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Deciphering the Ameliorative Potential of 5, 7-dihydroxyflavone (Chrysin) on Doxorubicin-Induced Cardiotoxicity by Modulating Oxidative Stress in Rats

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Abstract

Doxorubicin-induced cardiotoxicity is the leading cause of morbidity and mortality among cancer survivors. The present study aimed to investigate the ameliorative effect of 5, 7-dihydroxyflavone (chrysin) against doxorubicin-induced cardiotoxicity in Wistar rats. Thirty-five adult male Wistar albino rats were randomly allocated into seven groups (n = 5 each) which consisted of normal control (group 1) receiving phosphate buffer saline (0.4 ml), positive control (Group 2) received 2mg\kg of doxorubicin (DOX) through an intraperitoneal route once weekly for 21 days, chrysin low dose and chrysin high dose (Group 3 and 4) received oral administration of chrysin 50&100mg/kg for 21 days, chrysin low dose and DOX, chrysin medium dose and DOX and chrysin high dose and DOX(group 5, 6, and 7) received 2mg/kg of DOX once weekly with 50, 100 and 150mg/kg of chrysin for 21 days. Significant elevations in cardiac troponin I (cTnI) and histological lesions, which corresponded with oxidative stress, inflammation, apoptotic indicators, and cardiotoxicity when compared to controls, were indicative of DOX-induced cardiotoxicity. Malondialdehyde (MDA), a sign of oxidative stress, SOD, CPK (creatinine phosphokinase), TBARS (thiobarbituric acid reactive substance), and CAT (catalase) were also elevated in the DOX group. The DOX group also had increased levels of cardiac inflammatory markers, including as interleukin-1 (IL-1), interleukin-6 (IL-6), and the apoptotic marker caspase-3. 5, 7-dihydroxyflavone (chrysin) significantly mitigated, but did not entirely reverse, the cardiotoxicity caused by DOX by reducing the histopathological scores of cardiomyopathies and lowering cTnI in comparison to the DOX group. Additionally, chrysin reduced MDA to substantially similar levels as the control. Following chrysin administration, significant decreases in IL-1, IL-6, and caspase-3 were also seen in comparison to the DOX-only group. All things considered, these findings point to chrysin's protective action against DOX-induced cardiotoxicity, which may have been rendered possible by oxidative stress, inflammatory, and apoptotic suppression.

Keywords: Chrysin, Doxorubicin, Cardiotoxicity, Oxidative Stress.

1. INTRODUCTION

Doxorubicin (DOX) was introduced in cancer therapy in the late 1960s. It has come forth as one of the most potent broad-spectrum anti-tumor anthracycline antibiotics. DOX can be administered as a single agent or in conjunction with other chemotherapeutic agents. It is broadly used in the treatment of a variety of cancer types, including leukemia, lymphoma, soft-tissue sarcoma, and solid tumors. However, its clinical utility is markedly hampered by the high incidence of dose-dependent cardio-toxicity; irreversible degenerative cardiomyopathy, and congestive heart failure (Smith *et al.,* 2010). With the increasing use of this anthracycline antibiotic, acute cardio-toxicity has been recognized as a severe complication of DOX chemotherapy (Hayek *et al.,* 2005). The pathogenesis of DOX-induced cardio-toxicity is not entirely clear, but a solid piece of evidence indicates that oxidative stress, inflammation, and apoptosis are involved (Minotti *et al.,* 2004). Doxorubicin continues to be a potent and effective

intervention in various types of cancers. Therefore, it is still desirable to search for a safe and effective remedy that can reverse DOX-induced cardio-toxicity.

