and these compounds protect cells against the damaging effects of reactive oxygen species (ROS) [30]. Therefore, the study of plants as a resource of medicine has become more important in the context of present global trade scenario where oxidative stress is found to be one of the major causes of health hazards [31].

A significant reduction in the percentage change in body wt in disease control groups may be due to gastrointestinal toxicity and concomitant loss of the animal appetite with subsequent reduction of food ingestion [32]. Infiltration of the organs, tissue damage, and reduction in their functions lead to increase in organ wt (kidney and heart) in disease control groups (Group II) [33].

Decrease in urine volume and Cr Cl in cisplatin disease control group is due to decrease in renal blood flow and glomerular filtration rate which occurs within 3 h after cisplatin infusion [34]. Glomerular damage as a result of ROS generation increased the levels of S.Cr, total protein, S. urea, S. uric acid, and BUN in Group II [35,36]. Treatment with EBML increased the urine volume and Cr Cl with simultaneous decrease of S.Cr, total protein, S. urea, S. uric acid, and BUN levels proving the protective activity of the plant.

CK-MB and LDH are the cardiac enzymes primarily found in the MB used to evaluate the existence and extent of myocytes injury [37]. DOX disease control group rats increased these biomarkers in the extracellular fluid due to an increased leakage of these enzymes from mitochondria as a result of toxicity induced by DOX [38]. Administration of DOX interferes with the metabolism or biosynthesis of lipids increasing the plasma levels of TG, CH, and LDL in Group II rats of DOX. Whereas, treatment with EBML might decrease the interference with the metabolism and thus decrease the plasma levels of TG, CH, and LDL [39,40].

Administration of DOX showed peroxidation of membrane lipids which inactivated Na^+K^+ ATPase and Ca^{2+} ATPase. Decreased activity of Ca^{2+} ATPase increased intracellular concentration of free calcium and altered the signal transduction pathways and cellular fluidity [41].

Table 2: Effect of *B. malabarica* extracts on *in vitro* antioxidant parameters

Extracts	ABTS	DPPH	MC assay	Total AO activity	RPA
	IC_{50}±SEM	IC_{50}±SEM	IC_{50}±SEM	IC_{50}±SEM	
	Vit C IC_{50}=30.31	Vit C IC_{50}=15.33	EDTA IC_{50}=28.24	Vit C IC_{50}=52.94	µg/mg of AAE±SEM
Ethanol	36.50±01.10	21.33±01.60	29.87±01.68	57.14±04.41	70.83±01.64
EAF	57.54±03.98	53.33±02.46	41.42±02.82	76.82±02.50	54.33±01.36
ChF	45.12±03.55	38.51±02.45	31.24±01.19	67.91±07.22	66.17±01.17
Petroleum ether	59.83±03.69	69.45±03.98	59.46±03.39	82.08±07.22	42.67±01.30

IC_{50}: Half maximal inhibitory concentration, Vit C: Vitamin C, AO: Antioxidant, MC assay: Metal chelation assay, AAE: Ascorbic acid equivalents, RPA: Reducing power assay. *B. malabarica: Bassia malabarica*, EAF: Ethyl acetate fraction, ChF: Chloroform fraction, SEM: Standard error of mean, DPPH: 1, 1-diphenyl-2-picrylhydrazyl

Table 3: Effect of ethanolic extract of *B. malabarica* on body wt and urinary parameters

Groups	% change in body wt	Kidney wt (mg/100 g)	Urinary parameters	
			Urine Volume (ml/24 h)	CrCl (ml/h)
I	08.61±0.68	233.8±11.52	08.35±0.41	02.02±0.39
II	−15.08±1.67^	458.0±10.15^	01.79±0.34^	0.24±0.06^
III	−04.82±0.83*	307.8±08.04*	06.44±0.30*	01.19±0.24
IV	02.38±0.91*	253.3±13.10*	08.06±0.35*	01.41±0.26*
V	−11.96±1.67	418.5±13.55	03.10±0.31	0.68±0.10
VI	−09.68±0.86*	400.5±10.65*	04.06±0.37*	0.81±0.13
VII	07.86±0.67	246.2±12.45	09.24±0.35	02.00±0.34

Values are expressed as mean±SEM and n=8, ^p<0.05 when compared to Group I, *p<0.05 when compared to Group II. *B. malabarica: Bassia malabarica*, SEM: Standard error of mean, wt: Weight

