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(RESEARCH ARTICLE)

Assessment of the ameliorative potential of *A. cepa* and its fractions on doxorubicin-induced cardiotoxicity in Wistar rats

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Abstract

The assessment of the ameliorative potentials of *A. cepa* and its fractions on doxorubicin-induced cardiotoxicity in Wistar rats was evaluated in this study. 45 Wistar rats of both sexes were randomly divided into 9 groups of 5 animals each; as follows: group I, served as control and received 10 ml/kg body weight of 0.9% saline, group II, 10mg/kg body weight of doxorubicin, group III, 4 mg/kg body weight of vitamin E plus Dox. Group IV, 1000mg/kg body weight of crude extracts of *A. cepa* plus Dox. Group V, 1000mg/kg body weight of n-hexane fraction of *A. cepa* plus Dox. Group VI, 1000mg/kg body weight of DCM fraction of *A. cepa* plus Dox. Group VII, 1000mg/kg body weight of EA fraction of A.cepa plus Dox. Group VIII, 1000mg/kg body weight of methanol fraction of *A. cepa* plus Dox, and group IX, combinations of 1000mg/kg, 4mg/kg 10mg/kg body weight of crude extract of *A. cepa*, vitamin E and Dox respectively for 16 days. Groups I and II treatments lasted 14 days, while treatments for groups III-VIII lasted 16 days (making 14 day for respective treatments and addition 2 days for doxorubin administered once 48 hourly) before sacrificing. All substances in this study were administered orally except doxorubicin that was done intravenously. The results showed that doxorubicn administration (group II) significantly ($p<0.05$) elevated troponin and NO levels; CK and LDH activities, compared to the control group indicating cardiotoxicity. This cardiotoxic effect of doxorubincin was significantly reversed by administration of vitamin E, crude extract, DCM, n-hexane to groups III, IV, V and VI respectively. A significant ($p<0.05$) reduction of only NO was recorded with EA fraction, compared with group II (dox). Methanol fraction (group VIII) further escalated doxorubicin-induced cardiotoxicity with a significantly ($p<0.05$) elevated myoglobulin and NO levels and CK activity. But the combined treatment with vitamin E, Crude extract and dox significantly ($p<0.05$) reduced cardiotoxic markers in this study except myoglobulin where a significant ($p<0.05$) elevation was recorded. It can be concluded that fresh *A. cepa* leaves extract possesses cardio-protective properties and may be a suitable cardio-protector against drug-induced cardiotoxicity in crude extract form, fractions of DCM and n-hexane but definitely not with methanol fraction as shown in this study.

Keywords: Cardiotoxicity; Ameliorative; *A. cepa*; Heart; Doxorubicin

1. Introduction

Cardiovascular diseases (coronary artery disease, hypertension, heart failure, and stroke) have been reported to be leading causes of death in humans (Parabathina et al., 2011), with oxidative stress as the major cellular damage mechanism, resulting from an imbalance in the generation of free radicals and antioxidant defense molecules and affecting biological macromolecules causing their structural alterations that can lead to cell damage and death (Ryter et al., 2007).

Doxorubicin is a chemotherapeutic drug widely used for the treatment of patients with cancer (Gong et al., 2021). However, clinical use of this drug is hampered by its cardiotoxicity, which is manifested as electrocardiographic abnormalities, arrhythmias, irreversible degenerative cardiomyopathy and congestive heart failure (Santo et al., 2023).

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The cardiotoxicity of doxorubicin is associated with impairment of calcium homeostasis, generation of iron complexes, lipid peroxidation and formation of free radicals leading to oxidative stress (Ananthan et al., 2020), mitochondrial dysfunction and cell damage have been suggested as potential etiologic factors (Muscente et al., 2020). Due to its less developed antioxidant defense mechanism, the heart is the first organ of cytotoxic target of doxorubicin (Gong et al., 2021). Therefore, compounds that can neutralize the toxic effect of doxorubicin on cardiac cells without reducing the drug's antitumor activity are needed. In recent years, numerous studies have shown that herbal medicines and bioactive phytochemicals can serve as effective add-on therapies to reduce the cardiotoxic effects of doxorubicin ( ), one of such is Allium cepa (*A. cepa*), highly rich in antioxidants and is in constant use by a plethora of indigenous cultures for its several ameliorative effects in the prevention and treatment of most inflammatory disease; hence it is adopted in this study to investigate its ameliorative effects on doxorubicin-induced cardiotoxicity in Wistar rats.

