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Cardio-protective Activity of Aqueous Extract of Beetroot (*Beta Vulgaris*) Vegetable Plant on Doxorubicin-Induced Cardiotoxicity in Wistar Rats

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Abstract: *Beetroot (Beta vulgaris) is a multi-targeted supplement in cardiac-respiratory disorders. The study was to evaluate its cardio-protective activity in rats.Wistar rats grouped into four of eight each: Group I-Control received distilled water as a vehicle for 49 days + {0.2ml of normal saline, intra-peritoneal (ip)} on 21st, 28th, 35th, and 42nd day. Group II- received doxorubicin (4 mg/ kg, ip). Group III received extract (Beetroot, 300 mg/kg orally) + doxorubicin (4 mg/kg, ip) while group IV received extract (Beetroot, 500 mg/kg orally) + doxorubicin (4 mg/kg, ip). They were fed with feed and water ad-libitum. Electrocardiographic parameters (QT interval, ST interval and QRS complex), Hemodynamic parameters (SBP, DBP, MABP), Oxidant/antioxidant status of cardiac tissue (Catalase and Malondialdehyde) were measured by standard methods. Serum was measured for CK-MB, LDH, ALT and Troponin-1 by standard methods. There was significant ($p < 0.01$) decrease in cardiac enzymes (Serum Troponin-1, CK-MB, LDH and AST) amongst the Beetroot treated group, compared to the doxorubicin-induced group. There was a significant ($p < 0.05$) decrease in the ECG / Hemodynamic parameters in the treated beetroot groups in-comparison with the doxorubicin-induced.Aqueous extract of beetroot (at 300mg/kg and 500mg/kg body weight) possesses cardio-protective activity. Therefore, buttresses the fact that antioxidant nutrients in fruits and vegetables are important in the maintenance of human health. Extracts of beetroot could be effective for the management of hypertension.*

Keywords: cardiotoxicity, doxorubicin, ECG, cardiac, beetroot

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INTRODUCTION

Doxorubicin (dox), an anthracycline antibiotic is used to treat malignancies, such as leukamias and lymphomas [1]. Its most important side effect is dose-dependent cardiotoxicity often associated with oxidative stress apoptosis [2]. Early events in doxorubicin-induced cardiomyopathy is sarcoplasmic reticulum Ca^{2+} depletion which often correlates with cardiac cell death and heart failure [3-4]. Inhibition of mitochondrial cells biogenesis is presumed to be the mechanism of dox-mediated cardiotoxicity particularly by enhancing cell death via inhibition of topoisomerase 2β [5-6]. Such cardiotoxicity can be acute, sub-acute or chronic. Acute occurs in about 11% of cases [7-8], which usually shows in 2-3 days of treatment [8]. Cardioactivity is reversible and its onset often predicts the risk of heart failure in man [9]. Incidence of chronic cardiomyopathy is much less than the acute toxicity, however, sub-acute and chronic carditoxicity are permanent and irreversible [10]. Doxorubicin-induced cardiotoxicity can manifest as hypotension, tachycardia, transient arrhythmias or late onset cardiomyopathy in form of fatigue, dyspnea and lower limb edema [9]. An over-dose of anthracyclines causes heart failure [11] and all over the world, cancer and heart diseases are the leading causes of deaths[12].

Beetroot (*Beta vulgaris*) is an edible taproot with fluffy leaves and originated from the Middle East but now thrives worldwide [13-14]. It belongs to the family *Chenopodiaceae* and used in traditional medicine to treat constipation, gut, joint pain and dandruff [15]. As a nutritious plant, it has health promotional properties, such as anti-oxidant and anti-inflammatory effects [16], hepato-protective, etc. [17]. Beetroot is consumed as diet and used in manufacturing as colouring agent [18].

