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Ameliorative Effect of Methanol Extract of *Tectona grandis* Leaves on Cyclophosphamide-induced Cardiotoxicity in Wistar Rats

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ABSTRACT

Cyclophosphamide is a therapeutic agent with an extensive clinical application. It is used in treating acute and chronic leukaemia, lymphomas, multiple myeloma, rheumatoid arthritis and in preparation for bone marrow transplantation. However, cyclophosphamide has numerous organ toxicities that have limited its clinical use. The study aimed to investigate the ameliorative effect of the methanol extract of *Tectona grandis* leaf on cyclophosphamide-induced cardiotoxicity. Twenty female Wistar rats were randomly divided into four groups (n=5). Cardiac toxicity was induced in Wistar rats by administering cyclophosphamide 50 mg/kg BW IP daily for three days. *Tectona grandis* leaf extract (200 and 400 mg/kg) was orally administered immediately after cyclophosphamide treatment on the fourth day for 21 days. The control group received only feed and water. After the 21-day treatment, the rats were euthanized under anesthesia to obtain blood for biochemical analysis. Histopathological evaluation was also conducted. Data was analyzed using the statistical package GraphPad Prism version 8.0.2. Analysis of variance (ANOVA) and post hoc test were carried out. Cyclophosphamide administration significantly elevated ($p < 0.05$) the troponin level and activities of creatine kinase and lactate dehydrogenase compared with the control. Additionally, the cyclophosphamide alone-treated group showed elevated levels of malondialdehyde, reduced activities of antioxidant enzymes- superoxide dismutase, catalase and glutathione peroxidase and abnormal changes in lipid profile status compared with the control and other treatment groups. Treatment with methanol *T. grandis* leaf extract (MTGLE) reversed the changes by significantly ($p < 0.05$) reducing the levels of troponin and malondialdehyde, increasing the activities of creatine kinase, lactate dehydrogenase, superoxide dismutase, catalase and glutathione peroxidase while restoring the lipid profile of cyclophosphamide-induced rats. The result of the histopathological examination showed an improvement in the cardiac histo-architecture of MTGLE-treated groups, which supports the findings of the biochemical investigation. This suggests that *Tectona grandis* may possess a promising ameliorative effect against cyclophosphamide-induced cardiotoxicity in rats.

Keywords: Antioxidant, Cardiac biomarkers, Cardiotoxicity, Cyclophosphamide, *Tectona grandis* leaf extract

INTRODUCTION

The incidence of cancer increases globally, with over 19 million new cases detected annually (Juthani *et al.*, 2024). Chemotherapeutic agents are effective in cancer treatment, but with many deleterious effects on normal cells (Alshahrani *et al.*, 2022; Zeien *et al.*, 2022; Juthani *et al.*, 2024). The toxicity of chemotherapeutic agents is dependent on cancer type, location, response to the patient's immunity, and drug dose (Alshahrani *et al.*, 2022). With the advent of antineoplastic agents, there has been an improvement in cancer survival rate. Late onset of cardiovascular diseases, which is one of the adverse effects has become a management issue, mainly in childhood cancers, breast cancer, leukaemia, and lymphoma. The mortality rate in patients diagnosed with breast cancer is high as a result of cardiovascular disease (Ayza *et al.*, 2020a). Cyclophosphamide (CP) is a DNA alkylating agent with a broad spectrum of clinical uses. It is used in the treatment of cancer, autoimmune diseases and as an immunosuppressive protocol during stem cell transplantation (Rihackova *et al.*, 2023). Several reports have demonstrated multiple complications of cyclophosphamide on different organs such as the heart (Asiri, 2010; Omole *et al.*, 2018), liver (Sherif, 2018), kidney (Alshahrani *et al.*, 2022) and gonads (Meistrich *et al.*, 1992; Hari Priya *et al.*, 2024) that have limited its clinical use. CP is metabolized in the liver to 4-hydroxy cyclophosphamide by the CYP450. 4-hydroxy cyclophosphamide is converted to phosphoramidate and acrolein (Avcı *et al.*, 2017; Kurauch *et al.*, 2017; Alshahrani *et al.*, 2022). Phosphoramidate is responsible for the therapeutic effect, while its adverse effects are caused by acrolein through the generation of reactive oxygen species (ROS), disruption of nitric oxide production and induction of oxidative stress in the myocardium and endothelial cells. Acrolein forms adducts with lysine residues and depletes reduced glutathione thereby enhancing oxidative stress (Dhesi *et al.*, 2013). Cardiotoxicity is one of the adverse effects of cyclophosphamide. CP-induced cardiotoxicity disrupts endothelial function and results in fibrosis, inflammation, hypertrophy, apoptosis, angiogenesis and cell migration (Ayza *et al.*, 2020b; Morelli *et al.*, 2022), which has limited its clinical use. So many pharmacological agents are used to counteract the cardiac damage caused by anticancer drugs: besides, a wide range of these therapeutic agents have deleterious side effects. Given the oxidative mechanisms underlying CP-induced cardiac injury, antioxidant-based interventions, particularly from plant sources, are being explored as safer alternatives. The focus on the use of medicinal plants has greatly increased, based on reduced toxicity and minute or no adverse effects and possession of bioactive compounds with proven chemopreventive properties (Ola and Odunola, 2023). This has led to the use of nutraceuticals with antioxidant properties in conjunction with chemotherapeutic agents to ameliorate their adverse effects and the impact of oxidative stress on various organs upon administration (Sherif, 2018). *Tectona grandis*, commonly known as teak, belongs to the Verbenaceae family. Traditionally, it is used in the treatment of colds, headaches, wounds, bronchitis and skin conditions (Kamsu *et al.*, 2021; Hanna *et al.*, 2024). Several reports have demonstrated that *T. grandis* contains a wide range of secondary metabolites, which account for its pharmacological