2. Material and methods

2.1. Study Design and Site

The study was an experimental-based study and a laboratory animal model was adopted. The study was conducted between July and December, 2021 following protocol conditions in the Animal House of the Department of Medical Physiology, Faculty of Basic Medical Sciences, University of Uyo, Uyo, Akwa Ibom State, Nigeria.

2.2. Preparation of Plant Extract and Material

The extract was prepared separately from outer scales of the edible portion of onion bulbs. *A. cepa* leaves was collected, dried under shade and coarsely powdered and sent to the Department of Pharmacology, Uyo, for extraction and evaluation of Pharmacological action on Allium cepa. The powdered samples were stored in a clean glassware container until needed for analysis.

2.3. Partitioning of extract

1000 g of fine powdered plant material was weighed and dissolved in a jar containing 2.5 L of 70 % n-Hexane. The solution was soaked and macerated continually for 72 hrs for proper extraction of the plant's bioactive ingredients. At the end of the 72 hrs of maceration, the solution was first filtered with clean white virgin handkerchief and then later with Whatman No. 1 filter paper in order to obtain homogenous filtrates. The concentrates were then left open in evaporating dishes to be dried by air.

After the n-Hexane has been drained out and filtered, 2.5 litres of dichloromethane was then added to the filtrate in the jar. The solution was soaked and macerated continually for 72 hrs for proper extraction of the plant's bioactive ingredients. By the end of the 72 hrs of maceration, the solution was first filtered with clean white virgin handkerchief and then later with Whatman No. 1 filter paper in order to obtain homogenous filtrates. The concentrates were then left open in evaporating dishes to be dried by air.

2.4. Treatment Protocol

The animals were randomly divided into groups as presented in table 1 below:

Table 1 Experimental Design

S/N	Groupings	Treatments	Duration of treatment
1	I	10ml/kg of 0.9% saline	14 days
2	II	10mg/kg body weight of doxorubicin	14 days
3	III	4mg/kg body weight of vitamin E	16 days
4	IV	1000mg/kg body weight of crude extract of *A. cepa*	16 days
5	V	1000mg/kg body weight of n-hexane fraction of *A. cepa*	16 days
6	VI	1000mg/kg body weight of DCM fraction of *A. cepa*	16 days
7	VII	1000mg/kg body weight of EA fraction of *A. cepa*	16 days
8	VIII	1000mg/kg body weight of methanol fraction of *A. cepa*	16 days

9	IX	10mg/kg, 4mg/kg and 10mg/kg body weight of crude extract of *A. cepa* , vitamin E and doxorubicin respectively	16 days

2.5. Blood Sample Collection

For each group, body weight of rats was taken before and after doxorubicin administration, 48 hours after doxorubicin administration, blood and heart tissues were collected for serum troponin, Cr-K, and myoglobulin.