Cardiovascular disease is a major global health burden and its attendant complications (coronary artery disease, hypertension etc.) [19]. Brook *et al.*, [20] noted that a host of complementary and alternative medicine therapies, including dietary supplementations, traditional herbs, and medication, are regularly used for treating hypertension. Beetroot (*Beta vulgaris*), is noted as ergogenic compound and a multi-targeted supplement in vascular dysfunction, artherosclerosis, cardiac-respiratory disorders and diabetes [21-23]. Current studies on beetroot addressing its hypotensive and ergogenic properties, emphasized the essential role of inorganic NO_3 on the clinical effect of this vegetable and its by-products [23]. However, the results were found, to be mostly inconsistent. There is paucity of data regarding the use of Beetroot by hypertensive subjects. Studies are required to evaluate the efficacy and safety of beetroot dietary intervention in health and disease particularly in Nigeria. Thus, this study investigated the efficacy of Beetroot supplementation in doxorubicin-induced cardio-toxicity in rats, with the aim to highlight the potential cardio elicited enzymes, blood pressure and lowering properties as well as other associated cardio-protective aspects of Beetroot plant vegetable as a medicinal food.

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MATERIALS AND METHODS

Doxorubicin hydrochloride

Doxorubicin hydrochloride (vial of 20mg) was purchased from a registered DEMEK Pharmaceutical in Nigeria for the induction of cardiotoxicity in Wistar rats.

Identification of the Plant

Whole plants of Beetroot (*Beta vulgaris*) comprising of the tubers and leaves were collected in March, 2022 in Vom garden, Jos-Plateau State, Nigeria. The plant was identified and authenticated by the Head of Department of Botany, Faculty of Science, Delta State University, Abraka-Nigeria (Figure 1). The plant was deposited in the herbarium with a voucher specimen number (DELSU#136). The tubers and leaves of the plant were used in this study as a hot water decoction.

Fig. 1 Beetroot (*Beta vulgaris*) Vegetable plant
Source: Photograph of Beetroot Vegetable plant taken before drying

Preparation of Aqueous Extracts of Beetroot (Beta vulgaris) plant

The tubers and leaves of the plant were completely rinsed with distilled water to remove sand and any other surface contaminants. They were cut into beats and then air dried in the Laboratory to constant weight. A hundred and fifty grams of the cut tubers/leaves were ground using a Phillips blender to homogeneity. Five hundred ml of hot distilled water was added to the homogenate powder and allowed to stand for 30 min. Two more extractions were carried out with 300 ml of hot distilled water per extraction. The water was then filtered using white muslin cloth. The filtrate was evaporated to dryness on a hot plate and a sticky reddish residue was obtained. The percentage yield was calculated and found to be 20.4%. The residue was then stored in air tight water proof

containers, and kept at 4^0C. This served as stock, from where fresh preparations were further made when required.

Preparation of solution
Weighed quantity of the extract was suspended in fresh distilled water. The route of administration was oral. Required quantity of doxorubicin hydrochloride was dissolved in normal saline. The route of administration was intra peritoneal.

Acute Oral toxicity study
This was performed using OECD-423 guideline for animal study [24]. Male Wistar rats weighing 120-180 g, divided into two groups of six animals each were used. One group was given 2,000 mg/kg body weight, while the second group received 5,000mg/kg body weight of the extract orally. They were observed for symptoms of toxicity and mortality for three days (72 hr).

Experimental Animals
Apparently healthy adult male Wistar rats of weight 120g-180g were used for the study. They were obtained from the Animal Section of the Faculty of Basic Sciences, Delta State University, Abraka. The animals were housed in standard cages and kept under standard condition. The study had the approval of Faculty of Science constituted Ethical Committee with Ref no: FOS/ERC/21/06. The animals were given a standard diet and water *ad libitum.*

The principles for care and use of laboratory animals were adopted.

Experimental design and protocol
Thirty-two male Wistar rats were divided into four groups of eight animals each.
Group I: Control group, received distilled water as a vehicle for 49 days and 0.2ml of normal saline (intra-peritoneal) on 21^{st}, 28^{th}, 35^{th}, and 42^{nd} day.

Group II: DOX group, received doxorubicin (4 mg/ kg, intra-peritoneal) on 21^{st}, 28^{th}, 35^{th}, and 42^{nd} day.