properties, including antioxidant, anti-inflammatory, antimicrobial, antitumor, antidiabetic, antimalarial, and antihyperlipidemic effects (Krishna and Jayakumaran, 2010; Ramachandran *et al.*, 2011; Han *et al.*, 2023). Several studies on toxicity showed that the methanolic and aqueous extracts of the leaf and seed are non-toxic after oral administration to albino mice and rats (Dokupari *et al.*, 2017; Kamsu *et al.*, 2021). Therefore, this study investigates the ameliorative potential of methanol extract of *T. grandis* leaf on cyclophosphamide-induced cardiotoxicity in rats, focusing on antioxidant markers and cardiac biomarkers.

MATERIALS AND METHODS

Experimental Animals

A total of 20 female albino rats weighing 110 – 120 g were obtained from the animal house of the College of Veterinary Medicine, Michael Okpara University of Agriculture, Umudike, Abia State. The rats were kept in well-ventilated cages at the animal house of the Biochemistry Department, College of Natural Sciences, and were allowed to acclimatize for one week before commencement of treatment. Standard laboratory conditions (Temperature 22 ± 2 °C, relative humidity 55-60 %, 12-hour light/12-hour dark cycles) were maintained at the animal house. The experimental animals were given standard rat feed (finisher pellets) produced by Chikun Feeds, Crown Flour Mill Limited, Lagos state, Nigeria (crude protein = 19.90 %, metabolizable energy = 3209.64 Kcal) and water *ad libitum*. The experimental study was conducted with anesthesia and followed the guidelines of the National Institute of Health for Laboratory Animal Care and Use (National Research Council, Washington, USA, 2011).

Ethical Clearance

The College of Veterinary Medicine Research Ethics Committee, Michael Okpara University of Agriculture, Umudike approved this study (MOU/AVM/REC/202416). Animal use and handling in experimental research followed the guidelines of the National Institute of Health for Laboratory Animal Care and Use (National Research Council, Washington, USA, 2011).

Chemicals and Reagents

All chemicals and reagents used in this study were of analytical grade. Cyclophosphamide injection was supplied by Celon Laboratories, India. Assay kits for Creatine kinase (CK), Lactate dehydrogenase (LDH), Superoxide dismutase (SOD), Glutathione peroxidase (GPX) and Catalase (CAT) were purchased from Randox Laboratories Limited, Crumlin, Northern Ireland, United Kingdom. Troponin T Research Kit was supplied by Eagle Biosciences Company Limited, 105 State Route 101A, Unit 12, Amherst, USA.

Collection and Identification of Plant Materials

T. grandis leaf was collected from the Forestry Research Institute of Nigeria, Eastern station, Ahiaeke, Ndume, Umuahia, Abia State. It was identified (CABI, 2024) and authenticated by a plant taxonomist at the Herbarium unit of the Department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin; the voucher specimen (UBH-T538) was deposited for referral purposes.

Preparation of Plant Extract

The leaves of *T. grandis* were handpicked and thoroughly washed with tap water to remove impurities. They were shade-dried to a constant weight and ground into powder

using an electrical blender. 600 g of *T. grandis* leaf was soaked in 2 L of methanol (95%) for 72 hours and then filtered with a muslin cloth to obtain a crude extract. The crude extract was filtered again using Whatman Number 1 filter paper, and the filtrate was concentrated in a Water bath (Zenith Lab Water bath, DFS KW-1000DB) at 55 °C. The weight of the methanol extract obtained was 108 g. The concentrated plant extract, the methanol *T. grandis* leaf extract (MTGLE), was stored at 4 °C in a refrigerator (Haier Thermocool, HRF-135BA, PZ Cussons, Nigeria) until further use.

