Original Research Article

Cardioprotective effects of extract of *Sclerocarya birrea* stem bark on doxorubicin induced cardiotoxicity in rats

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ABSTRACT

This study aimed to investigate the protective effect of methanol extract of *Sclerocarya birrea (S. birrea)* stem bark on Doxorubicin (DOX) induced cardiotoxicity in rats. Tissue Malondialdehyde (MDA) level was increased in DOX treated group while activities of antioxidant maker enzymes; Catalase (CAT), Superoxide Dismutase (SOD) were significantly decreased. Cardiotoxicity was further confirmed by significant increase in the serum levels of cardiac markers; troponin, creatine kinase, aspartate transaminase and myoglobin in DOX treated group. Histological examinations show that *S. birrea* at 600 mg/kg have improved the heart structural abnormalities induced by DOX. This showed that the *S. birrea* stem bark extract had potential to prevent oxidative damage induced by DOX in the heart and could serve as novel adjuvant antioxidant therapy with chemotherapeutic agents.

***Keywords*:** Doxorubicin, *Sclerocarya birrea*, myocardial infarction, adjuvant, chemotherapeutic

INTRODUCTION

Cardiovascular Disease (CVD) refers to any disorder that affects muscles and vessels of the heart. They are considered one of the major causes of death globally. Heart disease cases nearly doubled over the period, from 271 million in 1990 to 523 million in 2019 [1]. The number of heart disease death rose from 12.1 million to 18.6

million representing 31 % of all global deaths [2]. CVDs are already the leading causes of deaths in woman in the African region [3]. Coronary Heart Disease (CHD) was previously considered to be rare in sub-Saharan Africa, but its prevalence is on the increase mainly because of the increasing prevalence of its risk factors, linked to trends in urbanization and changes in lifestyle [4]. The continuous rise of the disease is a manifestation of some risk factors such as increased blood cholesterol, Low Density Lipoprotein (LDL) cholesterol, LDL oxidation, hypertension, smoking, family history, physical inactivity and obesity [5].

Doxorubicin (DOX) is a broad-spectrum and potent anthracycline antibiotic that has been in use as a first-line chemotherapy to treat varieties of human neoplasms like breast and bladder cancer, as well as other lymphomas. Despite its anticancer efficacy, the clinical use of DOX is limited by dose-dependent cardiotoxicity often leading to cardiomyopathy and heart failure [6]. The high rate of cardiovascular diseases and the huge resources to manage it in sub Saharan Africa has necessitated the search for cost effective and available alternatives. The Role of herbs and their products in treating cardiovascular problems has been extensively reviewed [7,8]. As evident from many reports, DOX is linked to several toxicities due to generation of free radicals and hence, identification of any agent that would minimize the reactive radical generation and increase antioxidant defence would be a great hope to patients [9]. *Sclerocarya birrea* known in Hausa language as *danya* has been used for its medicinal, nutritive, economic potentials. Traditional healers use this plant as a remedy for several conditions including hypertension, malaria, fevers, diarrhoea, dysentery, stomach ailments, boils, rheumatism, blood circulation problems, headaches, toothache, backache and body pains [10]. Others include schistosomiasis, epilepsy, proctitis, gastric, infectious diseases and duodenal ulcers. Survey of medicinal plants used in the treatment of cardiovascular diseases in Sokoto State, reveals that stem bark of *S. birrea* is the frequently used with claims by herbalists to ameliorate complications of heart diseases. It is reported that free radical are involved in the pathogenesis of heart failure sequel to myocardial infarction [11]. The aim of this study was to investigate the cardioprotective potential of methanol extract of *S. birrea* stem-bark on some biochemical indices, Electrocardiogram (ECG) findings and histological studies of

doxorubicin induced myocardial infarction in rats.

MATERIALS AND METHODS

Experimental animals

Male Albino rats with an average weight (177–200 g) were purchased from the Department of Biological Science, Usmanu Danfodiyo University, Sokoto and were handled according to the guidelines contained in the guide for the care and use of laboratory animals and also in accordance with the principles of good laboratory procedure [12]. The rats were housed in an institutional animal facility under standard condition. They were fed with standard pellet diet and fresh water *ad libitum*. All animals were allowed to habituate to laboratory conditions for 7 days before commencement of the experiment.

Plants

Fresh stem-barks of *S. birrea* were purchased from a traditional herbalist in Sokoto State, Nigeria, and authenticated at the Herbarium unit, Department of Biological Sciences, Usmanu Danfodiyo University Sokoto, Nigeria, with voucher specimen number of (UDUH/ANS/0341).

A 600 g of the fresh stem-bark was washed, made into pieces and air-dried. It was then pounded to fine powder using motar and pestle. The powder was macerated in methanol for 72 h with occational shaking. The mixture was then filtered using muslin cloth (2 mm). The filtrate was concentrated under reduced pressure in a rotary evaporator (Bibby Rotary evaporator, ShanghaiEyela. Co Ltd.China). The crude brown solid extract was kept dried at room temperature and used throughout this study without further purification.

Chemicals

Doxorubicin hydrochloride (India), vitamin E (Greece), ketamine and xylazine were used. All other chemicals used were of analytical grade and purchased from Hali Shuaibu scientific chemicals (Sokoto, Nigeria).

