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Research article

Beneficial effects of *Bacopa monnieri* (brahmi) in Doxorubicin-induced cardiotoxicity in rats

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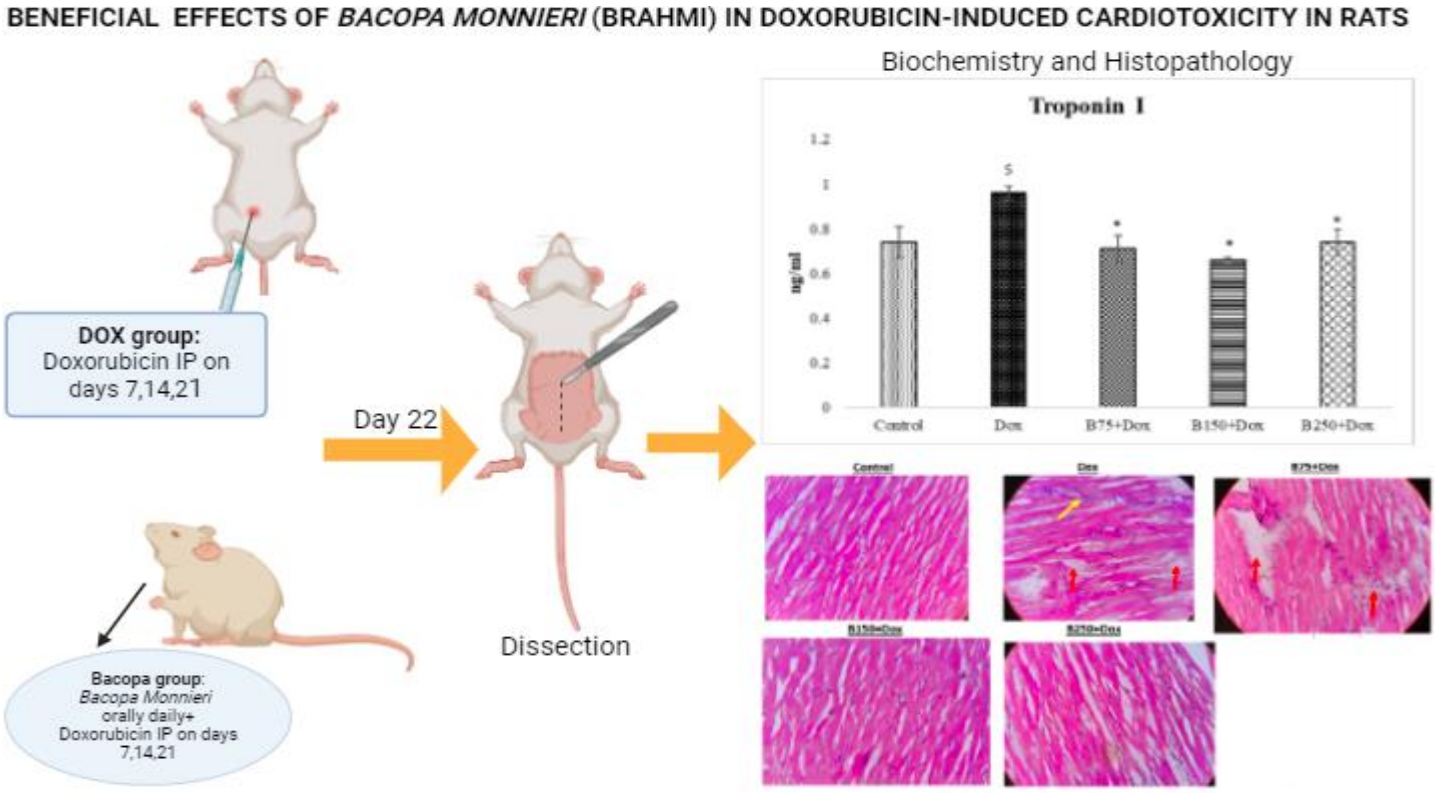
ABSTRACT

Cancer, a leading global cause of death, drives research for safer treatments. Doxorubicin is an effective anticancer drug but is associated with cardiotoxicity as a characteristic adverse effect. *Bacopa monnieri*, a traditional Ayurvedic herb rich in antioxidants, emerges as a potential adjunct in cancer treatment. The study aims to explore *Bacopa monnieri's* impact on doxorubicin-induced cardiotoxicity.



