



## **Doxorubicin-induced cardiotoxicity in Albino rats protected by *Adansonia digitata* (Baobab) leaf extract.**

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**Abstract:** Cardiovascular disease is the world's leading cause of death, killing between 17 and 19 million people each year. The usage of traditional drugs was influenced by the need for effective medications for the treatment of cardiovascular disease without side effects. The cardio-protective impact of *Adansonia digitata* leaf extract on doxorubicin-mediated cardiotoxicity was investigated in laboratory rats in the current research. Thirty-five albino rats were divided into five classes, each consisting of seven animals. Group 1 was given filtered water as a control, while Group 2 was given saline and doxorubicin, Group 3 received doxorubicin and Vitamin E, and Groups IV and V were myocardial oxidative animals treated with *Adansonia digitata* leaf extract (150 and 300 mg/kgbw) for two weeks. After the rats were sacrificed, their hearts were collected and homogenized for biochemical assays. The results on the activities of creatinine kinase (CK), lactate dehydrogenase (LDH), aspartate amino transferase (AST), nitric oxide synthase (NOS), superoxide dismutase (SOD), catalase (CAT), and malondialdehyde were determined. Histopathology examination was used in addition to assays to validate myocardial damage. In comparison to the control group, rats provided doxorubicin showed a significant increase in the activities of cardiac marker enzymes (CK, LDH, and AST), as well as a significant increase in malondialdehyde concentration with a concomitant decrease in antioxidant enzymes (SOD, CAT, and NOS), implying cardiotoxicity. In rats with doxorubicin-induced myocardial infection, pretreatment with *Adansonia digitata* leaf extract reduced myocardial damage and increased antioxidant defense, and these biochemical results were confirmed by histopathology. Finally, the new study demonstrates that *Adansonia digitata* has cardioprotective properties.

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**Keywords:** Cardiovascular disease, *Adansonia digitata*, doxorubicin, cardiotoxicity, leaf extract

### **Introduction**

Acute lymphocytic leukemia, breast cancer, bladder cancer, kaposi sarcoma, lymphoma, and lymphoma are also treated with doxorubicin (DOX) (Brayfield, 2013). It belongs to the anthracycline antibiotic family which functions by interacting with DNA activity. This medication's side effects include baldness, marrow suppression, weakness, itch, and mouth inflammation. Possible adverse effects include allergic reactions such as anaphylaxis, as well as heart injuries. Dilated cardiomyopathy, or cardiac failure, is the most serious doxorubicin side effect. Dilated cardiomyopathy is caused by doxorubicin-induced cardiomyopathy, which causes all four heart chambers

to swell (Chaterjeet al., 2010). This causes systolic and diastolic instability, as well as cardiac disease, which has a 50% mortality rate (Felkeret al., 2000; Jensen et al., 2002; Chaterjeet al., 2010). As a result of the adverse effects of commercially approved synthetic cardioprotective medicines. The cardioprotective properties of certain protected medicinal plants have been investigated. (AlthafHussainet al., 2012; MukeshNandareet al., 2013; PriyaSaxena andDhramueerPanjanwi, 2014). *Adansonia digitata*, also known as Baobab, is the *Adansonia* family's most commonly spread tree species and is native to Africa (Salimet al., 2012). Baobab is a multipurpose tree that produces berries, clothing,