Group III: Beetroot, received aqueous extract (300 mg/kg, per oral) for 49 days and doxorubicin (4 mg/kg, intra-peritoneal) on 21^{st}, 28^{th}, 35^{th}, and 42^{nd} day.

Group IV: Beetroot, received aqueous extract (500 mg/kg, per oral.) for 49 days and doxorubicin (4 mg/kg, intra-peritoneal) on 21^{st}, 28^{th}, 35^{th}, and 42^{nd} day. Total cumulative dose of DOX was 16 mg/kg, intra-peritoneal [25].

Body weight
Body weight of each rat was recorded weekly.

Serum parameters

On the last day, about 1ml of blood was collected from the retro-orbital plexus of each of the animals, into plain tube, allowed to clot and centrifuged at 3000rpm. It was labelled with dates for the analysis.

The Serum was analysed for lactate dehydrogenase (LDH), creatine phosphokinase-MB isoenzyme (CK-MB), AST using Midray Kits (Shenzhein, Germany) in an Auto-Analyzer (Midray: BA-88A). While serum Troponin-1 (biomarker of cardiac injury) was estimated by chemiluminescence immunoassay according to the method [26].

Electrocardiographic parameters

Animals were fasted overnight, but had access to water after the last dose administration of the drug on 49th day. On 50th day, animals were anaesthetized using urethane (1.25g/kg, intra-peritoneal). ECG was recorded by Oscillograph (Bioscience, UK) Instruments (with LABCHART-6 pro software). Needle electrodes were inserted under the skin of each of the animals for the limb lead at position II for ECG tracing [QRS complexes, ST interval, QT interval, and heart rate (HR)] measurements.

Hemodynamic parameters

The right carotid artery of each animal was cannulated with heparinized saline and connected to pressure transducer. After 30 min of stabilization, the hemodynamic parameters [systolic blood pressure (SBP), diastolic blood pressure (SBP) and mean arterial blood pressure (MABP)] were recorded by Power lab instrument.

Millar catheter was inserted in the right carotid artery. After 15 min of stabilization, the parameters max dp/dt, min dp/dt and left ventricular systolic pressure (LVSP) were recorded.

The animals were sacrificed, the heart removed and washed with physiological saline.

Oxidant / antioxidant status of cardiac tissue

0.5 g of the Heart sample was homogenized in 5 ml of saline at 4 °C using an electrical homogenizer. The homogenate was centrifuged at 3000 rpm for 15 min. The tissue homogenates were preserved at -20°C until used. The supernatant were collected and used for estimation of catalase **(**CAT**)** activity [27] and malondialdehyde (MDA) concentrations [28].

Statistical Analysis

The data were expressed as mean ± SEM. Level of significance between groups was done using one-way ANOVA and followed by Dennett's post-hoc test. A *p-value* of less than 0.05 was considered significant.

RESULTS

Acute toxicity

The acute toxicity test revealed that, the extract at 2,000 and 5,000mg/kg was non-toxic to the rats.

Body weight parameter

The group II animals (Doxorubicin- induced) showed a significant ($p < 0.01$) decreased in their weekly body weights compared with the group I-Control. Also the beetroot treated animals in groups III and IV revealed a significant ($p < 0.001$) increase in their body weights compared with the Dox group (Table 1).

Table 1. Effect of aqueous extract of Beetroot (*Beta vulgaris*) plant on Body weight of Doxorubicin-induced cardiotoxicity in Wistar rats

Weeks	Control	Dox(4mg/kg)	Beet(300mg/kg)	Beet(500mg/kg)
0	140.83 ± 4.58	112.50 ± 2.36*	132.46 ± 5.21**	136.38 ± 6;34**
1	149.70 ± 5.12	121.16 ± 3.16*	157.73 ± 4.24**	164.16 ± 6.72**
2	168.36 ± 4.81	120.89 ± 5.76*	156.89 ± 4.16**	164.28 ± 6.82**
3	179.42 ± 6.18	128.52 ± 6.12*	166.46 ± 5.12**	172.98 ± 6.24**
4	182.51 ± 7.20	132.68 ± 6.36*	178.16 ± 4.16**	186.34 ± 7.16**
5	198.48 ± 8.06	143.12 ± 7.42*	185.90 ± 5.26**	194.55 ± 7.26**
6	218.16 ± 9.12	156.71 ± 8.12*	202.81 ± 6.20**	208.06 ± 7.04**
7	226.32 ± 10.42	164.42 ± 10.14*	213.28 ± 5.68**	219.39 ± 6.42**

Values are expressed as mean ± SEM (n=8) $^{**}P < 0.01$ values compared to Dox Group. $^{***}P < 0.001$, $^{*}p < 0.01$ compared to the control group.