Induction of cardiac toxicity by DOX was done by dissolving it in normal saline and injected intraperitonially [13] to rats at (20 mg/kg bodyweight) on the 14th day after the last dose of the extracts to induce experimental myocardial infarction [14].

The rats were randomly divided into 6 groups consisting of seven rats each, while the DOX treated group has 10 rats for fear

of mortality from pilot study and reports from Ferreria *et al.* [15].

The rats were treated as follows:

- **Group 1 (Normal Control)** Received normal saline (10 ml/kg body weight) orally for 16 days.
- **Group 2 (DOX treated)** Received normal saline (10 ml/kg body weight) orally for 14 days followed by a single dose of doxorubicin (20mg/kgbody weight) intraperitonially on the 14th day (DOX treated group)
- **Group 3 (Sb 200 mg/kg + DOX)** Received methanol extract of *S.birrea* (200 mg/kg body weight) orally for 14 days followed by a single dose of doxorubicin (20 mg/kg body weight) intraperitonially on the 14th day.
- **Group 4 (Sb 400 mg/kg + DOX)** Received methanol extract *S.birrea* (400 mg/kg body weight) orally for 14 days followed by a single dose of doxorubicin (20 mg/kg body weight) intraperitoneally on the 14th day.
- **Group 5 (Sb 600 mg/kg + DOX)** Received Methanol extract *S.birrea* (600 mg/kg body weight) orally for 14 days followed by a single dose of doxorubicin (20 mg/kg body weight) intraperitoneally on the 14th day.
- **Group 6 (Vit E 100 mg/kg +DOX)** Received of vitamin-E (100 mg/kg body weight) for orally for 14 days followed by a single dose of doxorubicin (20 mg/kg body weight) on the 14th day.

***Electrocardiogram measurement* (ECG)**

Baseline ECG was recorded on the 14th day after the last dose of the *S. birrea* extract and before DOX induction. Another record was taken two days after induction (day 16) to detect if there were any changes in the ECG of the rats. Experimental rats were anesthesized using a combination of ketamine (50 mg/kg) and xylazine (10 mg/kg) intraperitonally. Rats were then placed on a wooden table to avoid electrical interference while both the recorder and assistant wore latex hand gloves. The five electrodes were applied to similar positions on the four limbs and the ventral thoracic region according to the manufacturer's instructions (EDAN VET ECG USA). Resting ECG was recorded for a minute while heart rate variability recording was done for 5 min and analyzed on computer software.

Sample collection

Blood samples were drawn from the animals by retro orbital puncture into a plain tube and after about 15 min, it was centrifuged at 4000 rpm for 10 min. The serum was then be aspirated and transferred to other sets of clean labelled sample tubes and stored at -4 °C.

The heart tissues were homogenized in 5 ml of Phosphate-Buffered Saline (PBS) (0.01M, pH 7.2) using a tissue homogenizer (name) to remove excess blood clots. The homogenate was centrifuged at 4,000 rpm for 20 min. The clear supernatant were aspirated into clean sample tubes and used for assay of lipid peroxidation marker and antioxidant activities of cardiac homogenate (CAT, SOD and GSH).

Histopathology was done using the method of Drury *et al.* [16]. The study was conducted at the histopathology unit of Usmanu Danfodiyo University Teaching Hospital, (UDUTH), Sokoto Nigeria. Random heart tissue from each group was fixed in either 10 % buffer formalin for 72 h or in 4 % aqueous solution of formaldehyde at neutral pH. Samples from the heart were dehydrated using alcohol and embedded in liquid paraffin. The embedded tissue was then trimmed, and mounted on a microtome. Thin sections were cut and stained with hematoxylin and eosin for photomicroscopic study. Photomicrographs of samples were taken. The slides were viewed under light microscope at X40, X100 and X400 magnifications.

Biochemical Analysis

Phytochemical screening to test for the presence of flavonoids, tanins, saponins, glycosides alkaloids, cardiac glycosides, steroids, saponin glycosides, balsams, anthraquione, volatile oils and phenols were conducted using the methods of (El-Olemy *et al.* [17], Harbone [18], Trease and Evans [19], and Sofowora, [20]). Similarly, quantitative analysis was done to estimate the contents of present secondary metabolities from the methods of Bohm and Koupai [21], Obadoni and Ochuko [22], Elizebeth and Kelly [23], and vitamin E by the method of Rutkowski *et al.* [24].

Analysis of Antioxidant Activity

The antioxidant potential of *S. birrea* stem bark extracts was investigated by 2, 2 diphenyl-1-picrylhyrazyl (DPPH) and Ferric Reducing Antioxidant Power (FRAP) assay using the methods of Gowchin Yen and Hui-yin chen [25] and Oyaizu, [26], respectively.

Analysis of Biochemical Parameters

Determination of Lipid Peroxidation

Malondialdehyde (MDA) as an index of lipid peroxidation was estimated using the method of Hartman [27].

Assays for the Activities of Antioxidant Enzymes

Catalase (CAT) activity was assayed according to the methods of Beers and Sizer [28].

Superoxide dismutase (SOD)

SOD activity was assayed using the method of Zou *et al.* [29].

