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Evaluation of Electrocardiographic Activity (ECG) and Blood Pressure Changes in Experimental Animal Models Treated with Doxorubicin and Hesperidin Co-Administration

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ABSTRACT

Background: The use of Doxorubicin as a common drug for the treatment of cancer can not be overemphasized. Despite its therapeutic effect, its clinical impact is compromised due to its high doses for effective treatment resulting in a side effect such as cardiotoxicity. Hesperidin, a citrus bioflavonoid with a wide range of biological activities including antioxidant, anti-inflammatory, anticancer, and cardio protective effects, may be protective

Aim: The aim of this study was to evaluate the electrocardiographic activity (ECG) and blood pressure changes in experimental animal models treated with doxorubicin and Hesperidin co-administration.

Methodology: Twentyfive male Wistar rats were separated into five cages containing 5 each. Doxorubicin(3mg/kg) was administered orally and Hesperidin (50mg/kg) supplemented for 28 days. Cardiovascular parameters (ECG, blood pressure changes) were determined using noninvasive machine. Blood samples were collected by cardiac puncture and centrifuged at 1000rpm to obtain serum for the determination of N-Terminal pro BNP using Elisa Kits.

Result: Results obtained showed that the QRS complex was significantly broadened while the Q-Tintervalbecame increased in Doxo group but reduced in other experimental groups. The R-R interval, P-R and R-T interval were also reduced in doxo group. Heart rate (HR)was significantly ($p<0.05$) increased in the Doxo+Hesperidin as well as the Doxo+ Captopril groups. HR was significantly ($p<0.05$) reduced in the doxo group. Mean arterial pressure, and N-Terminal proBNP were significantly elevated in Doxo group but decreased in the treatment groups.

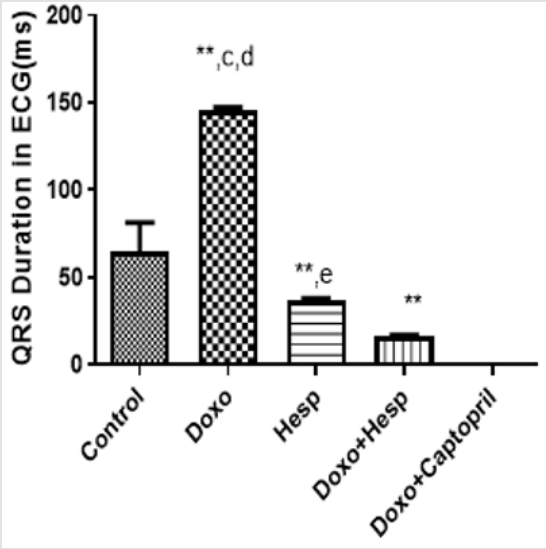
Conclusion: Hesperidin mitigates against the unpleasant alterations in electrocardiographic activities, blood pressure changes and secretion of N-Terminal proBNP resulting from use of Doxorubicin.

Keywords: Doxorubicin; ECG; N-terminal-PROBNP; Blood Pressure

Abbreviations: HR: Heart Rate; ECG: Evaluate the Electrocardiographic Activity; SEM: Standard Error of Mean; ANOVA: Analysis of Variance; ROS: Reactive Oxygen Species; NRF: Nuclear Factor Erythroid Related Factor

Introduction

Doxorubicin is a secondary metabolite that belongs to the anthracyclines family commonly used in treating different types of cancers, including leukemia, breast cancer etc., (Octia et al., 2012; Henriksen, et al. [1]). The use of this anthracycline derivative has over the years shown a prospective life expectancy in most cancer patients. Despite its clinical relevance, secondary and adverse effects have been associated with its use including cardiotoxicity, hepatotoxicity, myocardial infarction, heart failure, coronary artery disease and pulmonary toxicity (Take et al., 2008; Qi et al., 2020; Zhao, et al. [2]). This altered physiological function and organ activities have been reported and are said to be easily monitored using some basic techniques as echocardiography, dosing cardiac biomarkers (Renus, et al. [3]) like BNP and NT-proBNP (Nebigil, et al. [4]) as well as ECG (Zhao, et al. [2]) Several mechanisms have been identified through which doxo can induce toxicity especially if used at high dosages (Weiss, et al. [5,6]). Doxorubicin stimulates oxidative stress leading to the generation of ROS and superoxide anion radicals that initiate membrane lipid peroxidation (Qi et al., 2020), gradual cell death, depletion of calcium ions from the sarcoplasmic Reticulum thereby altering Ca2+ level and calmodulin-dependent kinase II (Takemura, et al. [7]), hampered mitochondrial activity causing cardiotoxicity, as well as by preventing DNA topoisomerase 2β activity resulting in damage to the DNA (Weiss, et al. [5,8]) While there is great potential to leverage on the phytochemicals or natreucitical component of plants for discovery as development of modern therapies, hesperidin use has shown a its potent anti-inflammatory, anti-apoptotic, anti- cardiotoxicity and improved mitochondria functions due to the presence of some antioxidant biomolecules (Figure 1).