Table 2. Effect of aqueous extract of Beetroot (*Beta vulgaris*) plant on Cardiac enzymes of Doxorubicin-induced cardiotoxicity in Wistar rats

Parameters	Control	Dox(4mg/kg)	Beet(300mg/kg)	Beet(500mg/kg)
CK-MB	20.00 ± 1.40	42.10 ± 2.60**	16.15 ± 1.60*	15.68 ± 1.40*
LDH	90.26 ± 1.16	145.98 ± 2.36**	82.58 ± 1.80*	69.47 ± 1.80*
AST	122.10 ± 3.36	252 ± .8.42***	196.84 ± 6.62**	184.68 ± 6.12**

Values are expressed as mean ± SEM (n=8) $^{**}P < 0.01$, $^{*}P < 0.05$ compared to Dox group. $^{***}P < 0.001$, $^{**}P < 0.01$ compared to control group

Table 3. Effect of aqueous extract of Beetroot (*Beta vulgaris*) plant on ECG parameters of Doxorubicin-induced cardiotoxicity in Wistar rats

Parameters	Control	Dox(4mg/kg)	Beet(300mg/kg)	Beet(500mg/kg)
ST interval(sec)	0.061 ± 0.0042	0.094 ± 0.0036**	0.074 ± 0.0028*	0.063 ± 0.0018*
QT interval(sec)	0.068 ± 0.0048	0.086 ± 0.0040**	0.069 ± 0.0042*	0.067 ± 0.0032*
QRT complex (sec)	0.015 ± 0.006	0.018 ± 0.0070**	0.014 ± 0.0008*	0.014 ± 0.0042*
HR	409.4 ± 16.80	290.2 ± 32.42**	349.0 ±32.45*	352.6 ± 38.16*

Values are expressed as mean ± SEM (n=8) *P < 0.05 compared to Dox group. **P < 0.01 compared to control group.

Table 4. Effect of aqueous extract of Beetroot (*Beta vulgaris*) plant on Blood Pressure parameters of Doxorubicin-induced cardiotoxicity in Wistar rats

Parameters	Control	Dox(4mg/kg)	Beet(300mg/kg)	Beet(500mg/kg)
Systolic(mmHg)	121.60 ± 1.36	168.28 ± 1.68**	148.24 ± 3.12*	142.30 ± 1.68*
Diastolic(mmHg)	94.18 ± 2.10	148.40 ± 0.42**	135.30 ± 3.10*	126.00 ± 2.68*
MABP(mmHg)	118.20 ± 2.16	152.10 ± 0.66**	124.90 ± 1.26*	120.16 ± 2.36*

Values are expressed as mean ± SEM (n=8) *$P < 0.05$ compared to Dox group. **$P < 0.01$ compared to control group.

Table 5. Effect of aqueous extract of Beetroot (*Beta vulgaris*) plant on Left Ventricular function parameters, CAT, MBA and Troponin-1 of Doxorubicin-induced cardiotoxicity in Wistar rats

Parameters	Control	Dox(4mg/kg)	Beet(300mg/kg)	Beet(500mg/kg)
Max dp/dt	1898 ± 136	1238 ± 89*	1342 ± 78**	1398 ± 12***
Min dp/dt	746 ± 38	426 ± 28*	468 ± 48**	610 ± 6.0***
LVSP(mmHg)	122 ± 3.6	88 ± 3.6*	98 ± 3.8**	116 ± 3.8***
CAT(U/g.tissue)	1.6841± 0.13	0.6751 ± 0.26*	1.3647 ± 0.16**	1.5178 ± 0.18***
MBA(nmol/g.tissue)	21.97 ± 3.16	85.74 ± 6.32***	38.46 ± 8.12**	31.18 ± 6.16*
Troponin-1(ng/ml)	0.006 ± 0.0046	0.168 ± 0.0068**	0.064 ± 0.082*	0.060 ± 0.081*

Values are expressed as mean ± SEM (n=8) **$P < 0.01$, *$P < 0.05$, compared to Dox group. ***$P < 0.001$, *$P < 0.01$ compared to control group.