Today, much awareness has been given to the usage of phytochemicals as a protective plan of action against DOX-induced cardio-toxicity (Xiao *et al.*, 2012). Natural polyphenolic phytochemicals called flavonoids are helpful in the prevention and treatment of a wide range of illnesses, including diabetes, cancer, cardiovascular disease, and neurological diseases (Khan *et al*., 2012). Natural polyphenolic phytochemicals called flavonoids are helpful in the prevention and treatment of a wide range of illnesses, including diabetes, cancer, cardiovascular disease, and neurological diseases (Khan *et al.*, 2012). This class includes chrysin (5,7-dihydroxyflavone), which is present in honey, propolis from bees, and a variety of plants (Barbarić *et al*., 2011). One of the flavonoids present in fruits, vegetables, and plants is chrysin; research suggests that its anti-inflammatory and antioxidant properties contribute to its protective properties against cardiovascular disease. By enhancing the antioxidant system, inhibiting pro-oxidant enzymes, scavenging free radicals, and chelating redox-active transition metal ions, chrysin scavenges free radicals and has an antioxidant impact. Chrysin improves the blood lipid profile by decreasing lipid production and increasing its metabolism. By making endothelial nitric oxide more bioavailable, chrysin controls vascular function. By reducing vascular inflammation, chrysin prevents the onset of atherosclerosis. Chrysin's anti-inflammatory properties could be attributed to its inhibition of the. It has various biological qualities such as antioxidant, anti-inflammatory, anti-apoptotic, and anti-cancer (Sultana *et al.*, 2012).

Despite significant advancements in study methods and investigation over the years, the precise mechanism responsible for DOX-induced cardiotoxicity is still unknown. Cardiolipin is a negatively charged phospholipid that is prevalent in the inner mitochondrial membrane and builds up inside the mitochondria of cardiomyocytes. DOX has a strong affinity for it (Parker *et al*., 2001). Numerous studies indicate that the primary mechanism responsible for DOX-induced cardiotoxicity is oxidative stress (Sangomla *et al*., 2018; Abdel-Daim *et al*., 2017). According to studies by Kuznetsov *et al*., (2011) and Signal *et al*., (2000), DOX decreases endogenous antioxidants and increases lipid peroxidation, which changes the structure and functions of cardiac cell membranes. DOX also causes excessive formation of reactive oxygen species (ROS) in the mitochondria, causing oxidative damage to biological macromolecules, including lipids, proteins, and DNA.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Thirty-five male rats weighing 100-200g were procured from and housed in the Department of Anatomy, University of Nigeria Enugu Campus. The rats were acclimatized to the environment for 2 weeks before experimental use. They were allowed free access to clean water and standard livestock pellets (Guinea Food Nigeria Limited). The body weights of the animals were recorded before, during, and after administration, using an electronic weighing scale. The procedures of this study were conducted according to Animal Care and Use Standard Operating Procedures and Guidelines (SOPGs), and ethical approval was obtained from the Ethics and Research Committee of the Faculty of Basic Medical Sciences, Enugu State University of Science and Technology.

2.2 Drugs

Chrysin (5, 7-dihydroxyflavone) was procured from Sigma-Aldrich Company, 3050 Spruce Street, St. Louis, USA. Doxorubicin was purchased from Open-Heaven Pharmaceutical Store, opposite ESUTH Parklane, Enugu, Nigeria.

2.3 Experimental Design

Thirty-five (35) adult male Wistar rats (weighing 100-200g) were used for this study. They were randomly divided into seven (7) different groups of five animals (n=5) each. The experimental animals were grouped and treated as tabulated below;

Table 1: Experimental animals grouping and design

	Groups	Rats	Treatment
1	Negative Control	5	Distilled water and oral phosphate-buffered saline (0.4ml) for 21 days.
2	Positive Control	5	Intra-peritoneal Doxorubicin at a weekly dose of 2mg/kg BW for 21 days.
3	Low dose Chrysin only	5	Oral Chrysin at a daily dose of 50mg/kg BW for 21 days.
4	High dose Chrysin only	5	Oral Chrysin at a daily dose of 150mg/kg BW for 21 days.
5	Low dose Chrysin + DOX	5	Oral Chrysin at a daily dose of 50mg/kg BW and intra-peritoneal Doxorubicin at a weekly dose of 2mg/kg BW for 21 days.
6	Medium dose Chrysin + DOX	5	Oral Chrysin at a daily dose of 100mg/kg BW and intra-peritoneal doxorubicin at a weekly dose of 2mg/kg BW for 21 days.
7	High dose Chrysin + DOX	5	Oral Chrysin at a daily dose of 150mg/kg BW and Intra-peritoneal doxorubicin at a weekly dose of 2mg/kg BW for 21 days.

2.4 Biochemical Assays

2.4.1 Malondialdehyde (MDA) and Glutathione (GSH) assay

According to the methodology provided by Satyam *et al*., the estimation of malondialdehyde (MDA) and glutathione (GSH) serum was examined for both MDA and GSH (2013; 2014). Using an iMark microplate absorbance reader, the optical density for MDA and GSH was measured at 540 nm and 412 nm, respectively. Based on their absorbance, serum MDA and GSH levels were computed and represented as milligrams per milliliter (mM/ml).