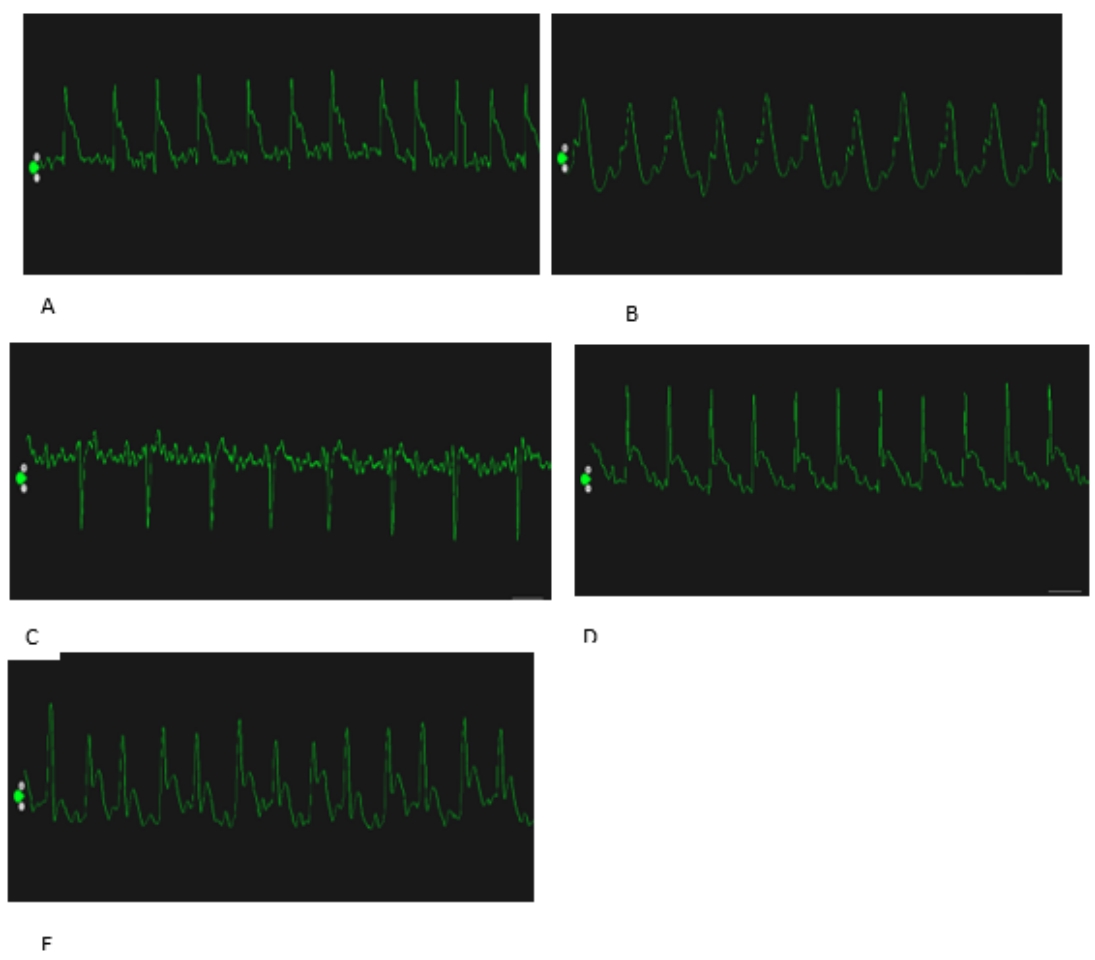
Note: RR-interval and the heart rate derived from the ECG were significantly ($p<0.05$) reduced in Doxo group compared to control and other groups. This is shown in Figure 1 while the QT interval was significantly ($p<0.05$) increased as shown in Figure 2. Treatment with hesperidin significantly($p<0.05$) lowered the RR-interval but increased the RR interval in the Captopril +Doxo group and QT interval was increased in the Doxo group but decreased significantly($p<0.05$) in the treatment groups.