2.6. Preparation of serum and tissue homogenate

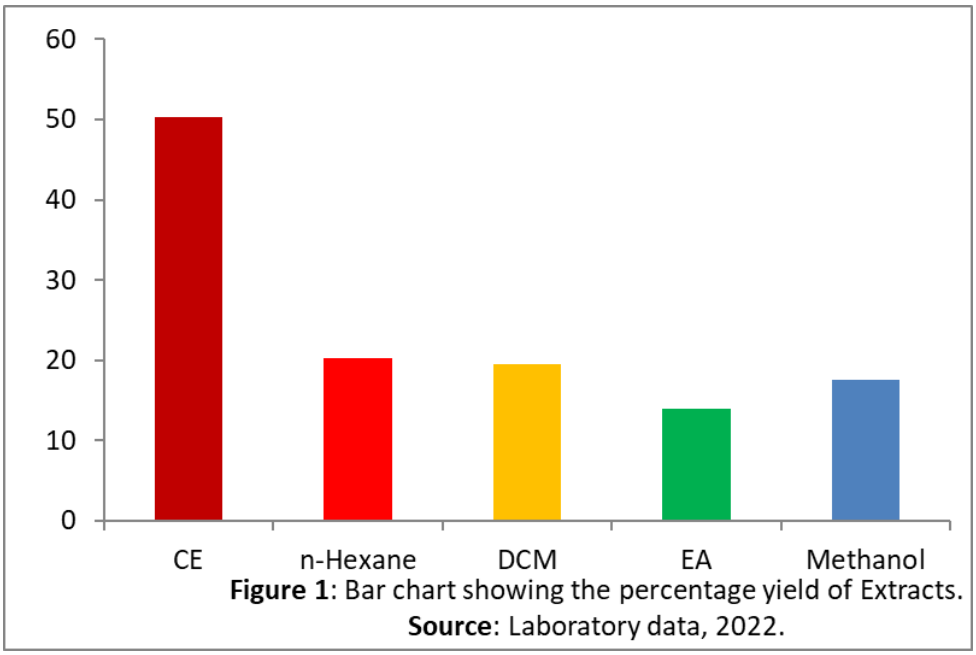
The blood sample collected was allowed to clot and serum obtained after centrifugation at a speed of 3000 rpm for 15 minutes. Excised heart for tissue homogenate investigation were rinsed in 1.15% KCl and homogenized in aqueous Tris—HC1 buffer (50 mmol/L, pH 7.4). Homogenates were then centrifuged at 6000 rpm for 20 minutes at 4oC to obtain supernatant fractions to be used for analysis. Antioxidant status was estimated in the heart homogenates by quantifying enzymatic (superoxide dismutase, catalase) and non-enzymatic (reduced glutathione) antioxidants.

2.7. Statistical Analysis

Data were expressed as the mean + standard error of the mean. Statistical analysis was carried out using window SPSS package (SPSS 22.00 version). Data were analyzed using one way analysis of variance (ANOVA), results obtained were further subjected to test for least significant difference (LSD). Values of $P<0.05$ were considered significant.

3. Results

The results of percentage yield of A. cepa extract and its fractions are presented in Figure 1. At the end of the extraction process with ethanol, a paste like substance weighing 503 g was obtained and called the crude extract. This represents the percentage yield of 50.3 %. In the different fractions of the extract, 102 g was obtained for n-hexane, 98 g for DCM, 70 g for ethyl acetate and 88g for methanol fractions. The percentage yield for nhexane, DCM, ethyl acetate and methanol fractions are 20.27 %, 19.48%, 13.92 % and 17.50% respectively.



Source: Laboratory data, 2022.

Figure 1 Bar chart showing the percentage yield of Extracts.

The results obtained following treatment with crude extract of *A. cepa* and its various fractions on troponin levels (ng/ml) were: 0.02 ± 0.02, 0.28 ± 0.03, 0.18 ± 0.02, 0.19 ± 0.02,0.18 ± 0.02, 0.19 ±

0.02, 0.23 ± 0.02, 0.23 ± 0.02, and 0.18 ± 0.02 for groups I, II, III, IV, V, VI, VII, VIII and IX respectively. The results showed doxorubicin administration to group II animals significantly ($p<0.05$) increased troponin level; as the crude extract of

A. cepa and its various fractions did not alter troponin level significantly compared with the control group I. The crude extract of *A. cepa* and its various fraction significantly ($p<0.05$) reduced troponin level compared with dox group II except groups VII and VIII (EA and methanol respectively) where no significant alteration was recorded, figure 2.