medication, and raw materials for a range of items. The baobab fruit pulp, nuts, bulbs, stems, and bark are all edible (Yazzieet al., 1994; Sidibe and Williams, 2002; Caluweet al., 2009; Chadareet al., 2009; Chadare, 2010). Vitamin C, calcium, phosphorus, carbohydrates, fibers, potassium, protein, and lipids are all found in abundance in this fruit (Diopet al., 1988; Eromosoleet al., 1991; Odetokun, 1996; Chadareet al., 2009; Mona et al., 2016). Malaria, tuberculosis, fever, microbial infection, diarrhea, anemia, dysentery, toothache, inflammation, and asthma are only a few of the illnesses that the plant's various sections are used to handle (Watt and Breyer - Brandwijk, 1962; VanWyk and Gericke, 2000; Brenderet al., 2003; Tapsoba and Deschamps, 2006; Wickens and Lowe, 2008; De Caluweet al., 2009; Ngutaet al., 2010). *Adansonia digitata* fruit offered cardioprotective effect from isoproterenol-induced myocardial damage (Mona et al., 2016). There is, however, no scientific evidence that *Adansonia digitata* leaf has cardioprotective properties. As a result, the aim of this study was to investigate whether a methanolic extract of *Adansonia digitata* leaf affected cardiac marker enzymes and oxidative stress markers in rats suffering from doxorubicin-induced myocardial infarction.

## Materials and Methods

### Plant Materials and Preparation of Methanolic Extract

Fresh leaves of *Adansonia digitata* (Voucher no: LHO 544) were collected from the Ladoko Akintola University of Technology Staff School Area, Ogbomoso, Oyo State, Nigeria, and classified and checked at Botany Section of the Department of Pure and Applied Biology, Ogbomoso. The plant leaves were air dried, powdered, measured, and soaked in cold methanol for 5 days before being condensed in a rotary evaporator and permitted to evaporate at room temperature to produce the semi-solid material known as the methanolic extract.

### Chemicals and Drugs

The majority of the chemical materials utilized during the study came from Sigma Chemicals Co. (St Louis, Mo, USA). Doxorubicin was provided by Pfizer Global Pharmaceutical Limited in Nigeria.

### Experimental Animals

Mature male Laboratory rats whose weight range between, 200g to 250g were obtained from my institution's Anatomy Department's animal house. The animals were housed in ventilated plastic cages with free access to water and a standard pellet diet.

### Design of experiment

The rats (35 in total) were divided into five groups, each with seven animals. Group I was provided purified water as a control, while Group II received regular saline and DOX (85mg/kgbw) intraperitoneally, Group III received vitamin E (150mg/kgbw) and DOX (85mg/kgbw) intraperitoneally, Group IV received 150mg/kgbw of the extract and DOX (85mg/kgbw) intraperitoneally, and Group V received 300mg/kgbw of the extract. The extract was provided for twenty-eight days, followed by five days of doxorubicin treatment.

### Blood Collection and Heart Homogenate Preparation

Cervical dislocation was used to sacrifice rats from both groups. To collect plasma for biochemical assays, blood was obtained from the heart into well-labeled heparinised bottles and centrifuged at 4,000 rpm for 5 minutes. The heart was quickly removed and rinsed in 1.15 percent KCl before being dried, weighed, and homogenized in a chilled 10mM Tris/HCl buffer pH 7.4 and 0.25M sucrose solution. To obtain the supernatant for biochemical assays, the homogenate was centrifuged at 12,000rpm for 60 minutes.

### Biochemical Analysis

#### Cardiac Biochemical Markers Estimation

Wurzburg et al. (1976) and Szasz et al. (1978) methods were used to determine the activity of creatinine kinase (CK). The activity of lactate dehydrogenase (LDH) was determined using the Witt and Trendelenburg method. The cardiac aspartate amino transferase (AST) activity was measured using the colorimetric system of Reitman and Frankel (1957), as defined by Ochei and Kolhatkar.

#### Cardiac Antioxidant Markers Estimation

The activity of superoxide dismutase (SOD) in the heart was measured using Misra and Fridovich's (1972) method, which was later modified by Kakkaret al. The activity of catalase was determined using the Aebi method (1974). The activity of nitric oxide synthase (NOS) was determined using the Marcocci et al. (1994) method. The level of lipid peroxidation as malondialdehyde (MDA) was determined using the Varshney and Kale principle (1990).