Figure 1: Effect of Hesperidin supplementation on QRS complex duration in Doxorubicin induced cardio toxicity in wistar rats. Value are expressed in mean SEM; n=5;**=$p<0.05$ vs Control : b=$p<0.05$ vs Doxo, c=$p<0.05$ vs Hesp; d=$p<0.05$ vs Doxo=Hesp.

Methodology/Design

Experimental Design

Twenty five male Wistar rats weighing 120-170g were used in this study. They were randomly divided into five groups containing five rats each. The control group received normal feed and water only. Group 2 received 3mg/kg body weight of doxorubicin orally, Group 3 received of Hesperidin only while group 4 received 3mg/kg of doxorubicin and 50mg/kg body weight of hesperidin dissolved in distilled water and administered orally. Group 5 received 50mg/kg of captopril and 50mg/kg body weight of hesperidin. Feeding and administration of drugs lasted for 28days after which blood samples were collected through cardiac puncture and centrifuged at 1000rpm for 10minutes to obtain serum. Non invasive recording of Electrocardiogram and blood pressure from animals in all groups was taken. The serum samples were stored at -10°C until biochemical analyses. Ethical approval for this study was gotten from the faculty of Medicine and Surgery, Lusaka Apex Medical University (LAMU/FMS/ZM/REC/2024/Vol 1/021) (Plate 1).



Note: Showing sharp QRS peaks with raised S-wave and uneven baseline (possibly weak multiple T waves. (b) Doxorubicin only: Broadened QRS complexes with no visible P waves T waves (merged. Suggesting Ventricular tachycardia(c)Hesperidin Broadened QRS complexes with no visible P waves. (subsumes T waves). (d) Doxo+Hesperidin: Broad QRS complexes with no visible P and T; (e)DOXO+Captopril: Broad QRS complexes with no visible P and T waves (Possibly merged with multiple T waves.

Data based electrocardiographic results after doxorubicin treatment and co-administration with hesperidin and captopril respectively.

Effect of hesperidin co-administration on QRS complex in doxorubicin–induced cardiotoxicity

Plate 1: Electrocardiographic in (a)Control.

Rat ECG Monitoring Protocol

Anaesthetized rats were laid prone on a prepared board set up on the laboratory bench. Animals were placed on their backs in a spread-eagled pose with their limbs stretched and secured to the board for easy electrode placement. The limbs were stretched out and electrodes (Gold cup electrodes; Grass Instrument Company) were placed on the inner surface of the two fore limbs as well as the ankle of the left hind limb to achieve the traditional "Einthoven Triangle" orientation. Electrodes were plugged into the ECG monitoring machine which was connected through the USB to a computer (Intel Core 2 Duo) running a signal recorder software. ECG signals were captured with the software and data logged to disk as a file in the sound (wave) format. Recordings were initiated when stable and consistent signal waveforms were observed on the computer monitor and each recording session lasted for between 1 and 2 minutes (Figure 2).