2.4.2 Superoxide Dismutase (SOD) And Catalase (CAT) assay

Antioxidant enzymes SOD and CAT were determined in cardiac tissue as per standard protocol activities of SOD measured by the method of Marklund and CAT activity was measured according to the method of Claiborne (Marklund & Marklund, 1974).

2.4.3 Cardiac Troponin, Creatinine Phosphokinase (CPK) And Lactate Dehydrogenase (LDH) estimation

Cardiac troponin and CPK were estimated using test strips, while LDH was estimated in serum by enzymatic kit using a biochemistry semi-auto analyzer, Nicholas Piramal 5010.

2.4.4 Apoptosis Analysis and Inflammatory Cytokines

The activity of the caspase enzyme in the brain tissue homogenate is measured. The cells that are suspected or have been induced to undergo apoptosis are first lysed to collect their intracellular contents. The cell lysate can then be tested for protease activity by the addition of a caspase-3- 3 specific peptide that is conjugated to the color reporter molecule p-nitroaniline (pNA). When caspase cleaves a peptide, it releases the chromophore pNA, which has a wavelength of 405 nm and may be measured spectrophotometrically. The color reaction is closely correlated with the amount of caspase enzymatic activity present in the cell lysate. IL-6 (interleukin-6) and IL-I (interleukin-1) platinum ELISA for rats using an Elisa Kit in accordance with the manufacturer's instructions.

2.4.5 TBARS Assay

The index of lipid peroxidation in the heart tissues was also estimated *via* measuring TBARS using 1% TBA in 0.05M sodium hydroxide (NaOH) incubated with the sample at 100°C for 15min and then measured at 530nm.

2.5 Statistical Analysis

All quantitative data were analyzed using GraphPad version 8 and SPSS Version 23 (IBM Corp., Armonk, NY, USA) software, using one-way ANOVA followed by Tukey's comparison test. Significance was set at P <0.05 (95% confidence interval). The results were represented in tables and bar charts to show the mean and standard deviation error of the mean.

3. RESULTS

3.1 BIOCHEMICAL RESULT

Table 2: Result of the Mean ± Standard Deviation of the Anti-Oxidative Biomarkers

GROUPS	SOD	MDA	GSH	TBARS	LDH	CPK	CAT
1	12.07±0.36	7.07±0.66	26.66±0.65^{A}	2.10±0.34^{A}	144.54±5.56	122.62±3.85^{A}	36.70±0.90^{A}
2	8.92±0.96*	8.97±0.18*	22.66±0.15*	3.59±0.11*	165.66±6.18*	147.41±6.55*	30.17±1.91*
3	11.94±0.32^{A}	7.43±0.24^{A}	25.43±0.50^{A}	3.88±0.34	148.91±3.09	127.52±0.77^{A}	34.42±1.10^{A}
4	10.67±0.21	8.44±0.13*	24.83±0.75	4.05±0.43*	156.55±2.16	136.51±2.70^{A}	32.93±0.80
5	10.80±0.48^{A}	7.82±0.13	25.19±0.15^{A}	3.89±0.43*	158.73±8.03	130.52±2.70^{A}	34.64±0.60^{A}
6	11.46±0.46^{A}	7.99±0.29	24.70±0.94	3.10±0.13*	160.70±8.02	132.42±5.40	33.10±0.30
7	11.56±0.91^{A}	8.08±0.11	24.94±0.60	3.81±0.41*	155.24±5.87	139.51±3.08*	32.79±0.80

Values were expressed as Mean ± Standard deviation; *p<0.05 showed a significant difference compared with the control group 1, while ^{A}P<0.05 showed a significant difference comparing group 2 to groups 3,4,5,6,7.