The study was conducted in 30 rats with 6 rats in each of the 5 groups: Group 1 was administered distilled water; Group 2 received Doxorubicin at 5 mg/kg by IP on days 7, 14, and 21. Groups 3, 4 and 5 were administered *Bacopa monnieri* at 75mg/kg, 150mg/kg, and 250mg/kg orally daily doses along with Doxorubicin at 5mg/kg by IP on days 7,14 and 21. The *Bacopa monnieri*-treated groups compared to the Doxorubicin(Dox) group showed a significant reduction in aspartate aminotransferase (AST), troponin I, and malondialdehyde (MDA) levels while the levels of antioxidants Superoxide dismutase (SOD), and Glutathione (GSH) increased. Histopathology showed fibrosis and inflammation in the Doxorubicin group while restoration of normal cardiac tissue in the *Bacopa monnieri*-treated group. The study illustrates *Bacopa monnieri's* ability to alleviate Doxorubicin-induced cardiac toxicity by its antioxidant properties.

Keywords: Doxorubicin, *Bacopa Monneiri*, Cardioprotective.

INTRODUCTION

Cancer remains a leading cause of death globally, with projections estimating 13.1 million deaths by 2030, prompting extensive research efforts over the past decade to discover novel therapies aimed at mitigating the adverse effects associated with conventional treatments [1,2].

Doxorubicin (Dox), a highly effective chemotherapeutic agent is used mainly in treating a wide variety of solid tumors in adult and paediatric cancers. However, despite its antineoplastic effects, concerns regarding adverse events, notably cardiotoxicity, have limited the extensive use of conventional doxorubicin in clinical practice. Cardiotoxicity refers to structural and functional changes in the myocardium, often accompanied by elevated levels of sensitive cardiac-specific markers such as troponins T and I, and NT-pro-BNP. Additionally, it can manifest as a subclinical or clinical reduction in left ventricular ejection fraction (LVEF) [1,3,4].

Dox-induced cardiotoxicity can either be a dose-dependent (acute onset) characterized by a prolonged QT interval, which can be reversible or cumulative (chronic) Dox-induced cardiotoxicity which is characterized by left ventricular dysfunction, a distinctive heart failure pathology that cannot be clinically managed or reversed. This form of cardiotoxicity is directly related to the cumulative dose of Dox [4]. Pathogenesis of DOX-induced myocardial injury involves multiple biological processes including oxidative stress, lipid peroxidation, DNA damage, mitochondrial injury, apoptosis, and autophagy. Among them, oxidative stress is a key process in DOX-induced myocardial damage [5].

Bacopa monnieri(B.M.) (common name- Brahmi; family- Plantaginaceae) is a known Phytomedicine that has been used in the Indian traditional medical system of Ayurveda as Madhya-rasayana (memory enhancing and rejuvenating) [6]. Due to its composition of several cytoprotective phytochemicals which have anti-proliferative, pro-apoptotic, natural antioxidant properties, it has emerged as promising adjunct therapy in cancer treatment [2].

The pharmacological properties of *B.M.* were due to the presence of dammarane-type triterpenoid saponins called bacosides. Bacoside-A (BA) is considered as the major active component. Either whole extract of *B.M.* or purified BA was effective in toxicity in cardio-myocytes. The whole extract was found to be more potent than BA [7].

While previous reports found cardio protective effects of *B.M.,* there was a scarcity of studies verifying its benefits in doxorubicin toxicity. Given its rich composition of beneficial alkaloids and flavonoids, along with its favourable effects on blood vessels and established ability to boost antioxidant activity, present study to investigated its potential benefit in doxorubicin-induced cardiotoxicity [5].