Experimental Design

The experimental animals were randomly divided into four groups of five animals each. Group 1 served as the normal control that received feed and distilled water, Group 2 was administered 50 mg/kg body weight cyclophosphamide (CP) daily intraperitoneally for 3 days. Group 3 received 50 mg/kg body weight CP intraperitoneally for 3 days and 200 mg/kg body weight MTGLE orally on the fourth day for 21 days. Group 4 received 50 mg/kg body weight CP daily for 3 days and 400 mg/kg body weight MTGLE orally on the fourth day for 21 days. The extract was dissolved in distilled water. The rats were starved 24 hours before sacrifice and were anesthetized intraperitoneally with ketamine-xylazine combination (125 mg/kg and 10 mg/kg doses respectively) according to the method reported by Uhwo *et al.* (2025). Blood was collected by retro-orbital bleeding (ROB) with a capillary tube and placed into sample bottles. Serum was separated from the clotted blood by centrifugation at 3000 rpm for 20 minutes using a table centrifuge (LABSCO 614B, Germany). The serum was used for biochemical analysis.

Determination of Cardiac Biomarkers

The separated serum was used to estimate cardiac enzyme biomarkers. Creatine kinase (CK) and Lactate dehydrogenase (LDH) activities were assayed using commercial kits purchased from Randox Laboratories (Antrim, Crumlin, United Kingdom) following the UV methods of Stein (1985) and Weisshaar *et al.* (1975), respectively. Following the manufacturer's instructions, the cardiac troponin level was determined using the Eagle Biosciences Troponin ELISA assay kit.

Determination of Oxidative Stress Biomarkers

Heart tissue homogenate was used. Heart tissue was collected and immediately washed in 0.01M ice cold phosphate buffered saline. 0.5 cm sliced heart tissue was homogenized, and the homogenate was mixed with the same concentration of PBS in the ratio of 1:9 (tissue weight: volume of buffer). The mixture was centrifuged at 1000 rpm for 10 minutes to obtain the supernatant. Superoxide dismutase (SOD) activity in heart homogenates of rats was measured at 450 nm by the colorimetric method described by Woolliam *et al.* (1983) and Arthur and Boyne (1985). The catalase (CAT) activity was measured at 405 nm by the spectrophotometric assay of Goth (1991). Estimation of glutathione peroxidase (GPx) activity was done according to the UV method of Paglia and Valentine (1967) and the absorbance was measured at 340 nm. The extent of lipid peroxidation was measured as malondialdehyde (MDA) at 532 nm following the colorimetric method described by Jentzsch *et al.* (1996). All enzyme activities were assayed using their respective

commercial kits purchased from Randox Laboratories, Antrim, Crumlin, United Kingdom.

Determination of Lipid Profile Parameters

Lipid profile parameters were determined using the respective Randox commercial kits following the manufacturer's instructions. Total cholesterol (TCHO) was determined according to the methods of Abel *et al.* (1952) and Roeschlau *et al.* (1974), the absorbance was read at 505 nm. The method described by Bucolo and David (1973) was adopted in the determination of serum triglycerides (TG). The methods of Friedewald *et al.* (1972) and Lopes-Virella *et al.* (1977) were used to determine the level of serum High-density lipoprotein (HDL). Low-density lipoprotein (LDL) and very-low density lipoprotein (VLDL) were calculated according to the methods of Friedewald *et al.* (1972) and Wilson *et al.* (1985), respectively.

Histological Evaluation

Heart tissues collected after the sacrifice of the rats were fixed in 10% neutral buffered saline formalin for a minimum of 24 hours. They were washed in increasing grades of ethanol, cleared with xylene, embedded in paraffin wax, sectioned with a microtome (4–5 µm), and stained with hematoxylin and eosin (H and E) and mounted on Canada balsam (Bancroft and Gamble, 2008). All the sections were examined under a light microscope under different (x10, x20 and x40) magnifications. An Olympus photo microscope was used to take Photomicrographs of the lesions (100x) for observations and documentation of histopathological lesions (Bancroft and Gamble, 2008).

Statistical Analysis: Data was analyzed using one-way analysis of variance (ANOVA) followed by Sidak's multiple comparisons test for separation of significantly different means. A probability value of 0.05 or less was taken as a criterion for a statistically significant difference. Results of the data analyses were expressed as means ± standard deviation (SD). The statistical analysis was performed with the aid of GraphPad Prism version 8.0.2.263 (GraphPad Software, San Diego, CA, USA).