Serum Biochemical and ECG parameters

There was a significant (($p < 0.001$) increase in the activity of ALT, CK-MB and LDH in the Dox-induced-group II compared to the Control rats-group 1. However, the Beetroot treated rats-groups III and IV showed a very significant (($p < 0.001$) decrease in the activities of ALT. CK-MB and LDH (Table 2). There was significant ($p < 0.05$) increase in the levels of ECG parameters (ST interval, QT interval and QRS complex in Dox treated animals-group II in-comparison with the Controls-group 1. While there was significant (($p < 0.05$) decrease in the ST interval, QT interval and QRS complex amongst Beetroot treated animals-groups III and IV compared with Dox-induced-group II (Table 3). Table 3 also showed a significant (($p < 0.05$) decrease in Heart rate in the Dox-induced animals-group II compared to the Controls-group 1. While there was a significant (($p < 0.05$) increase in the Heart rates of the Beetroot treated animals in comparison with the Group I1-Dox-induced.

Hemodynamic parameters

Table 4 showed a significant (($p < 0.05$) increase in the hemodynamic parameters (SBP, DBP and MABP) in the Dox-induced rats-group II when compared with the Control-group 1. There was a significant (($p < 0.05$) restoration of SBP, DBP and MABP in the Beetroot treated animals in-comparison with the Dox-induced-group II. There was a significant (($p < 0.05$) decrease in the max dp/dt, min dp/dt and LVSP in the Dox-induced animals-group II compared to the Control-

group 1. There was a significant (($p < 0.05$) increase in the max dp/dt, min dp/dt and LVSP in comparison with the Dox-group II (Table 5).

Cardiac injury biomarker, Oxidant / antioxidant cardiac tissue

The cardiac biomarker-serum Troponin-1 was significantly (($p < 0.01$) elevated in the Doxorubicin-induced rats-Group II compared to Control-Group I. While in the Beetroot treated rats-Groups III/IV the serum Troponin-1 activity was significantly (($p < 0.01$) decreased in comparison with the Dox Group (Table 5.). Also, Table 5 showed that cardiac activity of CAT was significantly (($p < 0.05$) decreased while the MDA concentrations was significantly (($p < 0.05$) increased in Dox-induced animals-Group II compared with the Control-Group I. The Beetroot treated Groups III/IV significantly (($p < 0.05$) increased the activity of the CAT with significant (($p < 0.05$) decrease in the MDA concentrations when compared with the Doxorubicin-induced Group.