MATERIAL AND METHOD

Animals

The study was conducted after obtaining approval from Institute Animal Ethics Committee (IAEC). The "Central Animal Research Facility," provided 30 healthy male Sprague Dawley albino rats, measuring between 180 and 250 grams and between 10 and 12 weeks old. CPCSEA guidelines for housing animals were followed and rats were kept in polypropylene sterile cages of size 41cm x 28cm x 14cm, with sterile paddy husk bedding (procured locally), 12hr alternate light and dark cycle in 25±3˚C temperature and 50% humidity and food pellets and water *ad libitum* was provided.

Drugs and Chemicals Used

Doxorubicin hydrochloride (50mg / 25ml) – 2 vials, Ketamine hydrochloride (250mg / 5ml) – 8 vials, Xylazine 30ml – 1 vial were purchased from a pharmacy store. All other reagents used were procured from Sigma and of analytical grade.

Bacopa Monnieri Extract

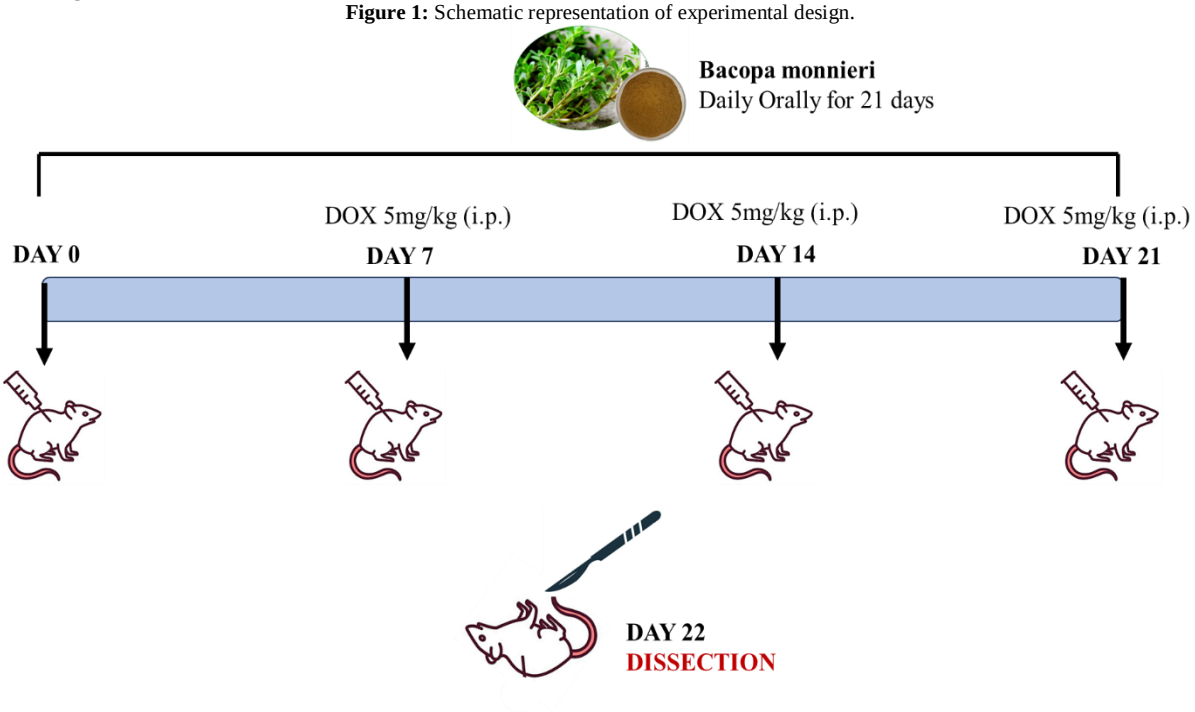
The ethanolic extract of *B.M.* was received as a gift sample containing a dried powder formulation which was greenish brown (Batch number RD/22017) from Natural Remedies Private Limited 5B, Veersandra Industrial Area, Hosur Road, Electronic City Phase 2, Bangalore 560100 Karnataka. *B.M.* was certified as a pure extract under the product name *Bacomind* extract.