***SOD = SUPEROXIDE DISMUTASE**
***MDA=MALONEDIALDEHYDE**
***GSH= GLUTATHIONE**
***CAT= CATALASE**
***LDH=LACTATE DEHYDROGENASE**
***CPK= CREATININE PHOSPHOKINASE**
***TBARS=THIOBARBITURIC ACID REACTIVE SUBSTANCE**

Table 3: Result of the Mean ± Standard Deviation of the Anti-Inflammatory Markers

GROUPS	IL-6	IL-1	CASPASE- 3	CARDIAC TROPONIN
1	204.35±5.36	131.09±9.27	4.98±0.30^{A}	0.04±0.02^{A}
2	238.48±5.96*	182.58±9.27*	6.90±0.19*	0.12±0.03*
3	215.31±0.60^{A}	138.58±6.62^{A}	5.40±0.32^{A}	0.08±0.02
4	219.94±3.58	157.30±2.65	5.52±0.16^{A}	0.10±0.02
5	222.89±4.17	150.28±8.61^{A}	5.61±0.23^{A}	0.11±0.02
6	222.47±9.53	148.88±5.30^{A}	6.07±0.23*	0.09±0.01
7	213.30±3.58^{A,}	150.28±3.31^{A}	5.93±0.16^{*A}	0.10±0.03

Values were expressed as Mean ± Standard deviation; *p<0.05 showed a significant difference compared with the control group 1, while ^{A}P<0.05 showed a significant difference comparing group 2 to groups 3,4,5,6,7.

***IL-1= INTERLEUKIN 1**
***IL-6= INTERLEUKIN 6**

3.2 BODYWEIGHT RESULT

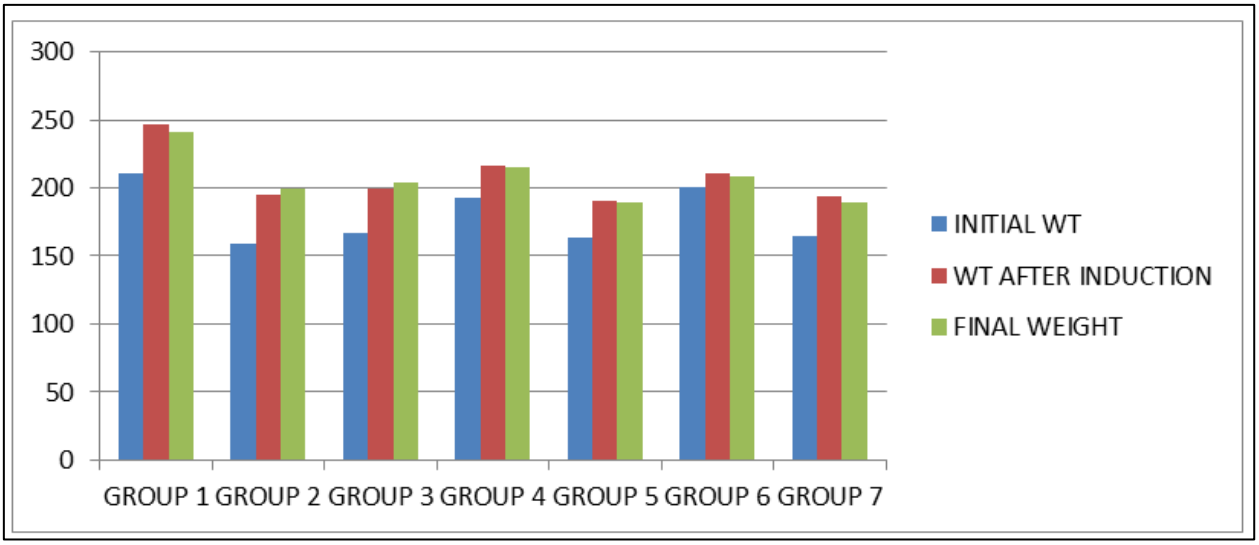
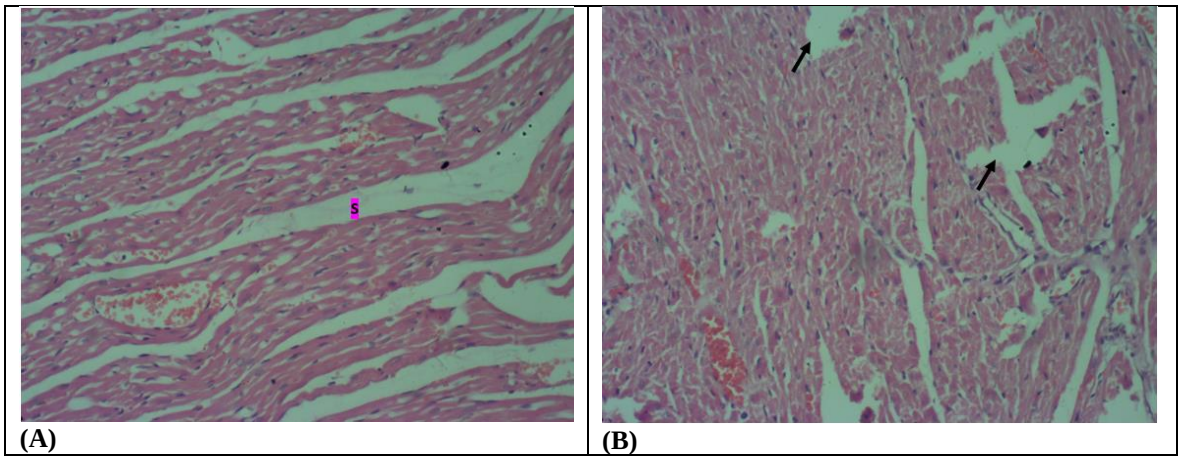