### Histological Analyses

The hearts were removed and immediately rinsed in saline before being fixed in 10% buffered formalin. The hearts were embedded in paraffin, sectioned at 5 $\mu$ m, and stained with haematoxylin and eosin after being stored in 10% buffered formalin. The histological changes in these sections were examined under a light microscope.

**RESULTS****Estimation of Cardiac Biochemical Markers**

Table 1 summarizes the effects of doxorubicin and *Adansonia digitata* methanolic extract on cardiac marker enzyme activities (CK, LDH, and AST). Doxorubicin caused significant myocardial damage, resulting in a significant ( $P < 0.05$ ) increase in cardiac LDH, CK and AST activities in pathogenic rats (Group II) when compared to the control rats (Group I), whereas methanolic leaf extract (Group IV and Group V) and Vitamin E treatment (Group III) significantly decreased the elevated activities of cardiac CK, LDH, and AST, as shown in Figure 1.

**Estimation of Cardiac Antioxidant Markers**

When comparing the pathogenic group (Group II) to the control group (Group I) rats, the activities of myocardial endogenous antioxidant markers (NOS, CAT, SOD, and MDA) were significantly reduced ( $P < 0.05$ ), but these reductions were significantly reversed in Groups III, IV, and V rats (Table 2 and Fig. 2). Pretreatment with a *Adansonia digitata* methanolic extract and Vitamin E significantly reduced the elevated level of malondialdehyde in Group II compared to Group I. (Table 2 and Fig. 2).

**Table 1: The effect of methanolic extract of *Adansonia digitata* on creatinine kinase, lactate dehydrogenase and aspartate aminotransferase activities in doxorubicin-induced myocardial injury in rats**

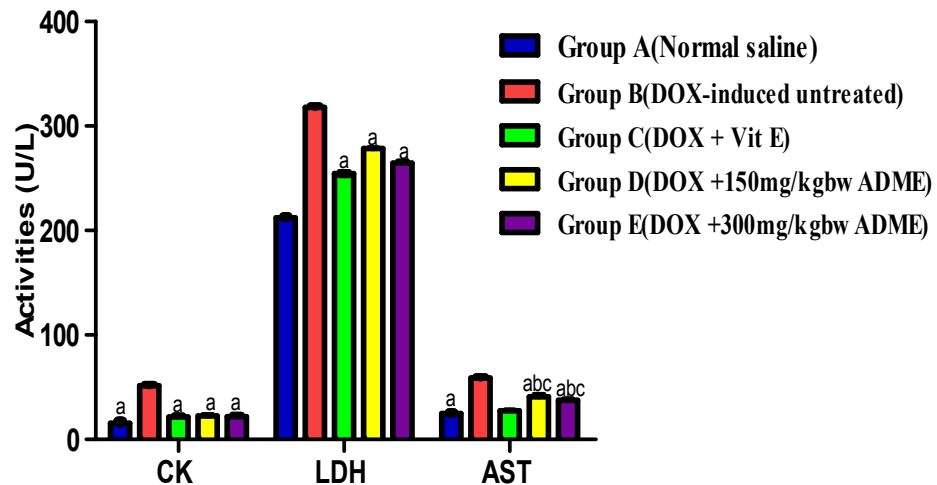
PARAMETERS	GROUP A (Normal saline)	GROUP B (DOX-induced untreated)	GROUP C (DOX-induced + Vit. E)	GROUP D (DOX-induced + 150mg/kgbw ADME)	GROUP E (DOX-induced + 300mg/kgbw ADME)
CK (U/L)	15.40 ± 1.97 <sup>a</sup>	51.63 ± 0.75	21.65 ± 1.60 <sup>a</sup>	22.64 ± 0.97 <sup>a</sup>	21.68 ± 1.99 <sup>a</sup>
LDH (U/L)	212.13 ± 0.91	317.73 ± 1.50	254.63 ± 1.68 <sup>a</sup>	278.50 ± 0.21 <sup>a</sup>	264.58 ± 1.3 <sup>a</sup>
AST (U/L)	24.78 ± 0.71 <sup>a</sup>	58.73 ± 0.97	27.38 ± 0.57	40.98 ± 1.81 <sup>abc</sup>	37.48 ± 1.18 <sup>abc</sup>