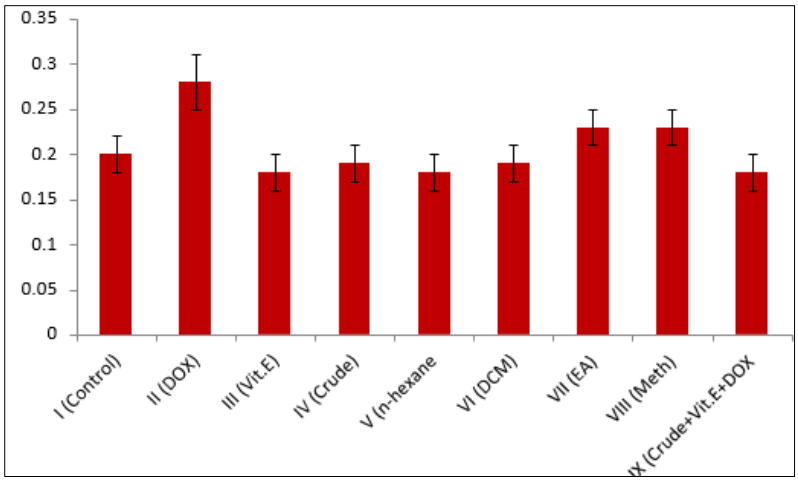
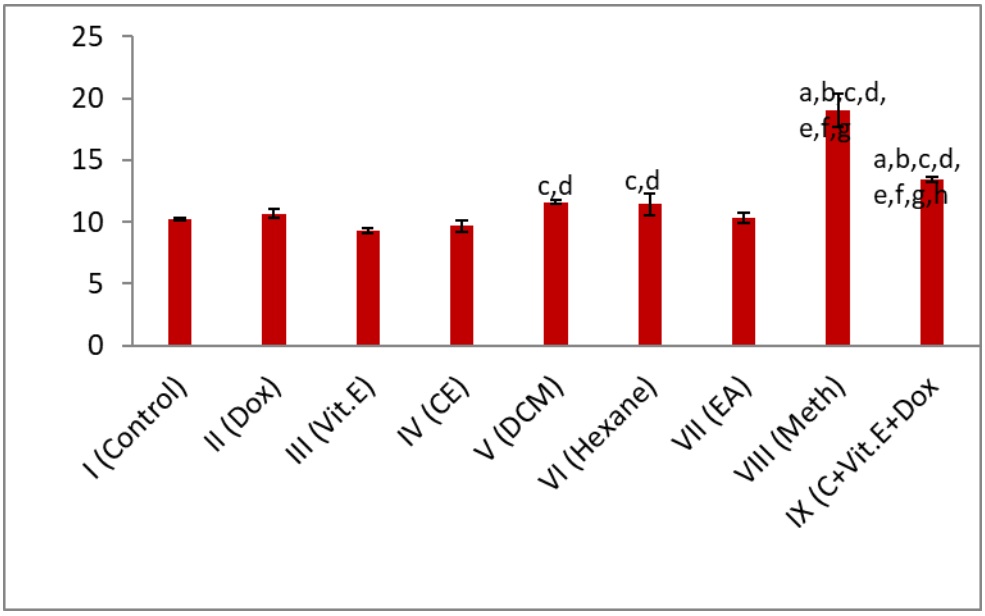


Figure 2 Effects of *A. cepa* and fractions on Troponin (ng/ml) concentration in all graphs presented as mean± SEM. a = versus I, b = versus III at $P< 0.05$….



Source: Laboratory data, 2022

Figure 3 Effects of A. cepa and fractions on myoglobulin (ng/ml) . a = versus I, b = versus II, c = versus III, d = versus IV, e = versus V, f = versus VI, g = versus VII, h = versus VIII. (All at ($p< 0.05$).