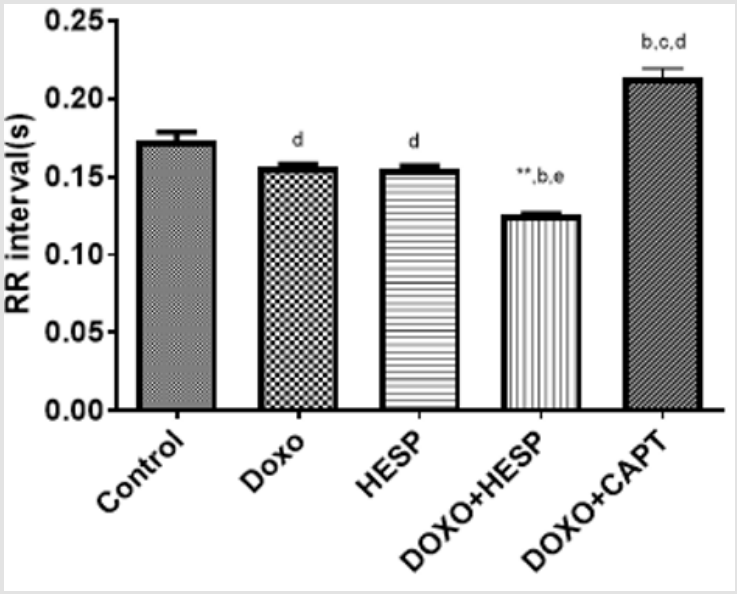


Figure 2: Effect of Hesperidin on R-R interval in CEG in Doxorubicin induced toxicity in Male Wistar rats. Value are expressed in mean SEM; n=5;**=p<0.05 vs Control : b=p<0.05 vs Doxo, c=p<0.05 vs Hesp; d=p<0.05 vs Doxo=Hesp e=p<0.05 vs Doxo+ captopril.

Method of Determination of N-Terminal-PROBNP

ELISA kits were used in the quantitative determination of Rat NT-proBNP concentrations in serum, in vitro according to the manufacturers prescription.

Statistical Analysis

The electrocardiogram parameter data such as R-R, QT, P-R, RT, QRS and HR) obtained, were reported as mean ± standard error of mean (SEM) and were analyzed using paired t-test and one-way analysis of variance (ANOVA) followed by Bonferroni's post-test. A probability of P<0.05 was considered significant.

Discussion

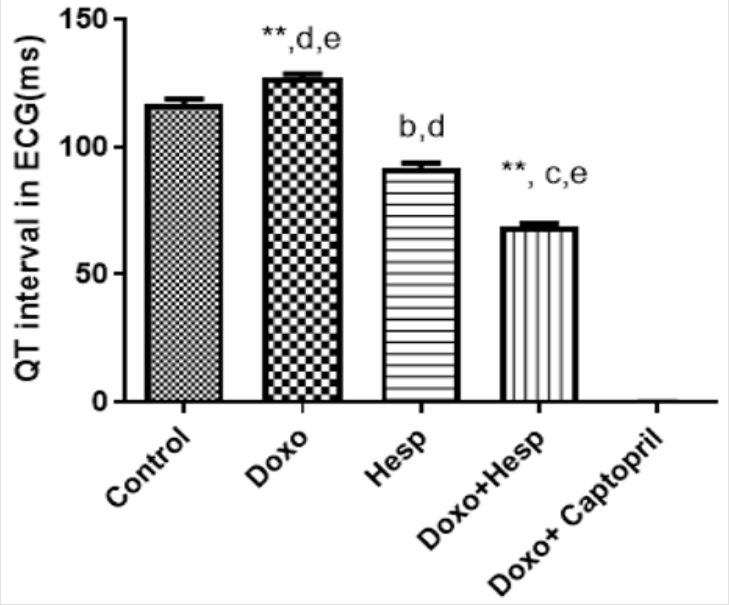
The use of doxorubicin (Doxo) in the management of cancer has recorded a tremendous success within the past decades although not with a negligible record of side effects especially within the cardiovascular system. Our study considered the use of doxorubicin in the treatment of malignancies and its attendant effect on physiological parameters such as blood pressure, heart rate and electrocardiographic studies as well as cardiac biomarkers like N-Terminal-proBNP. In this study, we implicated the use of Doxo as a causal agent in cardiotoxicity in experimental animal models. Electrocardiographic recordings from our study showed a significant increase in QT interval and P-R interval in doxo group. The QRS complex was broadened with a subsumed P and T-waves while the R-R interval was significantly (p<0.05) reduced as well as the Heart rate. Broadened QRS complex has been associated with some level of ultra structural changes in the myocardium such as the intercalated disc and myofibrillar derangement, all of which may lead to poor intraventricular conduction (Jensen, et al. [9]) Agen et al., 1994. The possible mechanisms by which Doxo cause cardiotoxicity and ECG changes have been reported to include generation of reactive oxygen species (ROS) and superoxide anion radicals that initiate membrane lipid peroxidation (Qi, et al. [5]) thereby altering the balance between antioxidant and oxidant status of the organism, altered calcium concentration and calmodulin dependence kinase II (Zhao, et al. [5]), mitochondrial impairment (Zhang, et al. [10]) and inhibition of topoisomerase 2β (Henriksen, et al. [1,11]).