The values are represented as mean SEM, with n = 7 rats and were reported significant at ( $P < 0.05$ )

<sup>a</sup> Symbolize a significant change in comparison with DOX, <sup>b</sup> Symbolize a significant change in comparison with normal saline, <sup>c</sup> Symbolize a significant change in comparison with DOX + Vit E,

DOX = Doxorubicin,

ADME = *Adansonia digitata* methanolic extract.



**Figure 1: Effects of methanolic leaf extract of *Adansonia digitata* on creatinine kinase, lactate dehydrogenase and aspartate amino transferase activities in doxorubicin-induced injury in male rats**

**Table 2: The Effect of methanolic leaf extract of *Adansonia digitata* on nitric oxide synthase, catalase, superoxide dismutase activities and malondialdehyde concentration in doxorubicin induced myocardial injury in rats.**

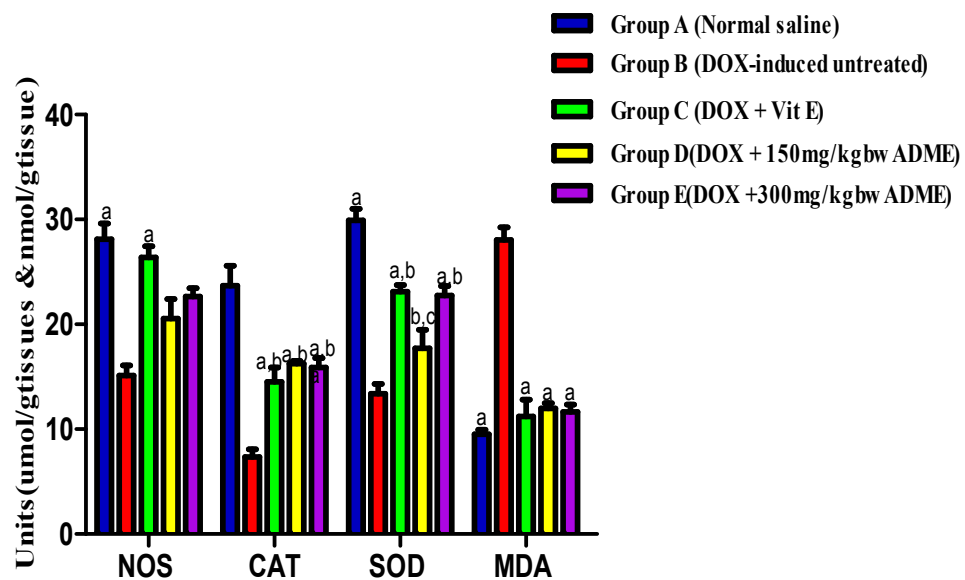
PARAMETERS	GROUP A (Normal saline)	GROUP B (DOX-induced untreated)	GROUP C (DOX-induced + Vit. E)	GROUP D (DOX-induced + 150mg/kgbw ADME)	GROUP E (DOX-induced + 300mg/kgbw ADME)
NOS( $\mu\text{mol/gtissue}$ )	28.10 $\pm$ 1.53 <sup>a</sup>	15.10 $\pm$ 0.98	26.40 $\pm$ 1.04 <sup>a</sup>	20.55 $\pm$ 1.86	22.65 $\pm$ 0.79
CAT( $\mu\text{mol/gtissue}$ )	23.68 $\pm$ 1.91	7.36 $\pm$ 0.73	14.53 $\pm$ 1.34 <sup>a,b</sup>	16.25 $\pm$ 0.28 <sup>a,b</sup>	15.90 $\pm$ 0.90 <sup>a,b</sup>
SOD( $\mu\text{mol/gtissue}$ )	29.93 $\pm$ 1.09 <sup>a</sup>	13.40 $\pm$ 0.91	23.13 $\pm$ 0.63 <sup>a,b</sup>	17.73 $\pm$ 1.74 <sup>b,c</sup>	22.75 $\pm$ 0.89 <sup>a,b</sup>
MDA(nmol/gtissue)	9.52 $\pm$ 0.42 <sup>a</sup>	28.05 $\pm$ 1.21	11.22 $\pm$ 1.59 <sup>a</sup>	11.98 $\pm$ 0.49 <sup>a</sup>	11.65 $\pm$ 0.70 <sup>a</sup>