Reduced glutathione (GSH)

The level of GSH is assayed using the method of Patterson and Lazarow [30].

Cardiac Troponin I (CTnI)

cTnI was estimated with Pars Biochem Rat Troponin I ELISA kit using the principle of Apple *et al.* [31].

Myoglobin (MYO)

Myoglobin (MYO/MB) was estimated using Pars Biochem Rat Myoglobin ELISA kit using the principle of Apple *et al*. [32].

Creatine Kinase Myocardial Band (CK-MB)

CK-MB was determined using ELISA kit (CHEMLEX LABKIT Ind. SPAIN).

Aspartate aminotransferase (AST)

Serum AST was determined using spectrum diagnostic kit through the method of Henry *et al.* [33].

Statistical Analysis

Data was expressed as Mean±Standard Deviation (SD), and were analysed using one-way Analysis of Variance (ANOVA) followed by turkey multiple comparison tests. Limit of statistical significance was set at (p<0.05).

RESULTS

Phytochemical and quantitative analysis

The analysisof phytochemical constituents and their quantifications in the methanol extracts of *S. birrea*revealed that the extract contained more of tannins (51.98 mg %), followed by saponins (7.71 mg %), flavonoids (4.59 mg %) and alkaloids (2.58 mg %), respectively as presented in Table 1. The phytochemicals are shown to play vital role in the treatment of cancer and other complex conditions.

In order to study the antioxidant potential of *S. birrea* extract, DPPH was used to investigate the radical scavenging activity against standard ascorbic acid. Figure 1 shows that *S. birrea* extract have high free radical scavenging activity. *S. birrea* showed reduced DPPH scavenging activity at lower concentrations of 0.2 and 0.4 mg/ml, respectively. It was also observed that radical scavenging activity was slightly higher at concentrations of 0.6 and .08

mg/ml and similar activity at concentration of 1 mg/ml when compared to ascorbic acid.

The electrocardiograph abnormalities on the effects of *S. birrea* are shown in Figure 2. The study shows alteration of ECG patterns in DOX administered rats as compared to normal control rats (Figure 2). The ECG pattern showed elevated ST segment, significant increase in the heart rate , irregular R-R intervals, prolonged QT and QTc intervals, altered QRS complex, altered P and T wave, and PR intervals. These characteristic alterations were improved following a dose dependent pretreatment of *S. birrea* extract to normal.

In addition, the ECG parameters were also recorded after 48 h of DOX injection (20 mg/kg), the ECG of different groups was compared. Rats treated with a single dose of doxorubicin (20 mg/kg) has shown significant increase ($p< 0.05$) in the heart rate (HR), prolonged QT, QTc, PR interval, QRS complex, P and T wave, and PR interval (Table 2) compared to the normal control. These ECG abnormalities have significantly attenuated in rats pre-treated with *S. birrea* extract in a dose-dependent manner.

The effect of the *S. birrea* methanol extract on lipid peroxidation using MDA as a marker was investigated. It was observed that the level of MDA increased significantly ($p <0.05$) in cardiac tissues of rats exposed to DOX as compared to the control group. However, prior administration of *S. birrea* methanol extract significantly reduced the level of MDA ($p<0.05$) in a dose dependent manner as presented in Figure 3 in comparison to the control group and vitamin E pre-treated group also showed a significant decrease ($p< 0.05$) in MDA as compared to the DOX treated group.

The influence of the extract on the antioxidant activities was also estimated. Figures 4, 5 and 6 show the protective effect of the extract on activities of antioxidant enzymes in the cardiac tissue. In comparison with the control group, the activities of CAT, SOD and GSH level were decreased significantly ($p<0.05$) after the innoculation of DOX. The extract at 200 mg/kg shows no significant increase ($p<0.05$) in the enzyme activities when compared to DOX treated group. Pretreatment with the extract at high doses significantly increase ($p<0.05$) the activities of all the antioxidant enzymes in the rat tissues. Vitamin E pretreated group also indicate significant increase ($p<0.05$)

in the activities of CAT, SOD and GSH level as compared with DOX treated group.

Serum cardiac biomarkers were investigated to determine the biochemical effect of the extract on myocardial damage markers in all the groups. Animals treated with DOX produced significant increase ($p<0.05$) in the levels of TROP, MYO, CK-MB and AST compared to normal control. However, animals receiving prior treatment with *S. birrea* extract indicate a dose dependent reduction ($p<0.05$)of these biochemical markers in the cardiac tissues and at high dose, it was statistically similar to that of Vitamin E treated group.