The prolonged Q-T interval recorded in this study agrees with the previously reported work by (Porta-sanchez, et al. [12]) Duan et al., 2017 (Roden, et al. [13]). It is quite essential in the confirmation of the beginning of arrhythmias resulting from prolonged ventricular depolarization, cardiac arrhythmias or sudden death (Roden, et al. [14]). Although extensive work has been done on the cardiotoxicity of Doxo, there is paucity of knowledge on the bioactivity of hesperidin and on its pharmacological damage. In our study, the co-administration of Doxo and hesperidin as well as Doxo plus captopril, caused a characteristic increase in R-R interval and a subsequent heart rate, reduced QT interval and with a normalized QRS complex. Hesperidin (3′,5,7-trihydroxy-4-methoxy flavone) is a natural flavonoid found in citrus fruits such as grapefruit, lemon, orange, and lime (Parhiz et al., 2015). It exhibits some potent antioxidant properties (Pollard et al., 2006) and act as an anti-inflammatory, anti-apoptotic and antioxidant agent in many experimental studies (Park et al., 2018; Dong et al., 2020). It is therefore not surprising that it exhibited a reversal and or

protective effect on the cardiotoxicity caused by doxorubicin. Moreso, results from our study showed altered physiological parameters, such as blood pressure and heart rate derived from the ECG recording. Interestingly, we observed a significant decrease in blood pressure and heart rate at high dose of DOX. This result contradicts other earlier research work that reported that doxo potentiates sympathetic excitation (Lončar-Turukalo, et al. [15-17]).

The suppressed sympathetic activity thereby causing cardiotoxicity. DOX-induced cardiotoxicity is associated with chemoreceptor dysfunction usually affected by changes in blood composition such as oxygen, pH and carbon dioxide levels (Schultz, et al. [18,19]) and impairs their ability to sense and respond to changes in blood gas levels via chemoreceptor response. This can easily disrupt autonomic regulation, leading to changes in blood pressure, heart rate, and respiration (Iturriaga, et al. [19]). DOX is also known to impair cardiac muscle function and disrupt calcium balance, (Octavia, et al. [20]) Thereby reducing pumping action of the heart and, consequently, lower blood pressure. Other factors such as direct vascular toxicity may also influence lower blood pressure (Lenneman, et al. [21]). In fact, reports have shown that Doxo can cause vascular endothelial cell restructuring and dysfunction, as well as having a direct influence on the sympathetic nervous system.

This changes may result in altered vascular function (Lenneman, et al. [21]) and decreased release of norepinephrine from the sympathetic nevous system respectively causing vasodilation and hypotension (Medeiros- Lima, et al. [22]). Furthermore, we investigated the effect of Doxo administration and hesperidin co-administration on N-Terminal-proBNP (an inactive molecule resulting from cleavage of BNP prohormone) (Ventura HO, et al. [23]). From our results, serum N-Terminal-proBNP was significantly increased following doxorubicin treatment. Similar results have been reported by Curigliano et al., (2010) and Michael et al., (2021) (Figure 3). One stimulus for the secretion of this hormone is myocardial stretching induced by volume overload and vasoconstriction (Emdin, et al. [24,25]). They play an important role in the control of blood pressure and both sodium and water balance by regulating both the renin-angiotensin and the sympathetic nervous systems (Ventura, et al. [23]) and are used in the diagnosis of acute heart failure (Dunlay, et al. [26]) and correlate with left ventricular dilatation, remodeling, and dysfunction (Groenning, et al. [27]).Co-treatment with hesperidin significantly dercreased N-terminal proBNP. This outcome might be due to the high content of antioxidants whose significant role is to inhibit doxo-induced cardiotoxicity and oxidative damages.