The values are represented as mean SEM, with n = 7 rats and were reported significant at (P<0.05)

<sup>a</sup> Symbolize a significant change in comparison with DOX, <sup>b</sup> Symbolize a significant change in comparison with normal saline, <sup>c</sup> Symbolize a significant change in comparison with DOX + Vit E,

DOX = Doxorubicin,

ADME = *Adansonia digitata* methanolic extract.



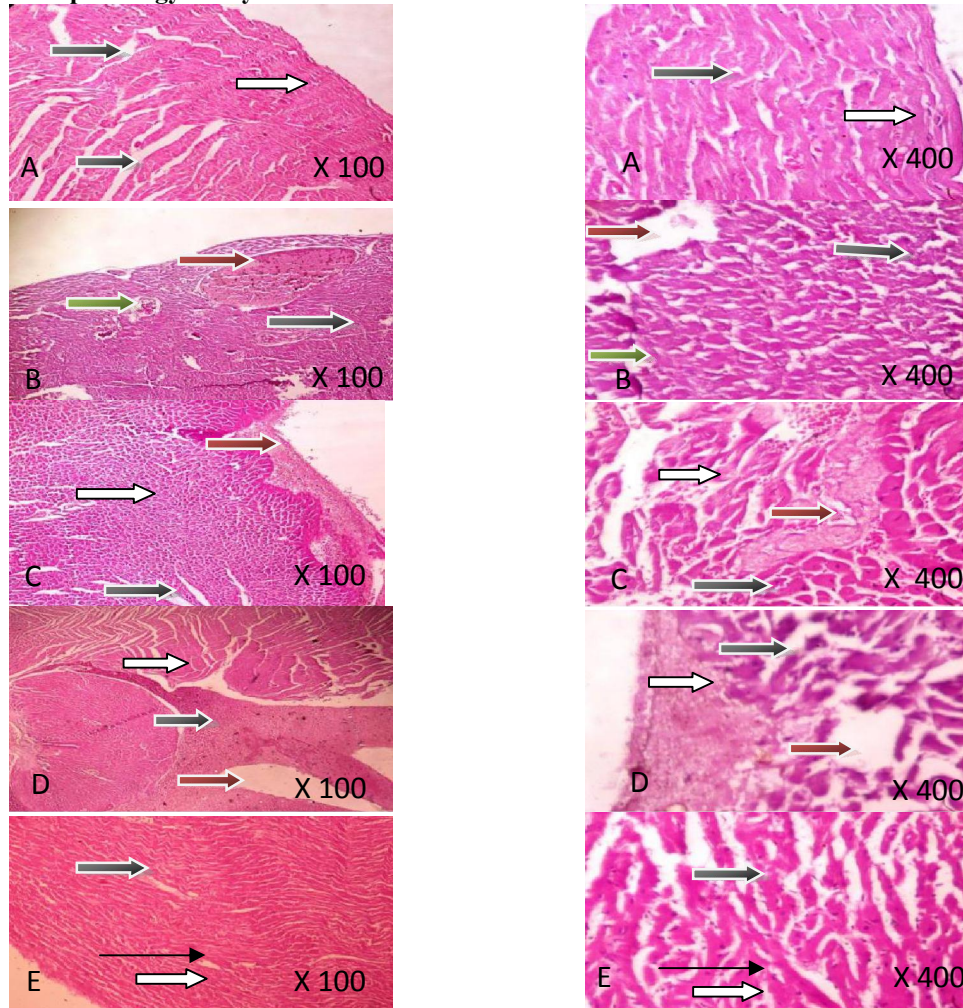
**Figure 2: Effects of methanolic leaf extract of *Adansonia digitata* on catalase, superoxide dismutase, nitric oxide synthase activities and malondialdehyde concentration in doxorubicin-induced injury in male rats**