Phytochemical analysis showed to contain mainly Triterpene glycosides, Bacopaside I, Bacopaside II, Bacoside A_3, Jujubogenin isomer of Bacopasaponin C, and Bacopasaponin C.

The dried powder of *B.M.* was suspended in distilled water initially and was administered.

Experimental Design

Figure 1: Schematic representation of experimental design.



Tissue and serum were collected for Biochemical parameters and Histopathology

Dose and Route of Drug Administration

A total of 30 rats were randomly allocated into five groups: Control group was administered distilled water; Dox group received Doxorubicin at 5 mg/kg by IP route; test groups received bacopa extract at 75mg/kg (B75), 150mg/kg (B150), 250mg/kg (B250) orally daily along with Doxorubicin at 5 mg/kg by IP route on day 7, 14 and day 21. (**Fig 1**) All the groups were treated for 21 days. *B.M.* extract was administered orally 1 hour before Dox. Rats were sacrificed under 125 mg/kg of ketamine anaesthesia and 10 mg/kg of xylazine by intraperitoneal route on day 22 and testis was dissected out for assessment.

Biochemical Parameters

Troponin I [8,9]

Serum cardiac troponin I (cTnI) levels were measured using an ELISA kit. 50 µl of the standard or sample were placed in each of the microplate wells. A prepared detection reagent was then added, and the mixture was incubated at 37°C for an additional hour. Following washing, 100 µl of a substrate solution was added to each well, and it was incubated at 37°C for 10 to 20 minutes. Then, 50 µl of a stop solution was added, and an ELISA reader was used to measure colour changes at 450 nm.

Aspartate Aminotransferase [10]

AST was estimated via modified International Federation of clinical chemistry (IFCC) method. Amino group transfer between L-aspartate and α-ketoglutarate catalysed by AST, forming oxaloacetate and glutamate. Malate Dehydrogenase aids the oxaloacetate-NADH reaction, producing NAD. A decrease in absorbance reflects AST activity.

Following 21 days, animals were euthanized with an overdose of ketamine. Subsequently, the heart was extracted and preserved in a solution at pH 7.4 and a concentration of 0.1M, maintained at a cold temperature. Tissue samples for histopathology were stored in a solution of 10% formalin.

Oxidative Stress Markers

The phosphate buffer with heart tissue was homogenised using a glass homogenizer. The homogenate was centrifuged at 10,000 rpm for 10 minutes the pellet was discarded and the supernatant obtained was used to assay the following biochemical parameters

Malondialdehyde (MDA) [11,12]

MDA is involved in unsaturated fatty acid breakdown. Thiobarbituric acid (TBA) is used as a colour reagent through colorimetric or fluorometric approaches to detect MDA, usually under acidic media and harsh heating at 95–100°C. Reaction with TBA yields a pink colour, quantified at 532nm. Tissue homogenate mixed with TBA, Trichloroacetic acid (TCA), and Hydrochloric acid (HCL), heated, and then centrifuged. Absorbance measured at 525nm.

Superoxide Dismutase (SOD) [13]

SOD enzyme catalyzes the dismutation of superoxide anions to H2O2, further reduced to H2O and oxygen. Autooxidation of adrenaline produces adrenochrome, indicating ROS activity and SOD function. Sodium bicarbonate buffer mixed with tissue homogenate and adrenaline bitartrate in a cuvette. Absorbance measured at 480nm over 0-60 sec using UV Spectrophotometer for SOD activity analysis.

Glutathione (GSH) [14]

Glutathione reductase reduces DTNB to a yellow compound. OD measured at 412nm. Tissue homogenate was mixed with TCA, centrifuged, and supernatant collected. In 96-well plates, supernatant, Ellman's reagent (DTNB) reagent, and Phosphate-buffered saline were added and incubated. Blank with homogenization buffer. Absorbance measured at 412nm. GSH is expressed in µmoles/mg total protein.