Table 1. Phytochemical and quantitative analysisof methanol extract of *S. birrea* stem bark

Parameter	**Inference**	**Concentration (mg %)**
Flavonoids	+	4.59
Tannins	+	51.98
Saponins	+	7.71
Glycosides	+	-
Alkaloids	+	2.58
Steroids	+	–
Saponin glycosides	+	–
Volatile oils	+	–
Antheraquinones	ND	–
Balsams	+	–
Cardiac glycosides	+	–
Phenol	+	–
Total phenol compounds		12.58
Vitamin E		7.08

+: Presence of the phytochemical constituents, ND: not detected

Table 2. Effect of *S. birrea* stem bark extract on ECG durations on experimental groups

Group/ parameter	HR (pbm)	P(msec)	PR(msec)	QRS(msec)	QT(msec)	QTc(msec)
Group 1	278.6±2.07a	36.4±1.14a	43.6±0.89a	17.6±0.55a	110.0±1.58a	255.0±1.23a
Group 2	366.0±0.71b	39.6±0.89b	53.6±0.89b	20.4±0.55b	147.6±0.55b	356.0±0.00b
Group 3	338.8±4.82c	38.2±0.84b	52.0±1.58b	19.0±0.71b	138.6±0.89ab	326.0±3.46ab
Group 4	324.8±4.26d	37.6±1.14a	47.2±0.83ab	18.4±0.55b	126.8±1.10c	284.8±1.10c
Group 5	298.6±5.12ab	36.8±0.83a	45.0±0.70ab	18.2±0.45b	116.2±0.45d	266.4±0.89d
Group 6	284.2±7.29a	36.6±1.14a	43.2±0.84a	17.8±0.45a	111.6±0.89a	261.6±0.89d

Values are expressed as mean ± SD of five replicates. Mean values with different superscript in a column are significantly different at $p< 0.05$ using one way analysis of variance (ANOVA) followed by turkey multiple comparison test.

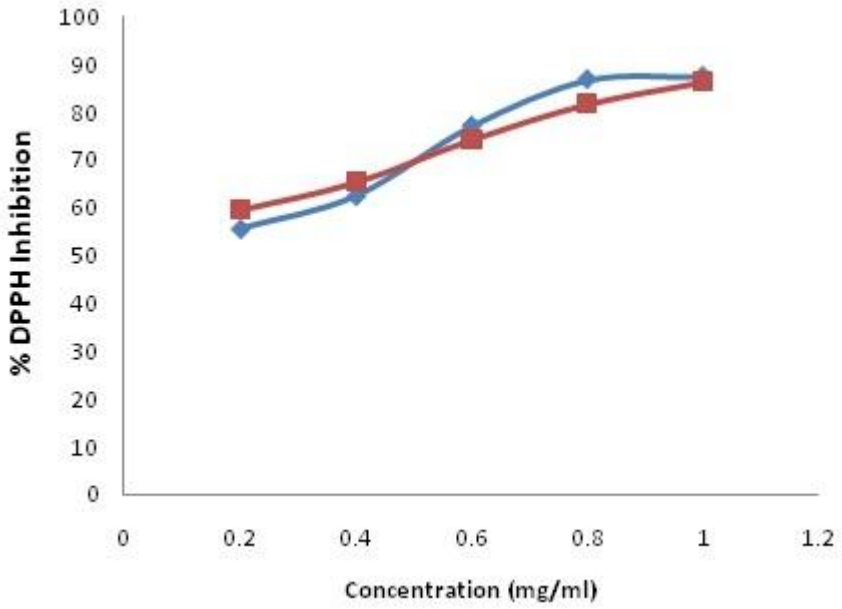

Figure 1. Percentage of DPPH inhibition of *S. birrea* against an ascorbic acid standard showing dose-dependent inhibition potential.