RESULTS

Cardiac Enzyme Biomarkers

The activities of creatine kinase (366.80 ± 36.77 IU/L) and lactate dehydrogenase (509.00 ± 22.32 IU/L) in CP-treated rats were significantly (p<0.05) compared to the control (219.30 ± 10.90 IU/L and 195.50 ± 8.35 IU/L), respectively. Similarly, cyclophosphamide significantly (p < 0.05) increased the troponin level (0.28 ± 0.03 mg/mL) in CP-treated rats compared to the control (0.14 ± 0.01 mg/mL). Administration of 200 and 400mg/kg body weight of MTGLE attenuated the damage caused by cyclophosphamide by significantly decreasing (p<0.05) the level of troponin and the activities of creatine kinase and lactate dehydrogenase when compared with the CP alone groups (Figures 1a-c).

Oxidative Stress Biomarkers

The activities of SOD, CAT and GPx were measured. The concentration of MDA was determined as an indication of the extent of lipid peroxidation. SOD activity of the CP alone group (28.40 ± 1.21 U/mL) was significantly lower (p<0.05) compared to the control group (37.11 ± 0.99 U/mL). CP + MTGLE 400 group (31.39 ± 0.97 U/mL) showed a significant (p<0.05) increase in SOD activity compared to the CP alone group (28.40 ± 1.21 U/mL). However, the group that received

CP + MTGLE 200 (29.97 ± 1.07 U/mL) showed a non-significant ($p < 0.05$) increase in SOD activity when compared with the CP alone group (28.40 ± 1.21 U/mL) (Figure 2a). CAT activity in the CP alone group (9.20 ± 0.40 U/mL) was significantly lower ($p < 0.05$) compared to the control (14.96 ± 0.41 U/mL). CP + MTGLE 200 and CP + MTGLE 400 (10.15 ± 0.28 and 10.70 ± 0.40 U/mL, respectively) significantly ($p < 0.05$) increased CAT activities compared to the CP alone group (9.20 ± 0.40 U/mL) (Figure 2b). There was a significant decrease in the activity of GPx in the CP alone group (15.02 ± 0.59 μ mol GSH) when compared to the control (23.24 ± 1.03 μ mol GSH). Administration of MTGLE

at 200 and 400 mg/kg body weight (19.05 ± 1.68 and 19.94 ± 1.26 μ mol GSH, respectively) significantly ($p < 0.05$) increased GPx activity compared to the CP alone group (15.02 ± 0.59 μ mol GSH) (Figure 2c). Malondialdehyde (MDA) level was significantly increased in the CP alone group (2.59 ± 0.16 μ mol/L) when compared with the control (0.93 ± 0.15 μ mol/L). CP + MTGLE 200 and CP + MTGLE 400 groups (1.93 ± 0.16 and 1.57 ± 0.14 μ mol/L, respectively) showed a significant decrease in the level of MDA compared to the CP alone group (2.59 ± 0.16 μ mol/L) (Figure 2d).

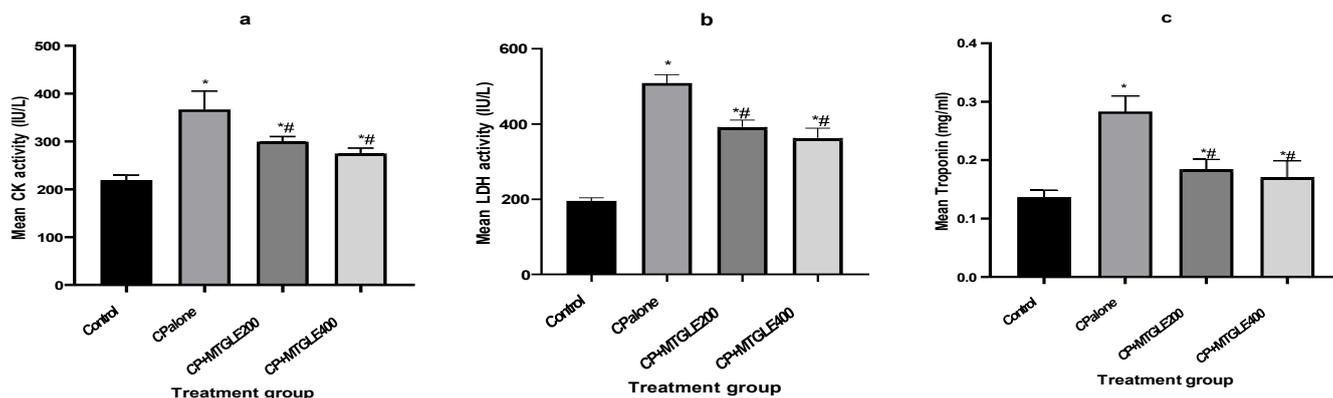


Figure 1: Effect of *Tectona grandis* on cardiac biomarkers of cyclophosphamide-induced rats. Values are represented as mean \pm standard deviation ($n=5$). Bars with * and # are considered significantly different at $p < 0.05$ when compared with the control and CP alone groups, respectively.