Histopathology

The histological examination of the heart was done using paraffin-embedded specimens. Bancroft and Stevens's 1990 procedure was followed and sections were stained with haematoxylin and eosin. After Incubation, tissue sections were cooled and kept in xylene for thirty min for the removal of wax.

Hydration of sections was done through different alcohol series (90%, 70% and 50%). Sections were washed with distilled water for five minutes and staining was done with haematoxylin. Sections washed in tap water for blueing. Staining was done with Eosin. Dehydration through different alcohol series was performed. Xylol for five to ten minutes and then mounted using Dibutyl phthalate Polystyrene Xylene (DPX) under a cover slip.

Once the slides are dried, H & E-stained tissues are observed under the light microscope.

Statistical Analysis

Statistical comparisons were performed using Graph Pad Prism 8.0.1 Version, by One-way analysis of variance (ANOVA) followed by "post hoc Tukey test," and student's t-test. Data were expressed as Mean ± S.D. P≤0.05 was considered significant.

RESULTS

Table 1: Body weight changes

Group	D1	D21	P
Control	351.83±33.4	366±29.5	0.001
Dox	324.83±44.8	276.67±39.73	0.01
B75+Dox	293.83±37.1	279.66±35.57	0.001
B150+Dox	284.5±28.21	267.67±15.74	0.04
B250+Dox	261.33+±13.5	251.5±17.9	0.02

Data are expressed as Mean ± S.D. Dox=Doxorubicin; B75, B150 and B250 are *Bacopa monnieri* groups at 75mg/kg, 150mg/kg and 250mg/kg respectively.

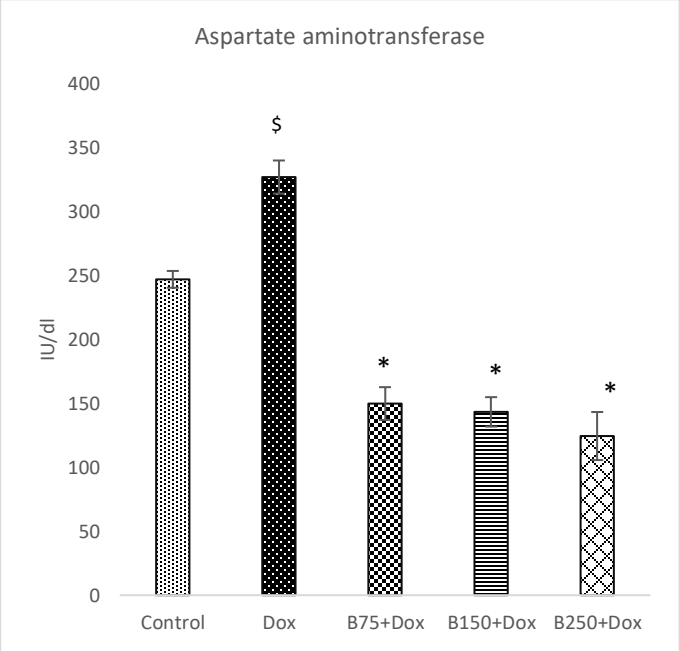
There was a significant increase in body weight in control group whereas body weight was decreased in the Dox group and the three Bacopa groups.

Biochemical Analysis

Aspartate Aminotransferase (AST)