DISCUSSION

Beetroot (*Beta vulgaris***)** has been noted as an ergogenic compound and a multi-targeted supplement in vascular dysfunction, artherosclerosis, cardiorespiratory disorders and diabetes [29-30]. Shah *et al.*, [25] noted that endogenous cardiac biomarkers: CK-MB and LDH as well as ALT and AST are released into the plasma as a result of Doxorubicin-induced cardiotoxicity in Wistar rats. Our results showed that 16mg/kg intra peritoneal cumulative dose of Doxorubicin lead to signs of cardiotoxicity in the animals. This is in agreement with the work [25] which made the same observation. The significant ($p < 0.001$) increase in the activity of ALT, CK-MB and LDH in the Dox-induced (Group II) compared to the Control rats (Group I) and their subsequent significant ($p < 0.01$) decrease in the activity of the enzymes in Groups III and IV is consistent with the work [25] though utilizing a different plant extract. Also, the significant ($p < 0.05$) alterations in the ECG parameters (ST interval, QT interval, and QRS complex which were however, significantly ($p < 0.05$) decreased in the Beetroot treated rats (Groups III and IV) is also in agreement with the works[25, 31]. Likewise, our observation of significant ($p < 0.01$) decrease in the Heart rate in Dox rats (Group II) which however, was significantly ($p < 0.01$) increased in the Beetroot treated rats (Groups III and IV) compared to the Dox Group II is consistent with the work [25, 31], which both noted the same observation. Our result of significant ($p < 0.01$) increase in the Hemodynamic parameters (SBP, DBP and MABP) in Dox-induced animals (Group II) compared with the Control (Group I), which was significantly ($p < 0.05$) decreased in the Beetroot treated Groups III and IV correlates with the studies [25, 31, 32]. It also corroborates with the findings [33] though, the blood pressure lowering study was on human subjects. Also, the seemingly restoration of the Left Ventricular function parameters which were significantly ($p < 0.05$) decreased by Dox-induced cardiotoxicity but significantly ($p < 0.05$) restored in Groups III and IV is an indication that the aqueous extract of Beetroot possesses cardio-protective activity in Doxorubicin-induced cardiotoxicity in rats. In our work, the indication of cardiac injury, as portrayed by the significant ($p < 0.01$) increase in the serum Troponin-1level in the Dox-induced Group II compared to the Control (Group I) and its subsequent significant ($p < 0.05$) decrease in the Beetroot treated Groups

III and IV in comparison with Dox-induced (Group II) is consistent with the observation of Azza *et al.,* [31]. Also, our study showed that the cardiac antioxidant enzyme Cat was significantly ($p < 0.05$) reduced while that of MDA concentrations were significantly ($p < 0.05$) elevated in the Dox-induced Group II animals compared to the Control (Group I). These observations are in line with the report [32-35] who both reported that Doxorubicin administration in rats evoke a significant decrease in Catalase activity and a significant elevation in MDA concentrations. This observation can be explained on the basis of the rats' exhaustion in combating the Doxorubicin-induced free radicals which invariably bind onto the bio-membrane resulting in increased MDA concentrations. Our findings are also in agreement with the statement [36-37] that Beetroot (*Beta vulgaris*) is the most potent antioxidant vegetable.

CONCLUSION

Our findings demonstrated that aqueous extract of Beetroot (*Beta vulgaris*) vegetable plant possesses cardio-protective activity on Doxorubicin-induced cardiotoxicity in Wistar rats. Therefore, could be of value in the management of hypertension.

Conflict of Interest

The authors declare that, there is no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

REFERENCES

1. Pendlebury A, DeBernardo R, Rose PG. (2017). Long-term use of pegylated liposomabdoxorubicin to a cumulative dose of 4600 mg/m2 in recurrent ovarian cancer. Anticancer Drugs. 28:815-817.
2. Rawat PS, Jaiswal A, Khurana A, Bhatti JS, Navik U. (2021). Doxorubicin-induced cardiotoxicity: An update on the molecular mechanism and novel therapeutic strategies for effective management. Biomedicine & Pharmacotherapy. 139: 111708: 1-14.
3. Octavia Y, Tocchetti CG, Gabrielson KL, Janssens S, Crijns HJ, Moens AL. (2012). Doxorubicin-induced cardiomyopathy: from molecular mechanisms to therapeutic strategie J. Mol. Cell. Cardiol. 52 (6): 1213-1225.
4. Zhao N, Li Q, Sui H, Zhang H. (2020). Role of oxidation-dependent CaMKII activation in the genesis of abnormal action potentials in atrial cardiomyocytes: a simulation study, BioMed Res. Int. 3: 1-13.
5. Priya LB, Baskaran R, Huang CY, Padma VV. (2017). Neferine ameliorates cardiomyoblast apoptosis induced by doxorubicin: possible role in modulating NADPH oxidase/ROS-mediated NFkB redox signaling cascade. Sci Rep. 7:12283.