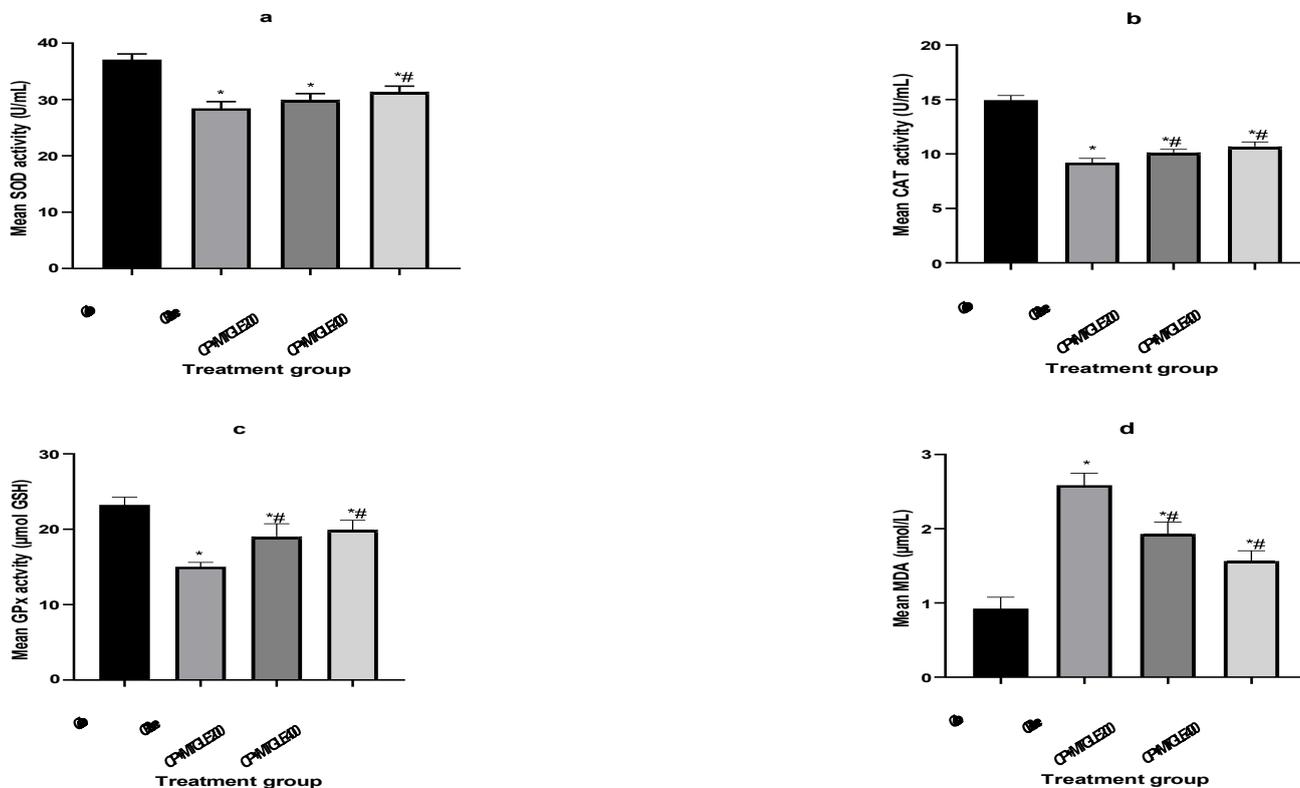


Figure 2: Effect of *Tectona grandis* on oxidative stress biomarkers of cyclophosphamide-induced rats. Values are represented as mean \pm standard deviation ($n=5$). Bars with * and # are considered significantly different at $p < 0.05$ when compared with the control and CP alone groups, respectively.