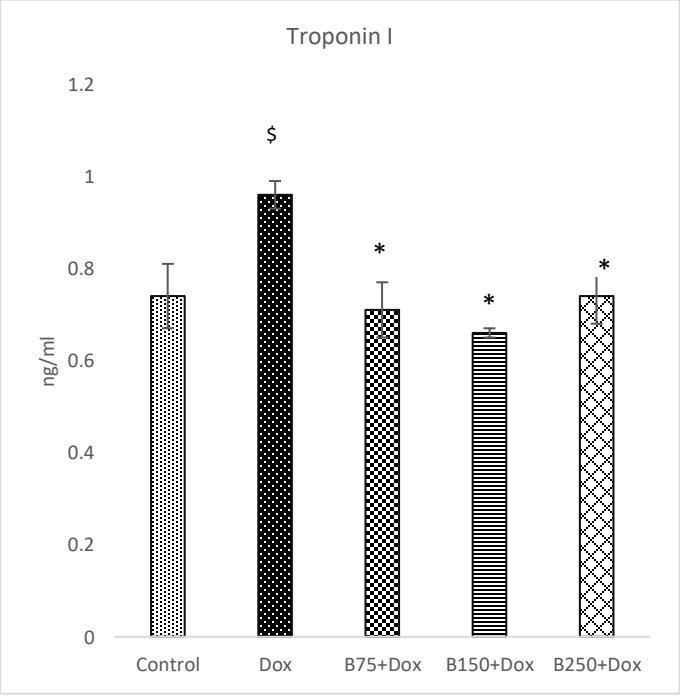
Data are expressed as Mean ± S.D. Dox=Doxorubicin; B75, B150 and B250 are *Bacopa monnieri* groups at 75mg/kg, 150mg/kg and 250mg/kg respectively. $P<0.05 Vs control; * P<0.05 Vs Dox. AST levels were significantly elevated in DOX group when compared to the control. However, the levels were reduced (p< 0.05) in treatment groups (B75+Dox, B150+Dox, B250+Dox) compared to DOX group. The levels of AST were significantly lesser in Bacopa-treated groups (B75+Dox, B150+Dox, B250+Dox) compared to the control group.

Figure 2: Effect of *Bacopa Monneiri* on Aspartate aminotransferase



Troponin I

Figure 3: Effect of *Bacopa Monneiri.* On Troponin I levels.



Data are expressed as Mean ± S.D. Dox=Dosorubicin; B75, B150 and B250 are Bacopa Monneiri groups at 75mg/kg, 150mg/kg and 250mg/kg respectively. $P<0.05 Vs control; *P<0.05 Vs Dox.

There was a significant rise in troponin I levels in the DOX group when compared to control. There were no significant changes in the DOX+Bacopa group in comparison to control. Significant reduction (p< 0.05) in troponin I levels were observed in the treatment group (B75+Dox, B150+Dox, B250+Dox) compared to Dox group.

Table 2: Estimation of Oxidative stress markers in heart tissue

GROUPS	MDA (nM/g protein)	GSH (µM/mg protein)	SOD (U/mg protein)
Control	78.27 ± 0.63	0.03063 ± 0.001	78.32 ± 3.04
Dox	135.5 ± 3.14 $	0.00856 ± 0.001 $	41.58 ± 1.66$
B75+Dox	109.7 ± 0.64 $*	0.02235 ± 0.00 $*	54.16 ± 2.86 $*
B150+Dox	114.7 ± 1.35 $*	0.01845 ± 0.001 $*	52.58 ± 1.39 $*
B250+Dox	126.9 ± 4.72 $*	0.01948 ± 0.001 $*	49.17 ± 4.95 $*

Data are expressed as Mean ± S.D. Dox=Dosorubicin; B75, B150 and B250 are *Bacopa monnieri* groups at 75mg/kg, 150mg/kg

And 250mg/kg respectively. $ P-value <0.05 vs control group, * p-value < 0.05 vs Dox induced.