Table 4: Effect of ethanolic extract of *B. malabarica* on serum parameters

Groups	S.Cr. (mg/dl)	Total protein (g/dl)	S. urea (mg/dl)	S. uric acid (mg/dl)	BUN (mg/dl)
I	0.23 ± 0.04	5.44 ± 0.21	12.64 ± 1.08	3.44 ± 0.42	05.90 ± 0.50
II	0.98 ± 0.08^	8.97 ± 0.22^	49.50 ± 3.95^	8.20 ± 0.49^	23.12 ± 1.85^
III	0.43 ± 0.05*	6.89 ± 0.38*	27.10 ± 1.39*	5.34 ± 0.39*	12.66 ± 0.65*
IV	0.36 ± 0.04*	6.58 ± 0.53*	15.62 ± 1.09*	4.41 ± 0.24*	07.29 ± 0.51*
V	0.61 ± 0.04*	8.68 ± 0.76	39.98±±1.82*	7.11 ± 0.46*	18.67 ± 0.85*
VI	0.50 ± 0.05*	7.86 ± 0.56	29.16 ± 1.53*	6.68 ± 0.34*	13.61 ± 0.71*
VII	0.27 ± 0.04	5.57 ± 0.56	14.02 ± 1.19	3.88 ± 0.22	06.55 ± 0.55

Values are expressed as mean ± SEM and n = 8, ^p < 0.05 when compared to Group I, *p < 0.05 when compared to Group II. *B. malabarica: Bassia malabarica,* SEM: Standard error of mean, S. urea: Serum urea, S. uric: Serum uric

Table 5: Effect of ethanolic extract of *B. malabarica* on *in vivo* antioxidant parameters

Groups	MDA (nM/g tissue)	GSH (nM/g tissue)	CAT (K/g Pr)
I	01.31 ± 0.14	45.99 ± 2.80	223.4 ± 6.28
II	13.85 ± 1.64^	06.87 ± 1.28^	67.14 ± 5.06^
III	04.23 ± 0.45*	23.68 ± 1.65*	157.6 ± 6.10*
IV	02.53 ± 0.20*	35.06 ± 2.92*	181.0 ± 7.74*
V	06.68 ± 0.29*	05.91 ± 1.55	93.57 ± 5.79*
VI	06.23 ± 0.33*	16.72 ± 1.96	127.4 ± 7.22*
VII	01.33 ± 0.19	45.50 ± 4.25	216.7 ± 4.96

Values are expressed as mean ± SEM and n = 8, ^p < 0.05 when compared to Group I, *p < 0.05 when compared to Group II. GSH: Glutathione, MDA: Malondialdehyde, CAT: Catalase, SEM: Standard error of mean, *B. malabarica: Bassia malabarica*

Table 6: Effect of ethanolic extract of *B. malabarica* on body wt, heart wt, and serum parameters

Group	% change in body wt	Heart wt (mg/100 g)	CK-MB (IU/L)	LDH (IU/L)	CH mg/dl	TG mg/dl	HDL mg/dl
I	08.31±0.88	199.0±14.64	17.02±01.71	396.7±19.44	76.0±6.04	63.71±3.62	34.72±1.78
II	−15.41±1.62^	448.0±22.97^	47.01±01.65^	738.3±18.29^	199.8±5.96^	165.0±7.27^	25.87±1.61^
III	−07.65±0.83*	276.8±11.79*	29.54±01.94*	577.8±23.73*	140.2±7.01*	117.1±5.35*	28.30±1.42
IV	02.09±1.07*	219.7±10.83*	25.03±01.77*	535.3±18.36*	115.4±5.72*	101.6±4.14*	33.85±1.35*
V	−11.81±1.03	395.0±08.97	36.39±01.40	683.0±22.13	189.8±5.77*	143.9±2.92*	26.00±1.37
VI	−09.81±0.62*	389.2±09.56*	31.10±02.09*	603.7±19.19*	163.7±5.85*	125.2±4.58*	26.61±1.33
VII	07.71±0.54	205.2±08.82	17.17±01.57	425.2±13.35	63.87±4.78	59.30±4.61	36.79±1.64

Values are expressed as mean±SEM and n=8, ^p<0.05 when compared to Group I, *p<0.05 when compared to Group II. CK–MB: Creatine kinase-myocardium, LDH: Lactate dehydrogenase, CH: Cholesterol, TG: Triglyceride, HDL: High-density lipoprotein, *B. malabarica: Bassia malabarica*, SEM: Standard error of mean