Fig 1: Chart showing the distribution of the animals' body weight before (initially) and after induction, and finally after treatment
WT= WEIGHT. Chart showing initial and final weight before and after induction.

3.3 EFFECT OF DOXORUBICIN (DOX) ON HISTOMORPHOLOGY OF THE MYOCARDIUM OF WISTAR RATS TREATED WITH CHRYSIN FOLLOWING DOX-INDUCED CARDIOTOXICITY



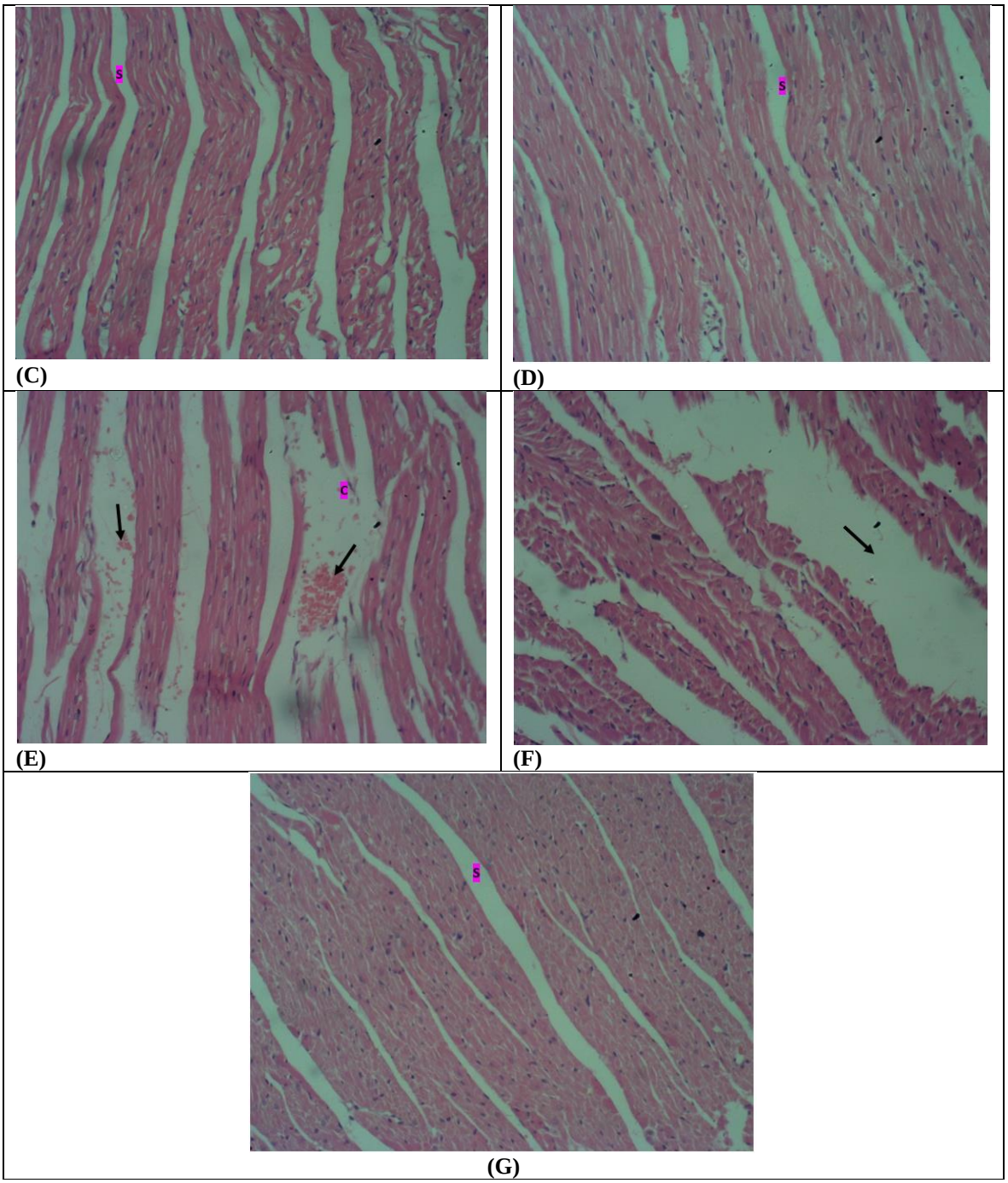


Fig 2: H&E; *Magnification ×200* (A) shows a photomicrograph of the Negative Control group demonstrating interspersed cardiomyocytes with connective tissue septa - the heart appears normal. (B) Positive Control group demonstrating cardiomyocytes with focal areas [black arrows] of myocardial infarct. (C) and (D) demonstrated interspersed cardiomyocytes with connective tissue septa - the heart appears normal. (E) demonstrated cardiomyocytes with focal areas showing hemorrhage [black arrows] and mild obliterative cardiomyopathy. (F) showed obliterative cardiomyopathy and mild interstitial tissue enlargement. (G) showed cardiomyocytes interspersed with connective tissue septa - heart tissue appears normal

4. DISCUSSION

The mechanism of doxorubicin-induced cardiotoxicity is still unclear and more likely to be multifactorial (Rochette *et al*., 2015). One of the suggested mechanisms is a dysfunction of cardiac muscle that may end up with heart failure (Kelleni & Abdelbasset, 2018). Oxidative stress is another mechanism of Doxorubicin (DOX) toxicity; damage of the myocardium by free radicals increases membrane permeability enhancing the release of enzymes (Swamy *et al.*, 2011), which are released from damaged myocytes and are sensitive indicators of cardiac injury (Herman *et*

al., 2000). Usually, during cardiac damage greater amount of troponin is released into the blood.