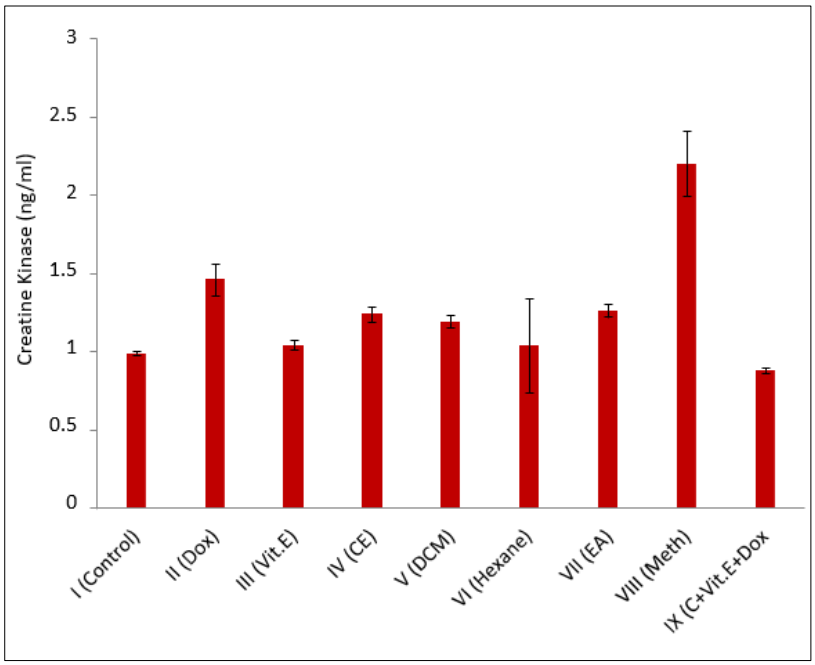
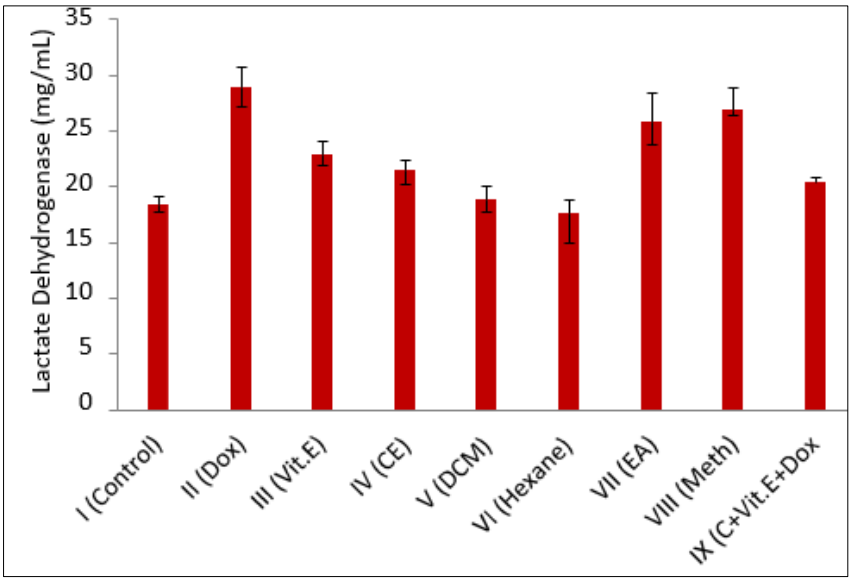
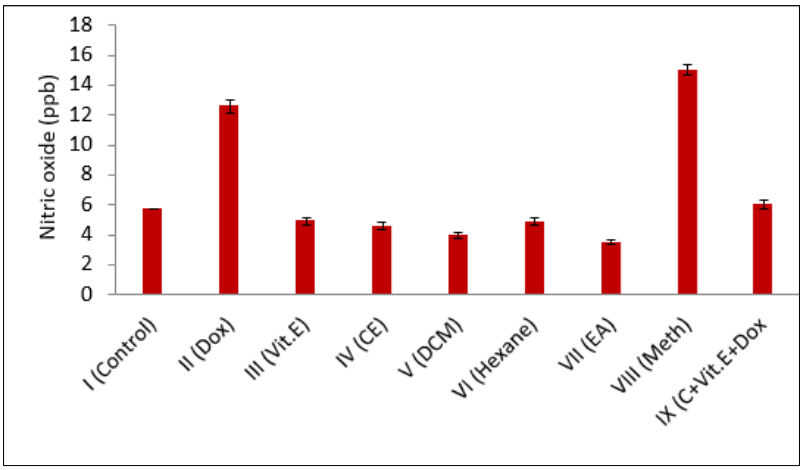


Figure 4: Effects of *A. cepa* and fractions on creatine kinase (ng/ml) concentration in all graphs presented as ±SEM. a = versus I, b = versus II, c = versus III, d = versus IV, e = versus V, f = versus VI, g = Versus VII, h = versus VIII at $p<0.05$



Source: Laboratory data, 2022

Figure 5: Effects of *A. cepa* and fractions on LDH (ng/ml) concentation in all graphs presented as ±SEM. a = versus I, b = versus II, c = versus III, d = versus IV, e = versus V, f = versus VI, g = versus VII, h = versus VIII at p<0.05