Table 7: Effect of ethanolic extract of *B. malabarica* on *in vivo* antioxidant parameters

Groups	MDA (nM/g tissue)	GSH (nM/g tissue)	CAT (K/g Pr)
I	03.28±0.40	12.14±1.10	74.14±6.98
II	14.27±1.03^	5.64±0.56^	9.86±3.34^
III	04.85±0.43*	11.13±1.11*	51.00±3.53*
IV	03.65±0.39*	11.63±1.09*	69.29±3.34*
V	11.51±0.46*	09.08±1.56	17.00±2.66
VI	09.21±0.48*	09.57±1.28	26.86±3.61
VII	02.80±0.40	14.19±1.31	76.43±5.33

Values are expressed as mean±SEM and n=8, ^p<0.05 when compared to Group I, *p<0.05 when compared to Group II. GSH: Glutathione, MDA: Malondialdehyde, CAT: Catalase, SEM: Standard error of mean, *B. malabarica: Bassia malabarica*

Table 8: Effect of ethanolic extract of *B. malabarica* on cardiac ATPases

Groups	$Na^+ K^+$ ATPase units*	Ca^{+2} ATPase units*	Mg^{+2} ATPase units*
I	4.037 ± 0.136	1.841 ± 0.116	0.336 ± 0.011
II	2.877 ± 0.104^	3.823 ± 0.116^	0.132 ± 0.011^
III	3.541 ± 0.140*	2.210 ± 0.155*	0.249 ± 0.013*
IV	4.027 ± 0.121*	1.960 ± 0.173*	0.300 ± 0.012*
V	3.253 ± 0.130	2.567 ± 0.106*	0.181 ± 0.013
VI	3.404 ± 0.171	2.343 ± 0.154*	0.220 ± 0.013*
VII	4.053 ± 0.142	1.793 ± 0.127	0.341 ± 0.013

Values are expressed as mean ± SEM and n = 8, ^p < 0.05 when compared to Group I, * *P* < 0.05 when compared to Group II, Units*: Milli mol of phosphorus liberated/min/mg of protein. ATP: Adenosine triphosphate, SEM: Standard error of mean, *B. malabarica: Bassia malabarica*

Treatment with EBML might have decreased the concentration of free calcium and thus increased the levels of Na^+K^+ ATPase and decreased the levels of Ca^{2+} ATPase.

Cisplatin (cis-diamminedichloroplatinum II) is a potent antineoplastic drug used in the treatment of solid tumors. The main dose-limiting side effect of cisplatin is nephrotoxicity [42-44]. Cisplatin generates ROS which inhibits the activity of antioxidant enzymes in renal tissues with increased lipid peroxidation and nephrotoxicity [45,46]. DOX is a naturally occurring anthracycline that is widely used in the treatment of a variety of hematological and solid malignancies such as leukemia, bladder, lung, and breast cancers [47]. Its clinical uses are often limited by the dose-dependent cardiotoxicity which leads to cardiomyopathy and eventually congestive heart failure [48]. Oxidative stress-generating ROS is the cornerstone of DOX-induced cardiotoxicity [49].

ROS generated on the administration of cisplatin and DOX in Group II rats caused peroxidation of lipids with a concomitant decline in the level of GSH. Inhibition in the activities of antioxidant enzymes leads to the generation of superoxide anion (O^{2-}) and hydrogen peroxide (H_2O_2), which in turn formed hydroxyl radical (OH.) and brought about a number of reactions harmful to structural and functional integrity [50].

Yogesh *et al.* reported that the presence of tannin (phenol) and flavonoids in the plant extract has antioxidant activity [51]. Thus, the administration of EBML having flavonoid and phenolic constituents might have augmented reduced GSH and antioxidant enzyme levels and scavenges lipid peroxides [52-54].

CONCLUSION

The results of the present study revealed the protective effect of EBML against cisplatin-induced nephrotoxicity and DOX-induced cardiotoxicity. The presence of phytochemical constituents might be responsible for a protective effect against free radicals generated by the administration of cisplatin and DOX.

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AUTHORS' CONTRIBUTION

Conceived and designed the experiments: KVSRG Prasad, Sujatha, and Sushma. Performed the experiment: Sushma. Analyzed data: Sushma and Sujatha. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

The authors have no conflicts of interest.

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