Note: P-R interval and the RT-interval derived from the ECG were significantly ($p<0.05$) reduced in Doxo group compared to control and other groups. This is shown in Figures 3 & 4 respectively. Treatment with hesperidin significantly($p<0.05$) lowered the PR-interval in the Doxo+Hesp group and RT interval in the Captopril +Doxo group.

Figure 3: Effect of Hesperidin supplementation on QT interval in ECG Doxorubicin treatment in Male Wistar rats.n=5; Result is expressed as mean +SEM; n=5;**=$p<0.05$ vs Control : b=$p<0.05$ vs Doxo, c=$p<0.05$ vs Hesp; d=$p<0.05$ vs Doxo=Hesp e=$p<0.05$ vs Doxo+ captopril.

Antioxidants generally, and more specifically hesperidin offer defense mechanisms to scavenge ROS to protect the organism from oxidative damage (Wang, et al. [28]). Reports have shown that hesperidin posses potent anti-inflammatory, anti-oxidant, antiarrhythmic, neuroprotective, anticancer, antidepressant and immunomodulatory properties (Simopoulos, et al. [29,30]). This property provides its basis for scavenging reactive oxygen species ability and protection of tissue from oxidative stress damages. ROS is a biological molecule that increases the vulnerability of cells to apoptosis and tissue necrosis (Nguyen, et al. [31]) due to its distortion in the balance of the organisms immune system. An increase in ROS level increases the expression of the nuclear factor erythroid 2-related factor (Nrf2), which promotes cell susceptibility to oxidative stress and cell death (Papaiahgari, et al. [32-34]). DOX has been reported to have the potentials to increase Nrf2/HO-1 expression and to cause cell injury and death (Barakat, et al. [35]). Thus, the presence of hesperidin counteracted the adverse effect of Doxo as shown in this study (Figure 4) [36-40].

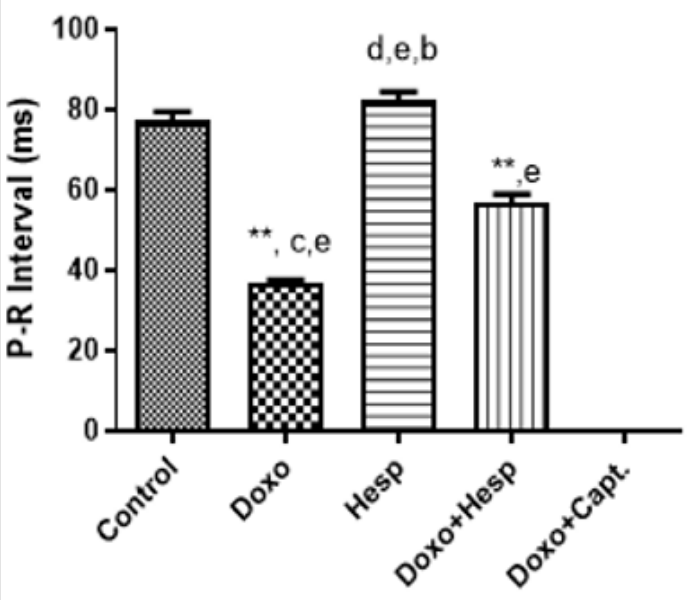


Figure 4: Effect of Hesperidin supplementation on P-R interval in ECG Doxorubicin induced cardio toxicity in Male Wistar rats.n=5; value are expressed as mean SEM; n=5;**=p<0.05 vs Control : b=p<0.05 vs Doxo, c=p<0.05 vs Hesp; d=p<0.05 vs Doxo=Hesp, e=p<0.05 *vs* Doxo+ captopril.

Conclusion

Hesperidin mitigate against the unpleasant alterations in electrocardiographic activities, blood pressure changes and secretion of N-Terminal proBNP resulting from use of Doxorubicin.

Conflict of Interest

The authors report no conflict of interest.

Acknowledgement

We sincerely appreciate the laboratory technologist for his overt assistance in the lab during the course of this work and Miss Nwabuike, Ozioma Emmanuel for her financial support and Commitment towards the successful completion of this study (Figures 5-8).