Source: Laboratory data, 2022

Figure 6: Effects of *A. cepa* extract and fractions on NO (ppb) concentration in all graphs presented as ±SEM. *a* = versus I, *b* = versus II, *c* = versus III, *d* = versus IV, *e* = versus V, *f* = versus VI, *g* = versus VII, *h* = versus VIII at P<0.05

4. Discussion

The results of percentage yield of *A. cepa* extract and its fractions are presented in Figure 1. At the end of the extraction process with ethanol, a paste like substance weighing 503 g was obtained and called the crude extract. This represents the percentage yield of 50.3 %. In the different fractions of the extract, 102 g was obtained for n-hexane, 98 g for DCM, 70 g for ethyl acetate and 88g for methanol fractions. The values of the extraction yields were calculated by subtracting the weight of the dry extract from the initial bark, root, or herb powder weight. The percentage yield for nhexane, DCM, ethyl acetate and methanol fractions are 20.27 %, 19.48%, 13.92 % and 17.50% respectively.

The results obtained following treatment with crude extract of *A. cepa* and its various fractions on troponin levels (ng/ml) were: 0.02 ± 0.02,0.28 ± 0.03, 0.18 ± 0.02, 0.19 ± 0.02,0.18 ± 0.02, 0.19 ± 0.02, 0.23 ± 0.02, 0.23 ± 0.02, and 0.18 ± 0.02 for groups I, II, III, IV, V, VI, VII, VIII and IX respectively. The results showed doxorubicin administration to group II animals significantly (p<0.05) increased troponin level; as the crude extract of *A. cepa* and its various fractions did

not alter troponin level significantly compared with the control group I. The crude extract of *A. cepa* and its various fraction significantly ($p<0.05$) reduced troponin level compared with dox group II except groups VII and VIII (EA and methanol respectively) where no significant alteration was recorded, figure 2.

The results obtained following treatment with crude extract of *A. cepa* and its various fractions on myoglobin levels (ng/ml) were: 10.18 ± 0.10, 10.68 ± 0.33, 9.28 ± 0.23, 9.68 ± 0.47, 11.60 ± 0.13,11.43 ± 0.90, 10.33 ± 0.40, 18.98 ± 1.35, and 13.45 ± 0.19 for groups I, II, III, IV, V, VI, VII, VIII and IX respectively. The results showed doxorubicin, crude extract of *A. cepa*, vitamin E, and *A. cepa* fractions did not alter myoglobin levels significantly compared with the control group I except groups VIII and IX where significant ($p<0.05$) elevations were recorded. Similarly, only groups V, VI, VIII and IX recorded significantly ($p<0.05$) higher myoglobin levels compared with groups II (dox), III (vit. E) and IV (crude extract of *A. cepa*). Comparison among fractions recorded significantly ($p<0.05$) higher myoglobin levels only in group VIII (methanol fraction), figure 3.

The results obtained following treatment with crude extract of *A. cepa* and its various fractions on CK-MB activity (ng/ml) were:0.99 ± 0.01, 1.46 ± 0.10, 1.04 ± 0.03, 1.24 ± 0.05, 1.19 ± 0.04, 1.04 ± 0.30, 1.26 ± 0.04, 2.20 ± 0.21, and 0.88 ± 0.02 for groups I, II, III, IV, V, VI, VII, VIII and IX respectively. The results showed doxorubicin to group II, crude extract of *A. cepa* (group IV), groups VII (EA) and VIII (methanol) significantly ($p<0.05$) altered CK-MB activity compared with the control group I. Similarly, only groups III (vit. E), V (DCM), VI (hexane), and IX recorded significantly ($p<0.05$) lower CK-MB activity, while only group VIII (methanol) recorded significantly ($p<0.05$) higher CK-MB activity compared with groups II (dox). Furthermore, group VIII (methanol) significantly ($p<0.05$) elevated CK-MB activity compared with the crude extract and other fractions, but group IX (crude extractof *A. cepa*+ vit. E + Dox) significantly ($p<0.05$) reduced CK-MB activity compared the extract and all fraction group, figure 4.