Lipid Parameters

Cyclophosphamide significantly increased ($p < 0.05$) the level of total cholesterol (TCHO) in CP-treated rats (84.45 ± 4.71 mg/dL) compared to the control (76.95 ± 1.56 mg/dL). On the other hand, the groups treated with graded doses (200 and 400 mg/kg body weight) of MTGLE (73.15 ± 5.05 and 68.25 ± 2.27 mg/dL, respectively) showed a significantly lower ($p < 0.05$) level of TCHO when compared with the CP alone group (84.45 ± 4.71 mg/dL) and control (76.95 ± 1.56 mg/dL) (Figure 3a). Similarly, significant ($p < 0.05$) increase in the level of triglycerides (TG) (87.35 ± 2.96 mg/dL), low-density lipoprotein (LDL) (20.08 ± 4.29 mg/dL) and very low-density lipoprotein (17.47 ± 0.59 mg/dL) was obtained in CP alone group compared to the control (71.75 ± 1.03 , 8.63 ± 1.06 and 14.25 ± 0.20 mg/dL, respectively). Consequently, treatment

with MTGLE at 200 and 400 mg/kg significantly ($p < 0.05$) reduced the level of TG (76.63 ± 1.56 and 74.73 ± 3.04 mg/dL, respectively), LDL (9.15 ± 4.48 and 3.88 ± 1.01 mg/dL, respectively) and VLDL (15.33 ± 0.21 and 14.95 ± 0.61 mg/dL, respectively) in comparison with the CP alone group. Furthermore, CP + MTGLE 400 (3.88 ± 1.01 mg/dL) showed no significant ($p > 0.05$) decrease in LDL level when compared with the control (8.63 ± 1.06 mg/dL) (Figures 3b-d). A significant reduction in high-density lipoprotein (HDL) level was obtained in the CP alone group (47.90 ± 1.65 mg/dL) compared to the control (53.98 ± 1.25 mg/dL). However, treatment with 200 and 400 mg/kg BW of MTGLE (48.68 ± 1.86 and 49.43 ± 1.90 mg/dL, respectively) showed no significant increase in HDL level when compared with the CP alone group (47.90 ± 1.95 mg/dL) (Figure 3e).