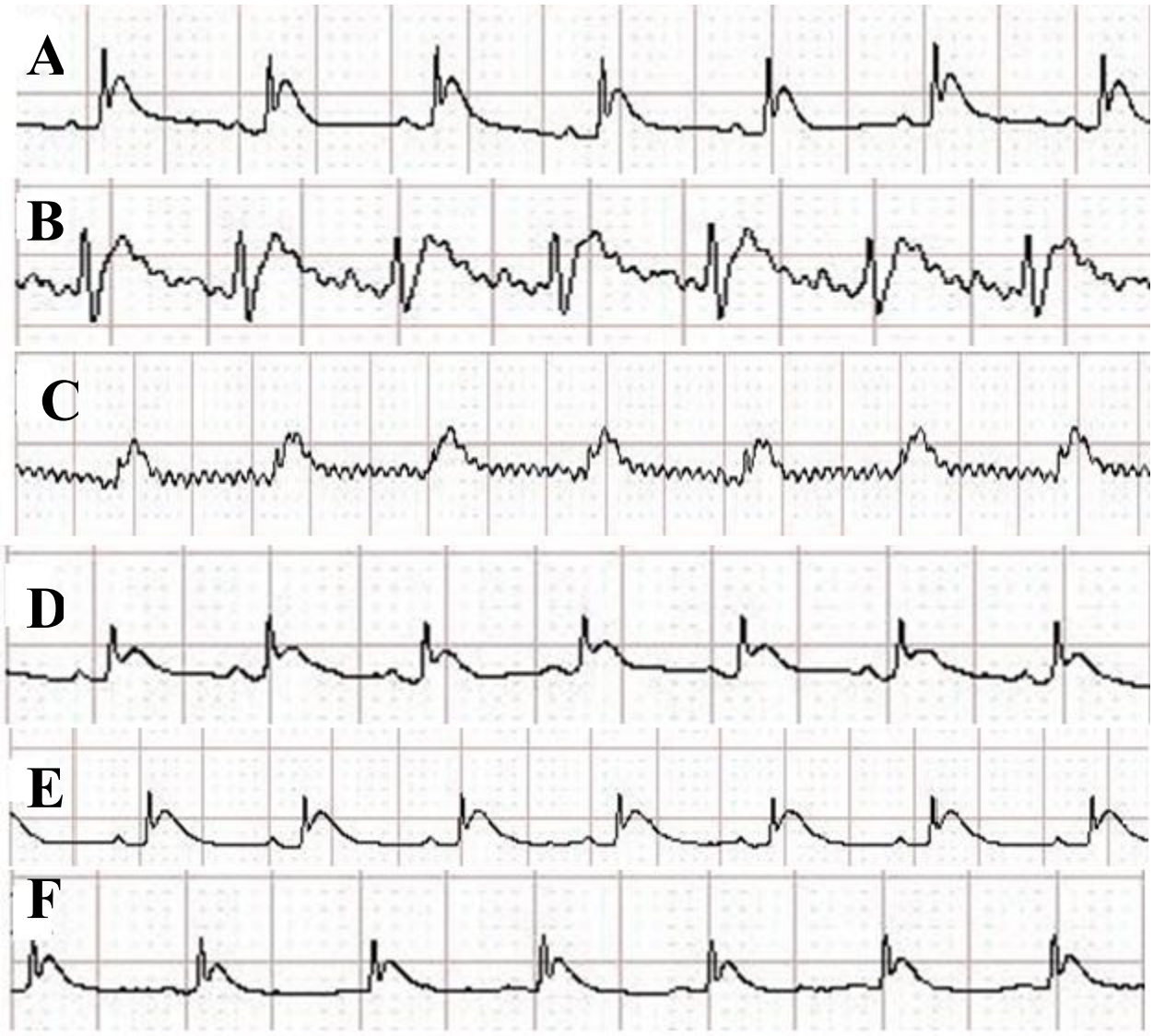

Figure 2. (A) ECG of normal control rat bearing normal P, QRS, T and regular R-R interval (normal rhythm).(**B)** ECG of group 2 rat showing Tall and biphasic P and T wave, irregular R-R interval with increased heart rate. (**C)** ECG of group 3 rat showing increased heart rate irregular R-R intervall. T wave taller than R, no P wave. (**D)** ECG of group 4 showing normal P, a wider T wave,regular R-R interval, increased heart rate and QRS. (**E)** ECG of group 5 rats showing normal P, QRS and T. (**F)** ECG of group 6 rat showing normal P, QRS and T waves.

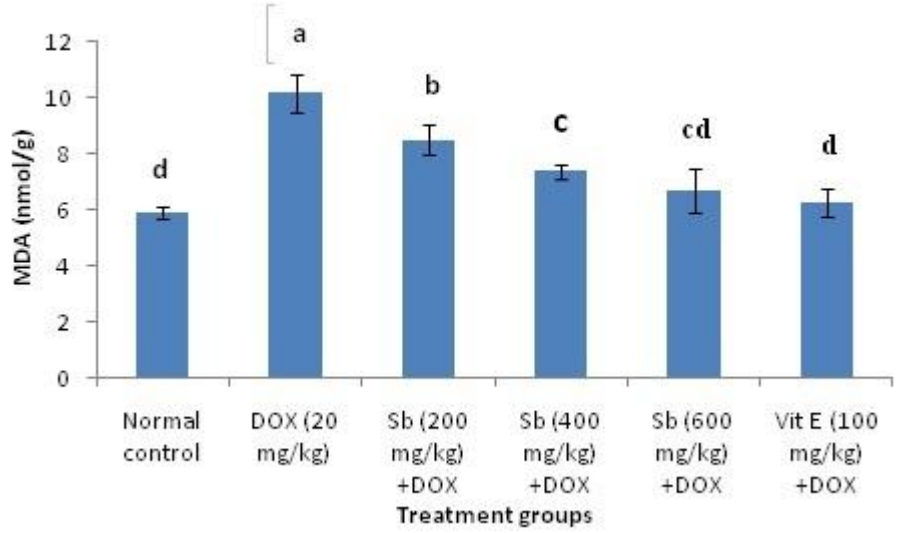

Figure 3. Effect of methanol extract of *S. birrea* stem barkon lipid peroxidationof cardiac tissue.

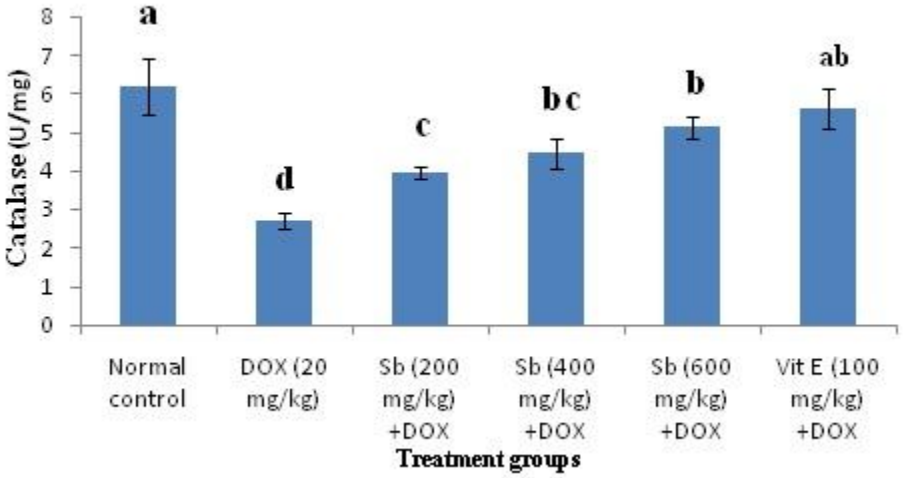

Figure 4. Effect of *S.birrea* stem bark extract on catalase activity in cardiac tissue.