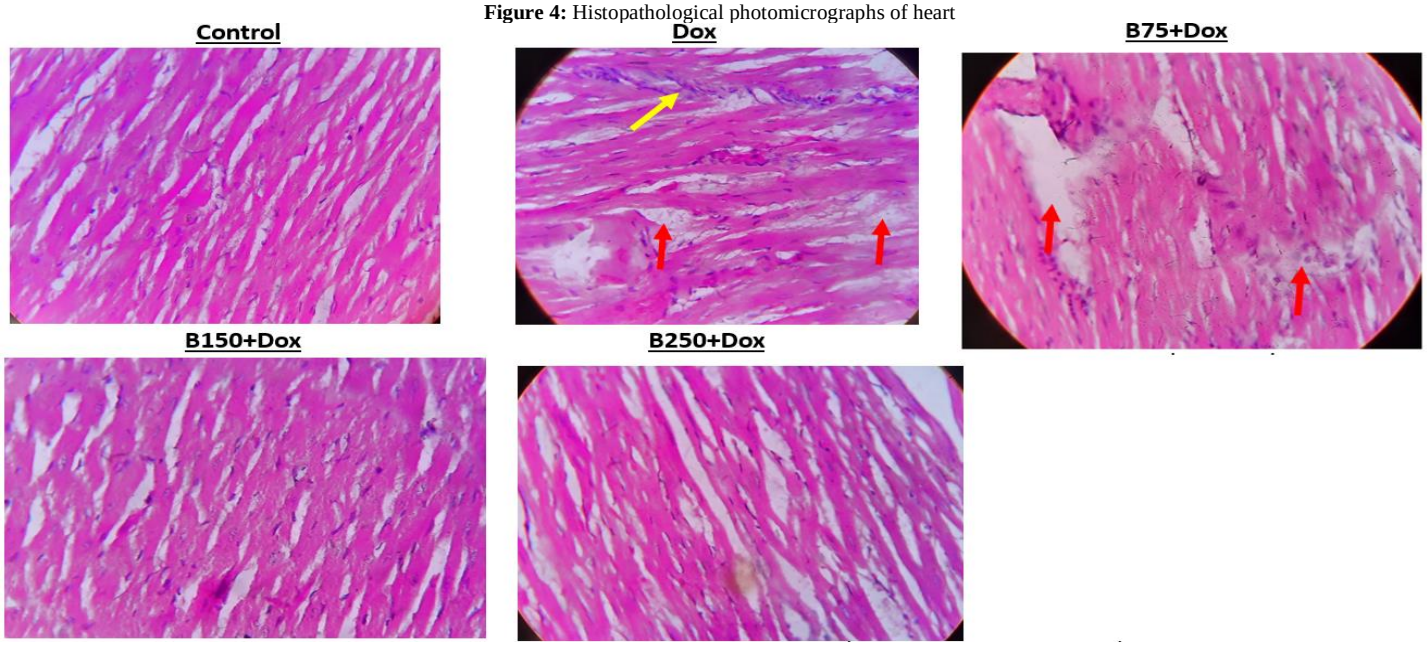
MDA levels was significantly increased (p< 0.05) in DOX group and in DOX+ Bacopa groups compared to control. But its levels significantly decreased (p< 0.05) in DOX+ Bacopa group when compared to DOX group.

GSH levels was significantly decreased (p< 0.05) in DOX group and DOX+ Bacopa groups compared to control. But its levels significantly raised (p< 0.05) in B75+Dox, B150+Dox and B250+Dox compared to DOX.

SOD levels were significantly decreased (p< 0.05) in DOX group and DOX+ Bacopa groups compared to control. Its levels increased significantly (p< 0.05) in B75+Dox, B150+Dox and B250+Dox compared to DOX group.

Histopathology

Figure 4: Histopathological photomicrographs of heart



Representative photomicrographs of Hematoxylin and Eosin (H&E) stained sections of cardiac muscle of Control, Doxorubicin, Doxorubicin + 75mg/kg Bacopa treated), Doxorubicin + 150 mg/kg Bacopa treated) and Doxorubicin + 250 mg/kg Bacopa treated) [Magnification: 40x10 X]

Hematoxylin and eosin (H & E)-stained sections of cardiac muscles of rats belonging to control group showed normal looking longitudinal and transverse sections of cardiac muscle fibers. Arrangement of myocardium appeared normal with very little extracellular space with normal looking extracellular matrix. Myocytes looked generally intact. Group 2 showed areas of interstitial myocardial fibrosis (indicated by red arrow) along with some areas of inflammatory cell infiltration (indicated by yellow arrow). In Group 3 B75 exhibited mostly normal cardiac muscle structure with a few areas of interstitial myocardial fibrosis (indicated by red arrow in figure).