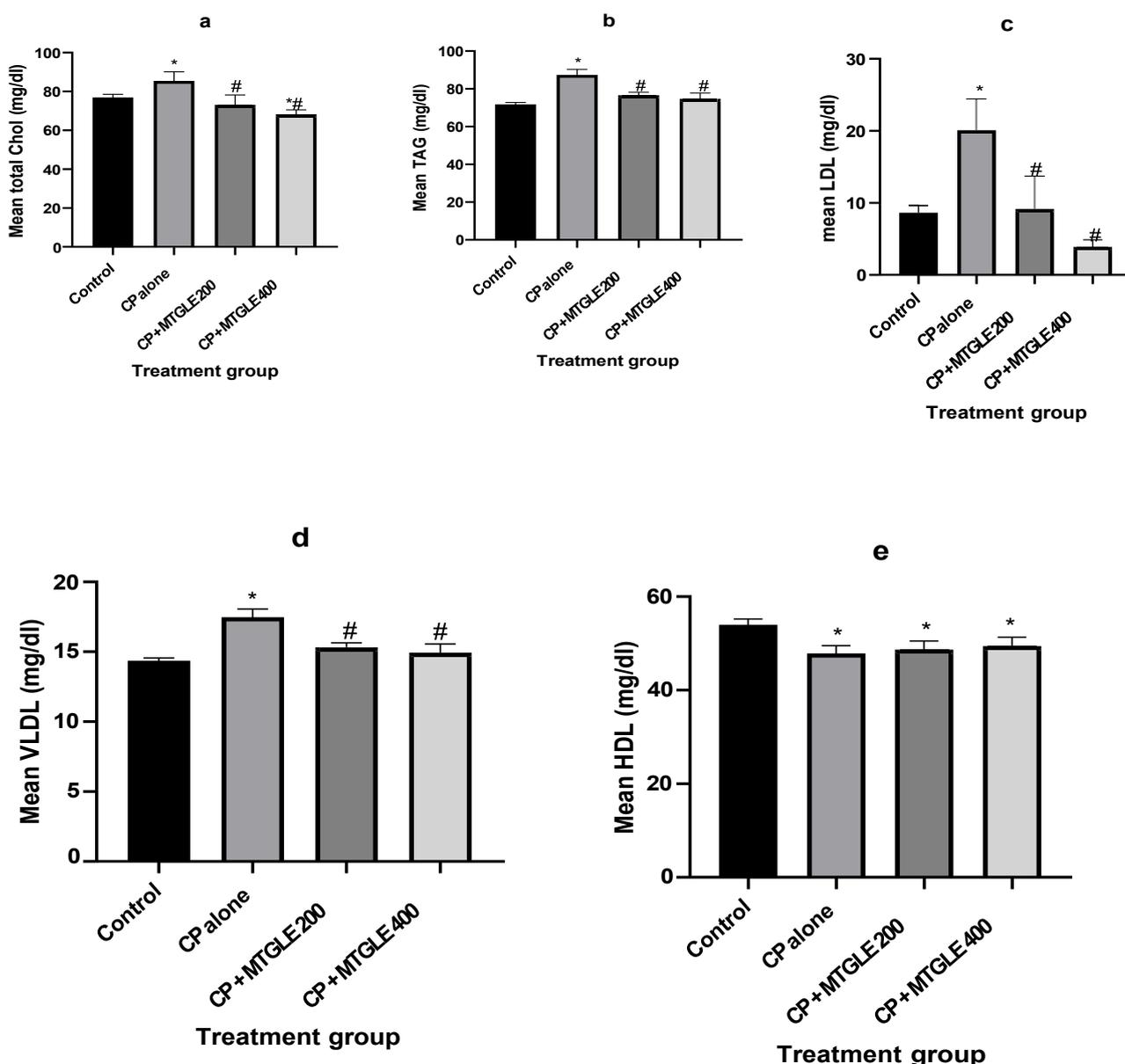


Figure 3: Effect of *Tectona grandis* on lipid profile of cyclophosphamide-induced rats. Values are represented as mean \pm standard deviation ($n=5$). Bars with * and # are considered significantly different at $p < 0.05$ when compared with the control and CP alone groups, respectively

Histopathological Observations

The histopathological examinations showed the restorative ability of MTGLE against CP-induced cardiac damage (Figure 13a–d). CP-induced pathological changes in the cardiac tissues showing severe myofiber necrosis, oedema and inflammation (Figure 13a). The treatment of the rats with

MTGLE reduced the severity of the damage caused by CP administration. The result showed mild myofiber necrosis and degeneration as well as interstitial mineralization at 200 and 400 mg/kg (Figure 13 b and c). The control rats showed normal myofibres (Figure 13d).

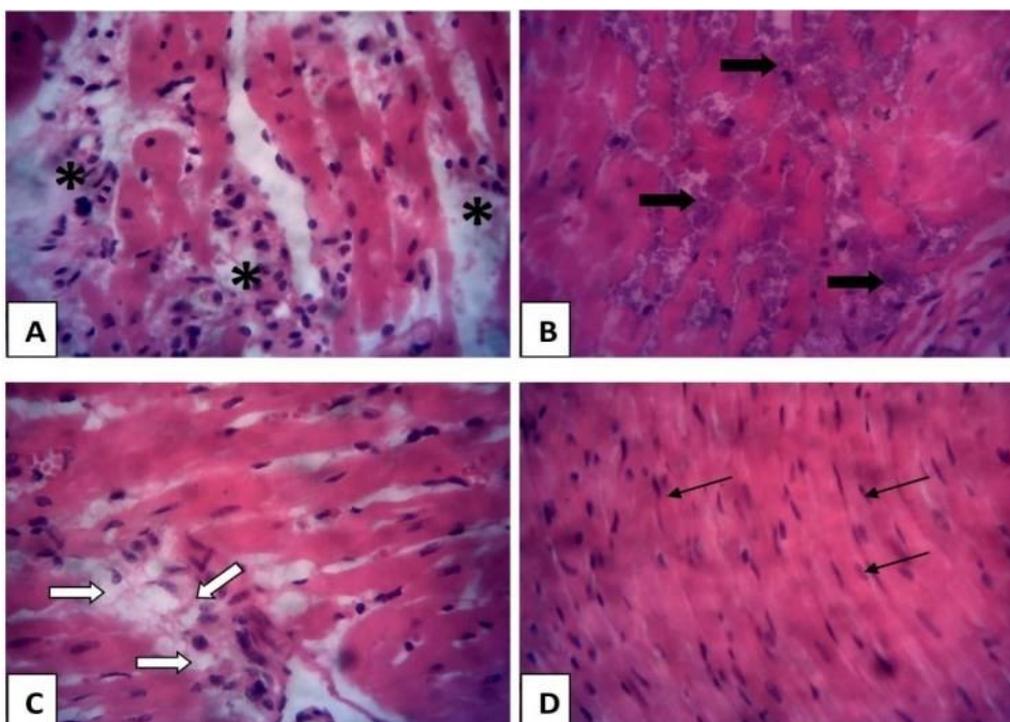


Figure 13: Histopathological changes in cardiac tissue of cyclophosphamide induced rats treated with methanol extract of *Tectona grandis* leaf showing severe myofiber necrosis, edema and inflammatory reaction (asterisk) in group A (CP alone treated rats), mild myofiber necrosis and interstitial mineralization (black arrows) in group B (CP + 200mg/kg MTGLE), mild myofiber degeneration and necrosis with edema (white arrows) in group C (CP + 400mg/kg MTGLE) while the heart in group D (Control) shows normal myofibres (thin arrows).