The heart's overall enlargement, ventricular dilatation, and inflammatory cells were all part of the common chronic response seen in the heart's gross morphological changes after receiving DOX. Reduced body weight and increased heart weight are two further effects of DOX-induced cardiotoxicity (Ascensão *et al*., 2005). Results of this study confirmed that a dose of 2mg/kg of doxorubicin produced significant cardiotoxicity as was observed in the focal area of myocardial infarction in heart tissue this was supported by work done by (Mantawy *et al.,* 2017) with 15mg/kg body weight of DOX was ameliorated by chrysin. The increase in these biomarkers was further validated by histopathological examination.

In this work, we assessed whether 5,7-dyhydroxyflavone could protect rats from acute cardiac damage caused by DOX. The assessment of certain cardiac tissue biomarkers, such as glutathione (GSH), lipid peroxidation products like malondialdehyde (MDA) level and superoxide dismutase and catalase (SOD and CAT), inflammatory biomarkers activities, and histopathological examination of heart tissue, was used to investigate doxorubicin-induced cardiotoxicity. The histopathological examination carried out on the heart shows tissue of various groups. Group one (negative control) which was given phosphate buffer saline appears normal with no pathology seen, there was no inflammation, apoptosis, or hemorrhage found. Group two (positive control) given doxorubicin only showed a focal area of myocardial infarcts, this indicates that 2mg/kg body weight of doxorubicin, used in this study had a cardiotoxic effect on the heart in support with other works like (Kwatra *et al.,* 2016). Groups three and four which received low (50mg/kg) and high (150mg) doses of chrysin respectively appeared normal and no pathology was seen. This could be because of the effect of chrysin, which helps to regulate cellular activity and fight off free radicals that cause oxidative stress on the body (Jethwani *et al.,* 2022).