A: Control (Normal saline); B: DOX- induced untreated; C: DOX + Vit E; D: DOX + 150mg/kg bw ADME; E: DOX + 300mg/kg bw ADME.

The myocardium of the control group animals had regular architecture, according to histopathology. (Plate 1A) but the heart section of doxorubicin treated pathogenic rats showed remarkable necrosis, edema and infiltration of chronic inflammatory cells with hemorrhage (Plate 1B). However, the photomicrograph of Vitamin E treated group showed normal epicardial layer (white arrow), normal myocardial layer (black arrow) and mild hemorrhage (red arrow). The heart section of DOX + 150mg/kgbw of the extract has moderate hemorrhage (black arrow), vocal area of mild edema (red arrow) as seen at the pericardial layer while other areas of epicardial layer appears normal (Plate 1D). The photomicrograph of the heart section of DOX + 300mg/kgbw of the extract has very mild infiltration of inflammatory cells (white arrow) at the pericardial layer, normal myocardial layer (black arrow) and

no haemorrhage as shown in Plate 1E indicating that the methanolic extract of the plant has significant cardioprotective effect and it also maintained myocardial membrane integrity.

### Histopathology Study



**Plate 1:** Haematoxylin and eosin staining shows the effect of a methanolic extract of *Adansonia digitata* on the histological morphology of the rat heart.

### Discussion

Cardiovascular disorders (CVDs) are a category of conditions that affect the heart and its components. Per the incidence of cardiovascular disorders around the globe, the most significant CVDs are elevated blood pressure, coronary heart attack, myocardial infarction, congenital heart abnormalities, cardiac arrhythmias, heart failure, and stroke (Mackay and Mensah, 2001). Heart attack kills more individuals worldwide than any other cause. According to Kandlepu et al. (2014), in 2012, almost 17.5 million people died of CVDs, representing 31% of all worldwide deaths. If current trends persist, a projected 23.6 million people would die from cardiovascular diseases by 2030. (Nazish and Kahl-UR-Shoukat,

2012). While certain current medications, such as organic nitrate, calcium channel antagonist, and  $\beta$ -blocker, are useful in preventing heart disease, their usage is also restricted due to side effects. Doxorubicin, an anthracycline compound, is a commonly prescribed chemotherapeutic agent for a variety of cancers, including breast cancer, bladder cancer, kaposissacroma, lymphoma, and acute lymphocytic leukemia (Wass, 1992; Jordan, 2002). The therapeutic activity of doxorubicin on tumor cells differs from that of its cardiotoxicity. DNA intercalation, which prevents macromolecule synthesis, DNA binding and DNA crosslinking, DNA damage caused by topoisomerase II inhibition, and induction of apoptosis caused by topoisomerase II inhibition are all proposed

mechanisms for its anti-malignancy effect (Gewirtz, 1999; Mumoth et al., 2004; Takemura and Fujirara, 2007). The cause of doxorubicin cardiotoxicity is thought to be elevated oxidative stress, which leads to increased amounts of reactive oxygen species and lipid peroxidation (Kalyanaraman et al., 1980; Doroshow, 1983; Singal et al., 1987; Takemura and Fujiwara, 2007). Reduced antioxidant and sulfhydryl group amounts (Doroshow et al., 1979; Olson et al., 1980; Singal et al., 1985; Odom et al., 1992), nucleic acid and protein synthesis inhibition (Arena et al., 1979; Monto et al., 1995), release of vasoactive amines (Bristow et al., 1980), and altered adren (Tong et al., 1991), decrease in cardiovascular expression are other mechanisms that has been proposed