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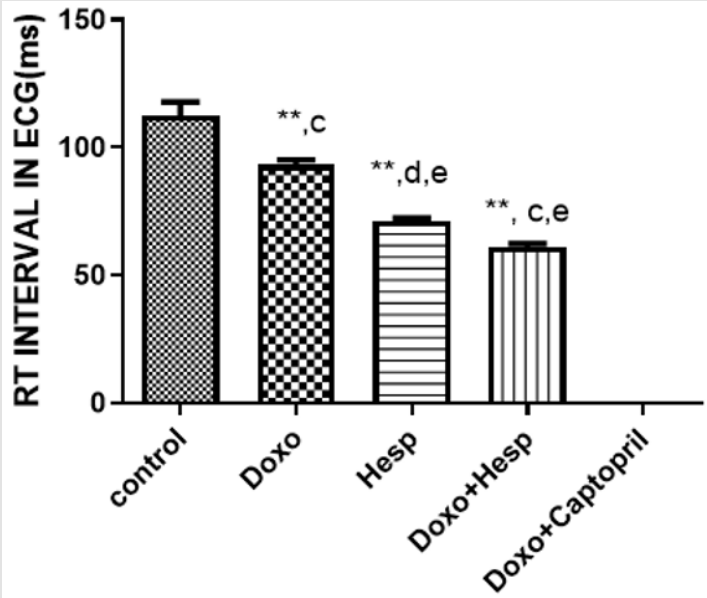

Figure 5: Showing the Effect of Hesperidin supplementation on R-T interval in ECG during Doxorubicin induced toxicity n=5; Result is expressed as mean+ SEM; n=5;**=p<0.05 vs Control : b=p<0.05 vs Doxo, c=p<0.05 vs Hesp; d=p<0.05 vs Doxo+ Hesp, e=p<0.05 *vs* Doxo+ captopril.

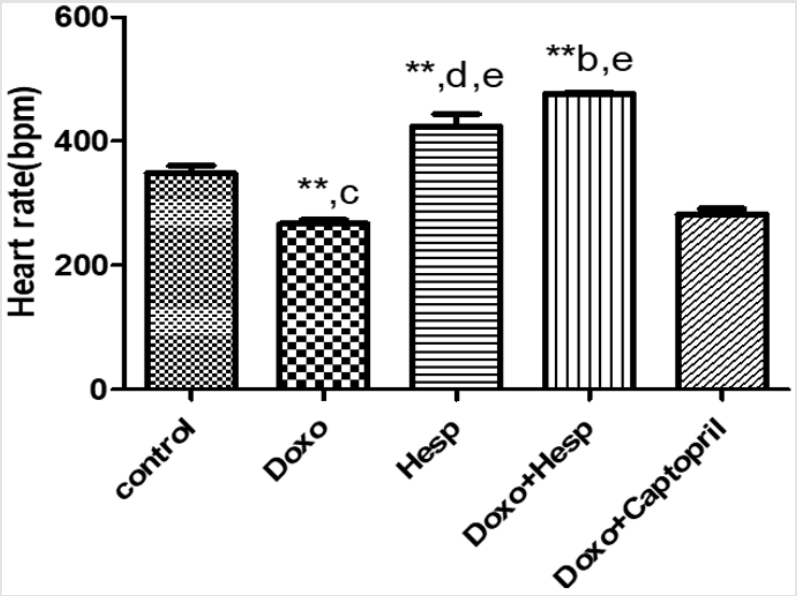

Figure 6: The Effect of Hesperidin and captoprll on heart rate in doxorubicin treated rates. Value are expressed in mean SEM; n=5;**=p<0.01 *vs* Control : b=p<0.01 vs Doxo, c=p<0.05 vs Hesp; d=p<0.05 vs Doxo+ Hesp, e=p<0.05 *vs* Doxo+ captopril.