6. Henriksen PA. (2018). Anthracycline cardiotoxicity: an update on mechanisms, monitoring and prevention, Heart. 104 (12): 971-977.
7. Cardinale D, Colombo A, Bacchiani G, Tedeschi I, Meroni CA, Veglia F, Civelli M, Lamantia G, Colombo N, Curigliano, G. *et al.*, (2015). Early detection of anthracycline cardiotoxicity and improvement with heart failure therapy. Circulation. 131:1981- 1988.
8. Gao J, Chen T, Zhao D, Zheng J, Liu Z. (2016). Ginkgolide B exerts Cardio-protectiveproperties against doxorubicin-induced cardiotoxicity by regulating reactive oxygen species, Akt and calcium signaling pathways in vitro and in vivo. PLoS One 11(12):e0168219.
9. Csapo M, Lazar L. (2014). Chemotherapy-induced cardiotoxicity: pathophysiology and prevention, Clujul Med. 87 (3) 135–142.
10. Curigliano G, Cardinal D, Dent S, Criscitiello C, Aseyev O, Lenihan D, Cipolla CM. (2016). Cardiotoxicity of anticancer treatments: epidemiology, detection, and management, CA Cancer J. Clin. 66 (4): 309-325.
11. Gianni L, Herman EH, Lipshultz SE, Minotti G, Sarvazyan N, Sawyer DB. (2008). Anthracycline cardiotoxicity: from bench to bedside, J. Clin. Oncol. 26(22): 3777-3784.12. Salvatorelli E, Menna P, Chello M, Covino E, Minotti G. (2017). Modeling human
myocardium exposure to doxorubicin defines the risk of heart failure from low-dose doxorubicin, J. Pharmacol. Exp. Ther. 362 (2): 263-270.
13. Agency, CFI. (2012). The Biology of *Beta vulgaris L*. (Sugar Beet). Canadian Food Inspection Agency; Canada: Government of Canada; [cited 2018]. Available From:http://www.inspection.gc.ca/plants/plants-with-novel-traits/applicants/directive-94 -08/biology-documents/beta-vulgaris-l-/eng/1330725373948/1330725437349.
14 Babarykin D, Smirnova G, Pundinsh I, Vasiljeva S, Krumina 1G, Agejchenko V. (2019). Red Beet (*Beta vulgaris*) Impact on Human Health. Journal of Biosciences and Medicines. 7: 61-79.
15. Hamedi S, Honarvar M. (2018). *Beta vulgaris*-A Mini-Review of Traditional Uses in Iran. Phyto-Chemistry and Pharmacology Current Drug Discovery Technologies. 15, 1
16. Georgiev VG, Weber J, Kneschke EM, Denev PN, Bley T, Pavlov AI. (2010). Antioxidant activity and phenolic content of betalain extracts from intact plants and hairy root cultures of the red beetroot *Beta vulgaris* cv. Detroit dark red. Plant Foods Hum. Nutr. 65, 105-111.
17. Clifford T, Howatson G, West DJ, Stevenson EJ. (2015). The Potential benefits of Red Beetroot Supplementation in Health and Disease. Nutrients. 7: 2801-282.
18. Chhikara N, Kushwaha K, Sharma P, Gat Y, Panghal A. (2018). Bioactive compounds of beetroot and utilization in food processing industry: a critical review. Food Chem. 272:192-200.
19. Bahadoran Z, Mirmiran P, Kabir A, Azizi F, Ghasemi A. (2017) The Nitrate-Independent Blood Pressure-Lowering Effect of Beetroot Juice: A Systematic Review and Meta-Analysis. Advanced Nutrients. 8: 830-838.

20. Brook RD, Appel LJ, Rubenfire M, Ogedegbe G, Bisognano JD, Elliott WJ, Fuchs FD, Hughes JW, Lackland DT, Staffileno BA *et al.*,. (2013). Beyond medications and diet: alternative approaches to lowering blood pressure: a scientific statement from the American Heart Association. Hypertension. 61:1360-83.

21. Coles LT, Clifton PM. (2012). Effect of beetroot juice on lowering blood pressure in free-living, disease-free adults: a randomized, placebo controlled trial. Nutr J. 11:106 –11.

22. Affourtit C, Bailey SJ, Jones AM, Smallwood MJ Winyard PG. (2015). On the mechanism by which dietary nitrate improves human skeletal muscle function. Front Physiol. 6: 211.