It can be noted that the Group 4 and 5 showed normal cardiac muscle structure similar to control (group 1).

DISCUSSION

This experimental study was carried out to assess the beneficial effects of *B.M.* in DOX-induced cardiotoxicity in animal model. The study revealed that DOX-induced cardiac toxicity was alleviated by administering increasing doses of *B.M.*

Cardiac injury induced by DOX primarily involves several mechanisms: oxidative stress and lipid peroxidation, DNA damage, and apoptosis, playing a role in its pathophysiology. Mitochondrial membrane depolarization, facilitated by the release of cytochrome C from mitochondria, plays a crucial role in DOX-induced cardiotoxicity, leading to an overproduction of reactive oxygen species (ROS). Additionally, DOX can create a complex with ferrous iron, further escalating ROS production. DOX binds to DNA topoisomerase-II β, causing DNA damage and triggering the activation of Poly (ADP-ribose) polymerase (PARP). This activation slows down glycolysis and mitochondrial respiration, resulting in cellular dysfunction and necrosis [4].

The administration of BM has demonstrated cardioprotective effects by promoting the recovery of cardiac damage and favourable

vascular effects. Previous studies on *B.M.* have indicated its beneficial effects on cardiac vascular dysfunction, including improved coronary flow and enhanced myocardial function. It exhibits anti-inflammatory and antioxidant effects, along with the reduction of calcium levels, thus offering protection against ischemic cell death [15]. Also, ethanolic extract of *B.M.* lowers blood pressure and has vasorelaxant effect (aorta, basilar, mesenteric, renal lobar, tail and femoral arteries) [16].

Earlier studies utilizing extracts of *B.M.* demonstrated antioxidant. These extracts possess the ability to neutralize superoxide anions and hydroxyl radicals, thereby reducing DNA damage [17]. DOX treatment have shown a strong association between cardiac inflammatory and oxidative stress [18]. Similarly in our study we found increase in oxidative stress and a decrease in antioxidant activity following the administration of DOX. Phytochemical screening of BM revealed the presence of flavonoids, saponins, and triterpenoids in the extract, which were responsible for its antioxidant activity. These components contribute to the protective action against lipid peroxidation and enhance cellular antioxidant defence, thereby safeguarding against oxidative damage. The significant beneficial effect of *B.M.* extract in DOX-induced cardiotoxicity can be attributed to the presence of these components.

Cardiac troponin I (cTnI) serves as a biomarker for assessing the degree of cardiac muscle injury. Raised plasma levels of cTnI indicates cardiac toxicity, and our study revealed an elevation in cTnI levels with cumulative doses of DOX. This rise in cTnI levels is attributed to DOX-induced myocardial damage. However, treatment with *B.M.* significantly reduced troponin I levels. The observed benefits were linked to its capacity to restore damaged cardiomyocytes, as evidenced by histological reports. (Fig. 4)

Earlier studies have highlighted *B.M.'s* ability to scavenge free radicals and protect against DNA damage. Treatment with *B.M.* has been shown to replenish non-enzymatic antioxidants such as Vit-C and Vit-E [19].Similarly, in our study, *B.M.* treatment notably elevated levels of antioxidant enzymes (SOD, GSH) and suppressed lipid peroxidation activity (MDA). The restor]/86+ation of normal cardiac muscle structure and functions was proved in histopathological reports.

CONCLUSION

The study demonstrates *Bacopa monnieri's* potential in alleviating doxorubicin-induced cardiotoxicity in animal models. Doxorubicin's cardiac damage involves oxidative stress and apoptosis, while *Bacopa monnieri* shows cardioprotective effects by reducing free radical-mediated damage to cardiac tissue and restoring the antioxidant activity. The study demonstrates the benefits of *Bacopa monnieri* which can be used as a supplement along with Dox to ameliorate doxorubicin-induced cardiotoxicity.

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