Groups five and six given DOX with chrysin low(50mg/kg) and medium(100mg/kg) doses showed hemorrhage with mild obliterative cardiomyopathy and mild interstitial tissue enlargement and obliterative cardiomyopathy, this shows that at 50 mg/kg and 100mg/kg 5,7-dihydroxyflavone(chrysin) did not affect the result of 2mg/kg DOX-induced cardiotoxicity, the present findings were supported by earlier reports of (Saad *et al.,* 2001; Swamy *et al.,* 2011; Saleem *et al.,* 2014; Su *et al.,* 2015). Meanwhile, Mantawy *et al.,* (2014) reported that the cardiotoxic effect from 15mg of DOX was ameliorated by 25mg/kg and 50mg/kg of chrysin. This could be because the rats were pretreated with these doses, before induction of DOX for a cardioprotective effect and chrysin which has beneficial anti-inflammatory effects and protects cells from oxidative damage that can lead to disease (Janabi *et al.,* 2020), preventing the effects of DOX.

An ameliorative effect was observed in group seven which received doxorubicin and a high dose of chrysin (150mg/kg) where the heart tissue appeared normal. Consequently, chrysin at 150mg\kg dose was ameliorative against doxorubicin-induced changes in the heart, and this agrees with the earlier report of Mantawy *et al.,* (2014). The mean level of troponin group 2 (positive control) was significantly higher than group 1 (Table 3) and was the highest compared to all other groups. The value in group 1 was significantly lower in comparison to other groups.

The elevated troponin activity may result from the release of lysosomal enzymes that worsen the injury or from the toxic metabolites of doxorubicin binding to cardiac macromolecules, causing damage and necrosis that releases intracellular contents into the systemic circulation as well as free radicals. This outcome is compared to a report from a previous investigation conducted by Senthilkumar *et al*., (2006).

When compared to the toxic group, the ameliorative groups (5, 6, 7) displayed a minute drop in troponin activity; nevertheless, this decrease was still significantly higher than that of the control group. The ameliorative agents' mediation of enhanced heart function may be the cause of the decline (Bhaskar & Rao, 2002). Groups 3 and 4 were somewhat higher but lower than the DOX group, and they did not exhibit any discernible changes from the control group. This may be due to chrysin's ability to control cellular activity and fend against free radicals, which put the body under oxidative stress (Saad *et al*., 2001).

When compared to the control group (group 1), GSH (glutathione), SOD (superoxide dismutase), and CAT (catalase) all increased in the DOX group (group 2), with groups 3, 4, 5, 6, and 7 showing a statistically significant increase compared to the group 2 (Table 2). Depletion of antioxidants and increased oxidative stress may be the cause of cardiac tissue damage. The mean levels of GSH, CAT, and SOD were significantly higher in group 5, which received a low dose of chrysin (50 mg/kg), than in the DOX group. This contrasts with findings from a related study that showed no discernible rise at 50 mg/kg when DOX was administered at 15 mg/kg body weight (Mantawy *et al*., 2017). This might be the case as it.

When compared to the other groups, the DOX group's mean level of malondialdehyde (MDA) was higher than that of the normal control group. According to data, DOX administration in rats resulted in a considerable increase in lipid peroxidation, which was demonstrated by marked elevations in MDA. This is

consistent with earlier research (Sarkar *et al*., 2015). Rats treated with 5,7-dihydroxyflavone showed a partial restoration of tissue antioxidant capacity; MDA levels were sufficiently impacted to resemble those in the control group, but the therapy did not significantly change MDA levels when compared to the DOX group. This outcome is consistent with earlier research (Sarkar *et al*., 2015; Shaker *et al*., 2018; Zhang *et al*., 2005; Ahmed *et al*., 2005; Yilmaz *et al*., 2006).

The DOX group had the lowest mean values of all the groups, with creatinine phosphokinase, lactate dehydrogenase, and thiobarbituric acid reactive substance (CPK, LDH, and TBARS) being greater than those of the control group. There was a discernible rise in myocardial TBARS in contrast to group 1. (control group). It is possible that free radicals formed from the interaction of superoxide radicals with hydrogen peroxide or from the reaction of drug toxic radicals with oxygen are what cause the toxic group's (DOX group) significantly higher TBARS values compared to group 1 (Table 2). This suggests that increased lipid peroxidation may be linked to cellular damage. While the ameliorative group's TBARS increased in this study when compared to the DOX-treated group, other studies indicate that the mean TBARS value of the ameliorative groups was much lower than the group treated with doxorubicin. The outcomes matched previous reports (Sharma *et al*., 2007; Swamy *et al*., 2011; Siddique *et al*., 2009).