Doxorubicin inflicts toxic harm to cardiomyocyte mitochondria, causing mitochondrial enzymes including NADH dehydrogenase, cytochrome P450 reductase, and xanthine oxidase to produce oxygen free radicals (Bachur et al., 1979; Davies and Doroshow, 1986), by inhibiting endothelial nitric oxide synthase, doxorubicin aids the production of intracellular hydroperoxide (Vasquez et al., 1997; Kalivendi et al., 2001). (Kotamraju and colleagues, 2000). The drug's downregulation of  $\alpha$ -actin, myosin light and long chains, troponin-I, and desmin proteins has been suggested as a potential trigger of doxorubicin cardiotoxicity. Reduced myofibrillar loss and myocardial contractile function are attributed to lower contractile protein expression (Kim et al., 2003; Lou et al., 2005). Downregulation of the sarcoplasmic reticular ATPase may result in abnormal myocardial diastolic behavior (Kim et al., 2003; Aries et al., 2004). Doxorubicin can also inactivate intracellular signal-regulated kinase (Louet et al., 2005). Commercially available synthetic cardioprotective medicines are harmful to certain communities and remain out of control. Some medicinal plants have been studied for their cardioprotective properties which showed to be both powerful and affordable (Karthik Mohan and Karthika, 2013; PriyaSaxena and Dharamveer Panjwani, 2014; Karunakar Hedge and Dhruvpatel Keerthi, 2015; Nagaraju et al., 2016). As a consequence, several scientists are interested in green products that have cardioprotective and antioxidative effects. *Adansonia digitata* has been used widely as a supplement for Western medicine in different therapies since prehistoric times. (Namratha and Baoba, 2015). Through reducing free radicals that trigger these chronic illnesses, baobab leaves and fruits may help to reduce oxidative stress-related diseases like cancer, aging, asthma, and cardiovascular disease. (Blumhoff et al., 2010; Kaur and Kapoor, 2001). The active constituents of polyphenols such as proanthocyanidins and flavonoids, saponins, and glycosides in the plant's leaf extract display cardioprotective effects in the

current analysis, which can be due to their active constituents of polyphenols such as proanthocyanidins and flavonoids, saponins, and glycosides (McDougal et al., 2005; Fernades de Olivera, et al., 2012; Sokeng et al., 2013). It has been documented that *Adansonia digitata* leaf extract is high in Vitamin C, which are phenolic compounds with hydroxyl groups in their form and have antioxidant activity (Vertuani et al., 2002; Besco et al., 2007; Brady, 2011). Polyphenols may also affect the function of main enzymes including glycosidase. A series of essential biological processes require glycosides (such as digestion, glycoprotein biosynthesis, and glucoconjugate lysosomal catabolism) that are linked to metabolic disorders and diseases such as diabetes, obesity, glycosphingolipids, lysosomal storage disease, HIV infections, and tumors (Kim et al., 2006). Glycosidase inhibition will be an innovative approach to treating the above complications. In the present research, the increased redox state of doxorubicin induced rats treated with *Adansonia digitata* leaf extract could have led to these compounds (Ayele et al., 2013). Further, methanol extract from the plant was shown as an inhibitor of nitric oxide concentration to reducing inflammatory plasma markers such as IL-6 and TNF-, which could aid in the suppression of peroxy radicals in diseases caused by free radicals (Ayele et al., 2013). In the present research, treatment with a methanolic extract of *Adansonia digitata* alleviated the problems induced by oxidative stress, as shown by improved oxidative stress biomarkers. Lactate dehydrogenase, creatinine kinase, and aspartate amino transferase are cardiac biomarkers, as are superoxide dismutase, catalase, nitric oxide synthase, and lipid peroxidation. Finally, the current study found that rats pretreated with a methanolic leaf extract of *Adansonia digitata* were shielded from doxorubicin-induced myocardial injury.

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