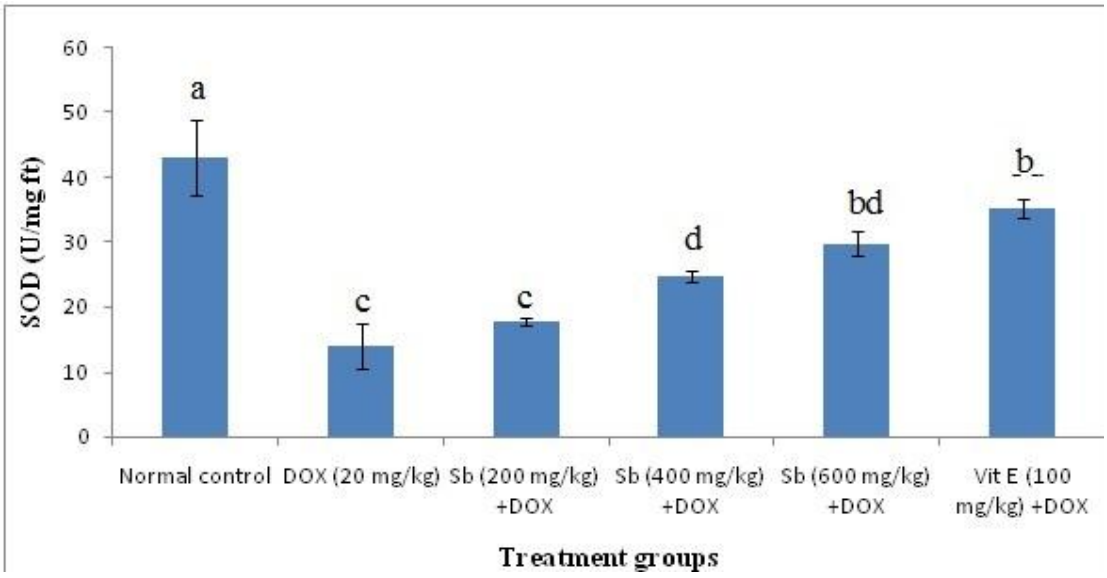

Figure 5. Effect of *S.birrea* stem bark extract on SOD activity in cardiac tissue.

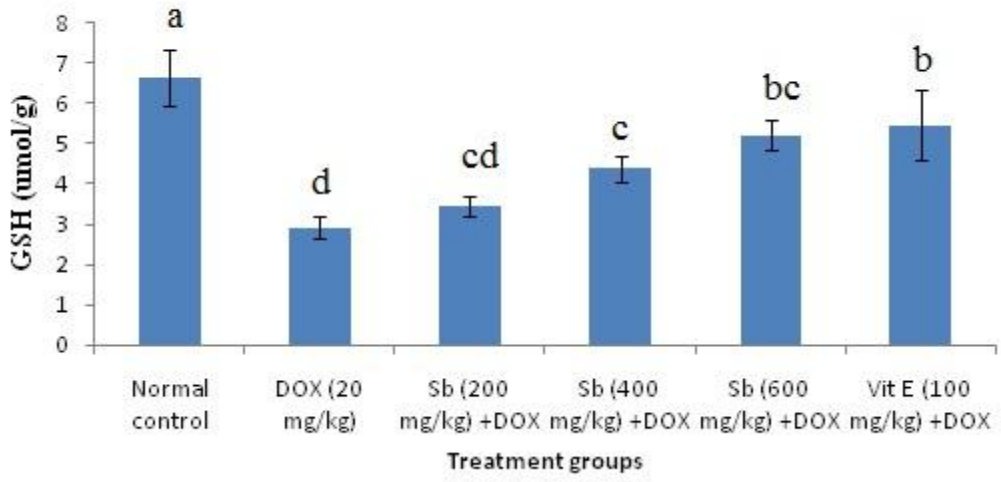

Figure 6. Effect of *S.birrea* stem bark extract on GSH in cardiac tissue.

Effect of S. birrea stem bark extract on the heart tissue histopathological Changes

Control group rats were microscopically examined and there was unaltered historarchitecture of the cardiac tissues at X 40, 100 and 400 magnification of the original size (Figure 7). DOX treated group cardiac tissue samples revealed

evident myocardial alterations within all examined groups. Alterations were in form of myocardial fibres architectural disarray along with congested vessels and severe haemorrhage. Groups 3 cardiac tissue samples also expressed a degree of histologic cardiomyocytes alterations, when compared to DOX treated group. Rats pretreated with high doses of *S. birrea* groups displayed milder microscopic alterations of cardiomyocytes in respect to both the extent and severity. On the other hand, these alterations were minimal in rats pretreated with vitamin E as compared to DOX treated group.