The study found that the DOX group had higher mean activity levels in CPK and LDH than group 1 did (Table 3). The elevated levels of CPK and LDH could potentially be attributed to the harmful byproducts of doxorubicin, which attached themselves to cardiac macromolecules, inflicting harm and necrosis that allowed intracellular contents to be released into the bloodstream. Additionally, the generation of free radicals or the release of lysosomal enzymes may exacerbate the injury. In comparison to the toxic group, the ameliorative groups (5, 6, and 7) and the chrysin-only group (3 and 4) displayed a moderate drop in CPK and LDH activity; nevertheless, this decrease was still much higher than that of the control group. The ameliorative agents' mediation of enhanced heart function may be the cause of the decline (Senthilkumar *et al*., 2006; Siddique *et al*., 2009; Swamy *et al*., 2011; Minotti *et al*., 2004).

When compared to group 1, the DOX group (group 2) in caspase-3 exhibited a rise and was the highest of the other groups. When compared to group 2, the ameliorative groups (5, 6, and 7) of Caspase 3 demonstrated an increase that was dose-dependent and increased with a greater dose. The pathophysiology of DOX-induced cardiotoxicity involves apoptosis (Minotti *et al*., 2004). Increased oxidative stress brought on by DOX sets off a number of signaling cascades, one of which is the activation of caspase-3, which causes the death of cardiomyocytes (Octavia *et al*., 2012; Dash *et al*., 2015). Similar to the findings published by Chen *et al*., (2015), the results of this investigation demonstrated a considerable increase in caspase-3 activity in cardiac tissue after DOX treatment (Chen *et al*., 2007). All things considered, it is plausible that our findings that 5, 7-dihydroxyflavone-mediated decreases the inflammatory mediators and that the partial improvement in cardiac tissue's antioxidant capacity highlighted decreases in DOX-mediated increases in cellular caspase-3 level, which were observed in groups (5, 6 and 7) as well as in the chrysin only groups (3 and 4).

The DOX group's mean level of IL1 and IL6 was lower than that of groups 3, 5, 6, and 7 and higher than that of the control group (Table 3). The pathophysiological basis for DOX-induced cardiomyopathy may be the increasing rise of pro-inflammatory cytokines inside heart tissue, as evidenced by current research (Pecoraro *et al*., 2016). In line with those publications, the current study's findings, which showed appreciable increases in cardiac IL-1 and IL-6 in the DOX group compared to controls, suggested an important role for inflammation in the pathophysiology of DOX-induced cardiotoxicity. Uncertainty surrounds the main underlying mechanism driving this rise in inflammatory indicators, while potential triggers include reduced tissue antioxidant capacity, elevated ROS levels, and consequent lipid peroxidation. It has been revealed recently that there is a correlation between elevated levels of oxidative stress and inflammatory mediators. Oxidative stress is believed to initiate inflammatory reactions by activating the NF-κB pathway, which in turn triggers the transactivation of cytokines (Sun *et al*., 2016; Dash *et al*., 2015). The results of this investigation showed that chrysin therapy significantly decreased cardiac IL-1 and IL-6 levels, indicating that chrysin has a consistent reversing effect on the DOX-mediated release of inflammatory mediators inside cardiac tissues. The final weight was measured prior to sacrifice, and measurements were made of the body both before and after induction. There was a considerable rise in body weight in the DOX, chrysin-only, and control groups. While the body weight did not significantly increase in the control group, it did decrease in the ameliorative groups 6 and 7 and the low dosage ameliorative group 5. Their toxic effects, particularly on heart tissue, may have disrupted basal metabolism, which has a negative impact on body weight. These results are consistent with the reports of Kalender *et al*., (2022) and Kozluca *et al*., (1995).

5. CONCLUSION

This study shows that 5,7-dydroxyflavone at a dose of 150mg/kg body weight has an ameliorative effect in the treatment of doxorubicin-induced cardiotoxicity in adult Wistar rats.

ETHICAL APPROVAL

Ethical approval was obtained from the Faculty of Basic Medical Science research ethics committee, Enugu State University of Science and Technology College of Medicine (ESUCOM), with the Ethical Right Permission Number: (ESUCOM/FBMS/ETR/2022/013) and the research was conducted according to the guidelines for the care and use of laboratory animals of ESUCOM.

Conflict of Interests: The authors declared no conflict of interest.

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