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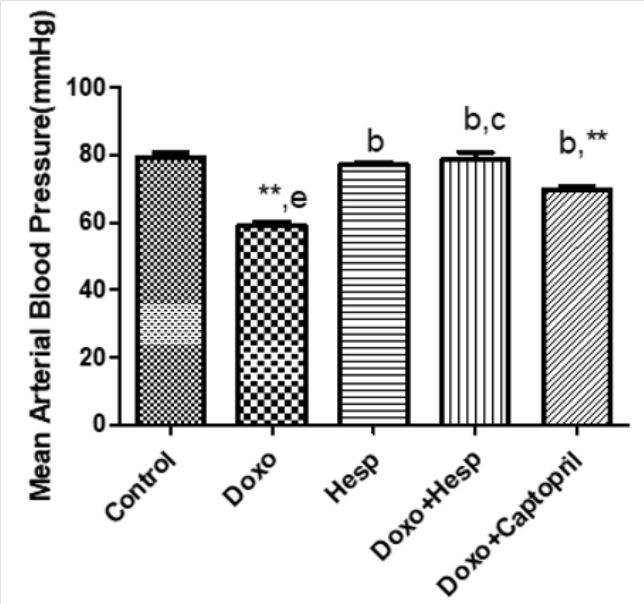
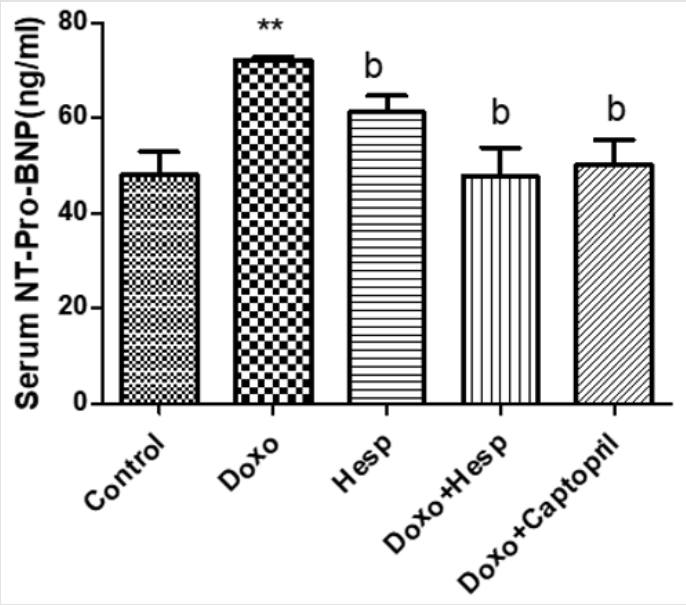


Note: Effect of Doxorubicin administration and hesperidin and captopril co-administration on Mean arterial pressure in male Wistar rats. The mean arterial pressure (MAP) was significantly($p<0.05$) lowered in the Doxo group when compared to control. Other treatment groups showed a significant ($p<0.05$) increase in mean arterial pressure when compared to doxo group only. This is depicted in Figure 7.

Figure 7: Effect of Hesperidin and captopril on mean arterial pressure in doxorubicin treated rates. Value are expressed in mean SEM; n=5;**=$p<0.01$ vs Control : b=$p<0.01$ vs Doxo, c=$p<0.05$ vs Hesp; d=$p<0.05$ vs Doxo+ Hesp, e=$p<0.05$ vs Doxo+ captopril.



Note: Effect of Doxorubicin administration and hesperidin and captopril co-administration on N-Terminal proBNP in male Wistar rats. Result obtained showed that N-Terminal-proBNP in Figure 8 was significantly($p<0.05$) elevated in doxo group compared to all other experimental groups. Treatment with hesperidin as well as Captopril significantly($p<0.05$) reduced the level of NT-proBNP.

Figure 8: Effect of Hesperidin and captopril supplementation on T-Terminal proBNP in doxorubicin treated rates. Value are expressed in mean SEM; n=5;**=$p<0.01$ *vs* Control : b=$p<0.01$ vs Doxo.

Authors Contribution

Nkanu, E.E designed, wrote the manuscript and revised the article for intellectual content; Esther George did data analysis, Sandra Lungu edited and finalized the manuscript. Moses Nyerinda proofread the manuscript and did most of the laboratory work.

Consent for Publication

All authors agreed and gave consent to make public the current manuscript. The work described has not been published and is not under consideration for publication elsewhere.

Ethics Approval and Consent to Participate

All authors were in agreement to participate in the study and to have the data published. All participants signed a written informed consent, which was revised by the local Ethics Committee, which then approved the study protocol.

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