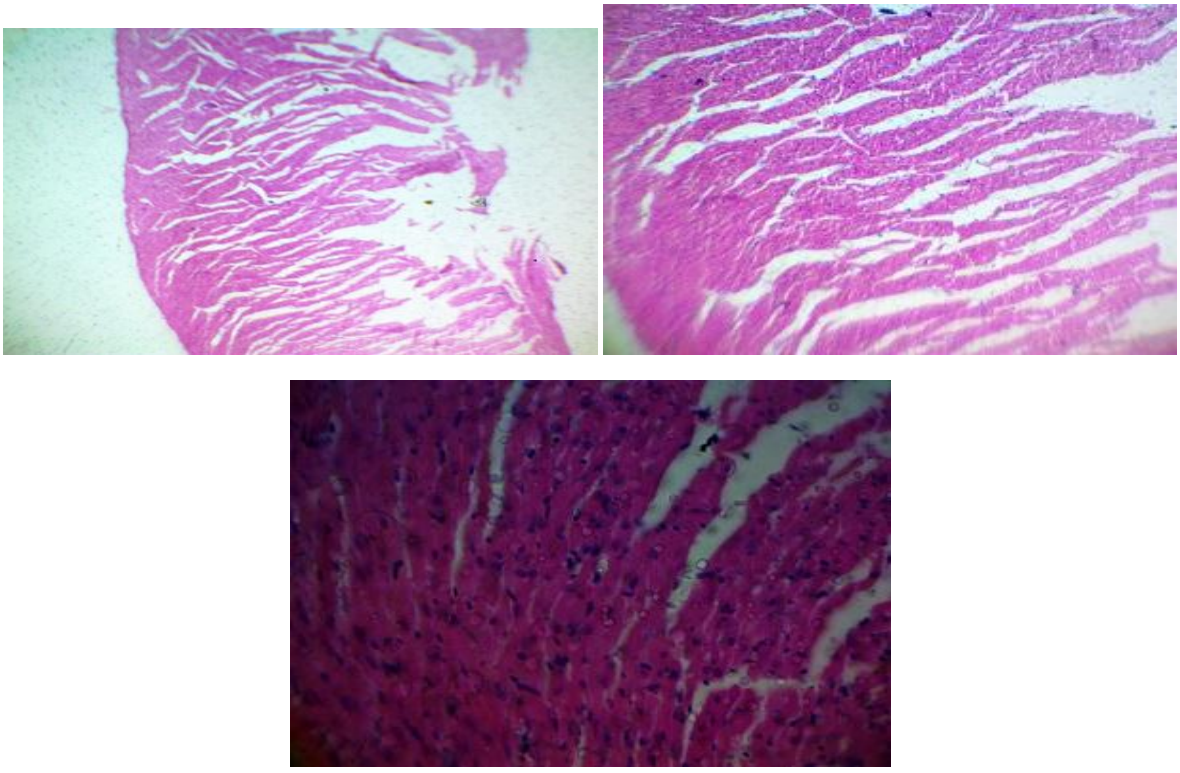

Figure 7. Micrographs of group 1 rat heart showing normal architectural structure. (a) X 40(b) X 100 (c) X 400 magnification.

DISCUSSION

Doxorubicin is an effective and widely used chemotherapeutic agent but its clinical use is limited due to off target dose dependent cardiotoxicity through increased oxidative stress resulting in heart failure. It has been studied that antioxidant treatment provides possible protection against DOX mediated cardiotoxicity. In view of that, medicinal plants are being investigated for their possible therapeutic potential against ROS induced damages. Preliminary phytochemical analysis of *S. birrea* stem bark revealed the presence of tannins, alkaloids, flavonoids, glycosides, cardiac glycosides, steroids, volatile oils, phenols and saponins. *S. birrea* provides a substantial source of secondary metabolites which acts as natural antioxidants.In addition to this, Aganga and Mosase [34] reported that bark from *S. birrea* contains a significant amount of high molecular weight tannins .This report however correlates with the results obtained in this study with 51.98 mg % of tannin in the stem bark extract. Abundance of flavonoids in this report shows that the antioxidant activity of flavonoids is recognised by their strong chain-breaking actions, thereby protecting cells against the detrimental effects of ROS. These secondary metabolites are reported to have biological and therapeutic properties. The results of the present study extend previous observations that *S. birrea* stem-bark extract exerts appreciable antioxidant activity. Two antioxidant assays of *S. birrea* stem bark extract were in agreement with earlier studies by Russo *et al.* [35] and Moyo *et al.* [36] reported high antioxidant activities. In this report, the methanol extract of the plant showed high propensity to quench DPPH free radicals as high as 87.5 %, compared to ascorbic acid which is used as standard. The scavenging activity was slightly higher at 0.6 and 0.8 mg/ml and was equal at 1.0 mg/ml. This corresponded to a rapid decrease in absorbance in the presence of a plant extract, indicating high antioxidant potency of the extracts in terms of electron or hydrogen atom-donating capacity. Similarly, the stem bark extract was assessed for their ability to reduce the Fe^{3+}/ferricyanide complex to the ferrous (Fe^{2+}) form. The result presents the dose-dependent ferric-reducing powers of the sample extracts and ascorbic acid. The reducing power of ascorbic acid was significantly more pronounced relative to the plant extracts. Nevertheless, *S. birrea* stem-bark extracts have the capacity to act