23. Mirmiran P, Houshialsadat Z, Gaeini Z, Bahadoran Z, Azizi F. (2020). Functional properties of beetroot (*Beta vulgaris*) in management of cardio-metabolic diseases Nutrition & Metabolism. 17(3): 1-15.

24. OECD. Co-operation and Development. (2002). Guidance Document on the Recognition, Assessment and Use of Clinical Signs as Humane Endpoints for Experimental Animals Used in Safety Evaluation, Paris: OECD Publishing.

25. Shah SL, Mali VR, Zambare GN, Bodhankar SL. (2012) Cardioprotective Activity of Methanol Extract of fruit of *Trichosanthes cucumerina* on Doxorubicin-induced Cardiotoxicity in Wistar Rats. Toxicol Int. 19(2): 167-172.

26. Melanson SE, Tanasijevic MJ, Jarolim P. (2007). "Cardiac troponin assays: a view from the clinical chemistry laboratory". Circulation. 116 (18): e501-4.

27. Aebi H. Catalase. (1984). In: L. Packer(Ed), methods in enzymology, Academic pres, Orlando, 105: 121-126.

28. Esterbauer H, Cheeseman KH, Danzani MU, Poli G, Slater TF. (1982). Separation and characterization of the aldhyde products of ADP/Fe2+C stimulated Lipid peroxidation in rat liver microsomes. Biochem.J. 208:129-140.

29. Hoffman Daniel J. (2020). Use of Beetroot Juice Extract for Hypertension Treatment in Low-and Middle-Income Countries. Amer Society Journal of Nutrition. 150(9): 2233-2234.

30. Siervo M, Shannon O, Kandhari N, Prabhakar M, Fostier W, Kochl C, Rogathi J, Temu G, Stephan BC, Gray WK *et al.*,. (2020). Nitrate-rich beetroot juice reduces blood pressure inTanzanian adults with elevated blood pressure: a double-blind randomized controlled feasibility trial. J Nutr. 150(9):2460-8.

31. Azza AA Galal, Naglaa ZH Eleiwal, Kame MA. (2013). Protective effect of *Zingiber officinale* (ginger) on doxorubicin induced oxidative cardiotoxicity in rats. Life Science Journal. 10(2): 2924-2934

32. Hobbs DA, Kaffa N, George TW Methven, Lovegrove JA. (2012). Blood pressure-lowering effects of beetroot juice and novel beetroot-enriched breads in Normotensive male subjects. Br J Nutr. 108:2066-74.

33. Sundqvist ML, Larsen FJ, Carlström M, Bottai M, Pernow J, Hellénius ML,Weitzberg E, Lundberg JO. (2020). A randomized clinical trial of the effects of leafy green vegetables and inorganic nitrate on blood pressure. Am J Clin Nutr,111:749-56.

34. Thippeswamy A, Shirodkar A, Koti BC, Sadiq AJ, Praveen DM, Swamy AHMV, Patil M. (2011). Protective role of Phyllantus niruri extract in doxorubicin-induced myocardial

toxicity in rats. Indian J Pharmacol. 43(1): 31-35.

35. Ragavendran P, Sophia D, Arulraj C, Gopalakrishnan VK. (2012). Cardio-protective effect of aqueous, ethanol and aqueous ethanol extract of *Aerva lanata* (Linn.) against doxorubicin-induced cardiomyopathy in rats. Asian Pacific Journal of Tropical Biomedicine. 2(1): 212-S218.
36. Vodnar DC, Călinoiu LF, Dulf FV, Ştefănescu BE, Crişan G, Socaciu C. (2017). Identification of the Bioactive Compounds and Antioxidant, Antimutagenic and Antimicrobial Activities of Thermally Processed Agro-Industrial Waste. Food Chemistry. 231: 131-140.
37. Whaley-Connell A, Mc Cullough PA, Sowers JR. (2011). The Role of Oxidative Stress in the Metabolic Syndrome. Reviews in Cardiovascular Medicine. 12:21-29.