The results obtained following treatment with crude extract of *A. cepa* and its various fractions on LDH activity (mg/mL) were: 18.40 ± 0.71, 28.88 ± 1.75, 22.80± 1.28, 21.38 ± 0.94, 18.85 ± 1.22, 17.63 ± 1.16, 25.78 ± 2.65, 26.88 ± 2.01,and 20.35 ± 0.45for groups I, II, III, IV, V, VI, VII, VIII and IX respectively. The results showed significant ($p<0.05$) elevation of LDH activity in groups II (Dox), III (vit. E), VII (EA) and VIII (methanol) compared with group I (control), while group VI (n-hexane) recorded significantly ($p<0.05$) lower LDH activity compared with group I. Significantly ($p<0.05$) lower LDH activity was also recorded in groups III, IV, V, and IX compared with group II (Dox). Comparison among the standard drug (vit. E), extract and fractions showed only groups VII and VIII (EA and methanol respectively) significantly ($p<0.05$) elevated LDH activity, figure 5.

The results obtained following treatment with crude extract of *A. cepa* and its various fractions on NO levels (ng/ml) were: 5.69 ± 0.01, 12.58 ± 0.41, 4.92 ± 0.25, 4.59 ± 0.27, 3.98 ± 0.18, 4.87 ± 0.27, 3.51 ±0.12, 15.03 ± 0.30, and 6.01 ± 0.28for groups I, II, III, IV, V, VI, VII, VIII and IX respectively. The results showed significant ($p<0.05$) elevation of NO levels in groups II (Dox), and VIII (methanol) compared with group I (control), while groups III, IV, V, VI, and VII recorded significantly ($p<0.05$) lower NO levels compared with groups I and II. But significantly ($p<0.05$) higher NO level recorded in group II compared with the standard drug group III (vit. E) extract and other fractions, figure 6.

5. Conclusion

There are currently no clinical imaging techniques or biomarkers available to detect DOX- cardiotoxicity before functional decline. In addition to ECG, echocardiography, coronary angiography, etc, circulating biomarkers are essential for the diagnosis of myocardial infarction. Cardiac troponins (Tn1) or (cTn) remains the old standard for the diagnosis of acute myocardial infarction (AMI). Cardiac troponins are one of the most critical biomarkers to diagnose cardiovascular diseases, including acute myocardial infarction. The cardio-toxicity biomarkers (Tn1, myoglobin, LDH) guide clinical applications (diagnostic methods, risk stratification, and treatment). Also, research have showed the association of cTn with different biomarkers can contribute to the early diagnosis of cardiotoxicity. In a similar context, another study reported troponin as a significant biomarker in the diagnosis of the cardiac dysfunction associated with several types of chemotherapeutic drug: anthracyclines, anti-human epidermal growth factor receptor 2 treatments, and anti-vascular endothelial factor therapy. All substances in this study were administered orally except doxorubicin that was done intraperitonealy. The results showed that doxorubicin administration (group II) significantly ($p<0.05$) elevated troponin and NO levels; CK and LDH activities, compared to the control group indicating cardiotoxicity. This cardiotoxic effect of doxorubicin was significantly reversed by administration of vitamin E, crude extract, DCM, n-hexane to groups III, IV, V and VI respectively. A significant ($p<0.05$) reduction of only NO levels and CK activity. But the combined treatment with vitamin E, crude extract and dox significantly ($p<0.05$) reduced cytotoxic markers in this study except myoglobulin where a significant ($p<0.05$) elevation was recorded. It can be concluded that fresh *A. cepa* leaves extract possesses cardio-protective properties and may be a suitable cardio-protector against drug-induced

cardiotoxicity in crude extract form, fractions of DCM and n-hexane but likely not with methanol fraction as shown in this study.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare no conflicts of interest for this paper.

Statement of ethical approval

Ethical approval for the study was sort from the University of Uyo, Institutional Health Research Committee (IHERC), UU/CHS/IHERC/VOL.1/030.

Scientific responsibility Statement

The Authors declare that they are responsible for the article's scientific content including the study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Data Availability

All data generated or analyzed during the study are included in this article.

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