as electron donors, indicating their potential to react with free radicals, which they can convert to more stable products. This indicates that secondary metabolites in *S. birrea* stem bark could have played these roles. The effects could probably be ascribed to the presence of tannins in the plant. As natural antioxidants, tannins play important role in scavenging free radicals and preventing degenerative diseases such as cardiovascular diseases [37]. In fact flavonoids, phenolic derivatives and tannins have been reported to possess various nutritional and medicinal properties such as immunomodulating effects, antibacterial, antifungal, antiviral, free radical scavenging, anti-inflammatory, anti-diarrhoeal and anti-tumour activities [38,39], and their presence could be responsible for its antioxidant activity. Studies coined from different research has shown that naturally occurring vitamin E forms as α-tocopherols have antioxidant properties widely distributed in plants. It functions as a lipid-soluble biological antioxidant and protects against lipid peroxidation through the scavenging of free radicals [40].

Visible signs of general weakness with diarrhoea, redness in the eye and nostrils, scruffy fur, and necrosis at injection site have been seen in the DOX-treated group. These observations were significantly less in rats pretreated with *S.birrea*at 600 mg/kg. This suggests that the extract could prevent the detrimental effect of DOX.

Electrocardiograph abnormalities are the main criteria generally used for a definite diagnosis of myocardial infarction [41]. ECG exam was also recorded to observe changes in the rats electrophysiology. The administration of DOX resulted in significant elevation in heart rate compared to the control group. The ECG shows tall and biphasic or fluttering P and T wave, irregular R-R interval, indicating left atrial and ventricular fibrillation and increased heart beat (tachycardia) which could be sign of pathology or chronic infarction. At higher doses of 400 and 600 mg/kg, and Vitamin E, it prevented the pathological alteration in ECG induced by doxorubicin. These results was consistent with other studies where it was hypothesized that reactive oxygen species generation may cause disturbance in calcium homeostatsis through increase in intracellular calcium of pace-maker cells in the sinoatrial node and other cells in the cardiac conducting system, thus increasing the heart rate [42].

Doxorubicin induces endogenous lipid peroxidation through persuaded production

of oxygen free radicals. In this study, the rise in MDA level was mitigated by prior administration of *S. birrea*. The ameliorative effect of the extract might be due to reduction of lipid peroxidation through its antioxidant activity achieved by its active compounds. The cardiac antioxidant defence system was also challenged due to doxorubicin effect, activities of the cardiac antioxidant enzymes; CAT, SOD and GSH level, was significantly reduced in DOX treated group. This indicates that the defensive abilities of these antioxidant enzymes seem to be swamped up by enhanced ROS. It is however also likely that the heart was attempting to detoxify ROS but this effort was insufficient and the defence system was overwhelmed. Pretreatment with the extract however showed remarkable significant increase in the activities of these enzymes and demonstrating a potent relationship between oxidative stress and lipid peroxidation in doxorubicin induced cardiomyopathy [43].

Similarly, administration of doxorubicin induced cardiotoxicity manifested by significant increase in serum troponin, Myoglobin (MYO) CK-MB, and AST. The serum levels of biomarkers in groups pretreated with *S.birrea* extracts also mitigated this significant increase in a dose-dependent manner. The reduction in the protein and enzyme level from the result indicates that the extract is responsible for maintenance of normal structural and architectural integrity of the cardiac myocytes, thereby restricting the leakage of these enzymes, accounting for membrane stabilizing property of *S. birrea*. This suggests that there could be a synergic effect among the phytochemical constituents and vitamin E content of the extract; thus, it could pass as a successful candidate for cardioprotection.

DOX generates reactive oxygen species which play a vital role in the development of cardiotoxicity and gives an insight of pathology [44]. In this study, a representative of the heart histological appearance of each group was studied. Cardiac tissues of DOX-treated rats showed widespread marked architectural abnormalities such as severe vascular congestion, haemorrhage and cellular infiltration. However, at the highest dose of 600 mg/kg, the extract reduced these abnormalities of the heart tissues to normal.

CONCLUSION

In conclusion, the present study reported the protective effects of *S. birrea* against doxorubicin induced myocardial infarction in rats. The ECG abnormalities (Prolongation of QRS, QT interval) and heart rate caused by DOX was observed to change towards normal following pretreatment with *S. birrea* extract. Pretreatment with *S. birrea* extract in a dose dependent manner significantly ($p<0.05$) decreased lipid peroxidation and consequently increased the level of GSH and activities of weak endogenous antioxidant enzymes (CAT, SOD,) caused by the detrimental effect of doxorubicin. The extract also showed a significant decrease ($p<0.05$) in clinical makers of myocardial infarction (cTnI, MYO, CK-MB and AST) in a dose dependent manner. In conclusion, collective results from phytochemical, electrocardiographic, biochemical, and histopathological parameters provides potential cardioprotection against DOX toxicity and thus, *S. birrea* effectively prevented tissue damage by decreasing the oxidative stress through antioxidant therapy which could be attributed to its free radical scavenging activity, making it a suitable candidate to ameliorate myocardial infarction caused by doxorubicin.

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