DISCUSSION

Chemotherapeutic agents do not selectively target cancer cells and thus have deleterious effects on normal cells, resulting in multiple organ toxicities (Truesdell *et al.*, 2024). Numerous studies on chemotherapeutic agents support cardiotoxicity as the main adverse effect (Adhikari *et al.*, 2021; Morelli *et al.*, 2022). Cyclophosphamide causes cardiotoxicity by enhancing excessive production of reactive oxygen species, an increase in oxidative stress and a decrease in the antioxidant system (Asiri, 2010; El-Agamy *et al.*, 2017; Kurauchi *et al.*, 2017). In recent times, herbal medicines have been used against multiple ailments, owing to and low toxic profile. Medicinal plants are used traditionally to deal with several clinical symptoms (Adhikari *et al.*, 2021; Ayza *et al.*, 2020b; Swamy *et al.*, 2013). Several researchers have reported the efficacy of natural antioxidants from plant sources against organ toxicities induced by cyclophosphamide (Sherif, 2018; Ayza *et al.*, 2020a, 2022). This study evaluated the ameliorative effect of the methanol extract of *T. grandis* on cardiac damage biomarkers, lipid profile, antioxidant system and heart histomorphology of rats exposed to cyclophosphamide. This is the first study

demonstrating the cardioprotective effect of *T. grandis* methanol extract in CP-induced rats. Troponin, creatine kinase and lactate dehydrogenase are biomarkers of cardiac damage. In the present study, elevated levels of troponin and activities of creatine kinase and lactate dehydrogenase in CP-treated rats compared to the control indicate cardiotoxicity. Troponin, CK and LDH are found in cardiomyocytes but are released into the bloodstream when there is cardiac damage. The observed increase in the levels of troponin and activities of CK and LDH is consistent with previous studies on cardioprotective effects of medicinal plants (Swamy *et al.*, 2013; CetikYildiz *et al.*, 2018; Omole *et al.*, 2018; Ayza *et al.*, 2020b; Tesfaye *et al.*, 2021). CP, as a cardiotoxic agent, causes endothelial damage and destruction of cardiomyocytes (Mudd *et al.*, 2021). The observed increase in the troponin level and the activities of CK and LDH can be linked to the overproduction of ROS by cyclophosphamide's toxic metabolite, acrolein, thereby causing myocardial membrane damage through lipid peroxidation, resulting in disruption of the integrity of the membrane. Treatment with MTGLE at 200 and 400 mg/kg body weight attenuated CP-induced cardiac damage by reducing the level of troponin and activities of CK

and LDH, which is an indication that MTGLE maintained the integrity of the membrane. The observed effect might be attributed to the presence of bioactive compounds in MTGLE (Asdaq *et al.*, 2022; Hanna *et al.*, 2024). CP-induced cardiotoxicity is mediated through the induction of oxidative stress, characterized by an overproduction of ROS and a reduction in the antioxidant defense system. Myocardial tissues are prone to oxidative damage by free radicals due to a decrease in antioxidant enzymes (Uhuo *et al.*, 2022). SOD converts superoxide radicals to hydrogen peroxide; CAT converts hydrogen peroxide to water and oxygen. In contrast, GPx converts glutathione to oxidized glutathione, reducing hydrogen peroxide to water, and lipid hydroperoxides to their corresponding stable alcohol (Omole *et al.*, 2018). Administration of CP significantly decreased the activities of SOD, CAT and GPx. MDA is an important determinant in the evaluation of lipid peroxidation, oxidative stress and antioxidant status in tissues. The observed reduction in the activities of SOD, CAT and GPx is because of oxidative stress induced by CP. Free radicals generated by the CP metabolite, acrolein, caused lipid peroxidation as indicated by high MDA levels. Enhanced lipid peroxidation decreased the activities of antioxidant enzymes, resulting in disruption of the function and integrity of the myocardial membrane. Treatment with MTGLE protected the myocardial tissue from oxidative damage by counteracting the effect of the free radicals. At the graded doses, MTGLE increased the activities of SOD, CAT and GPx. Consequently, the level of MDA was significantly reduced. The observed effect may be due to its ability to decrease oxidative stress and protect the activities of antioxidant enzymes, as *T. grandis* has been reported in previous studies to possess antioxidant properties (Han *et al.*, 2023; Hanna *et al.*, 2024).

Triglycerides, TCHO, LDL, VLDL and HDL are parameters used to ascertain the lipid profile status of humans. High levels of TG, TCHO, LDL and VLDL are characterized as hyperlipidemia and are associated with a high risk of coronary heart disease (Nelson, 2013). Cyclophosphamide induced elevation in TCHO, TG, LDL and VLDL levels. Free radicals cause cholesterol accumulation by increasing cholesterol synthesis and a decrease in its utilization through activation of HMG CoA reductase (Swamy *et al.*, 2013). The observed increase in TCHO, TG, LDL and VLDL may be due to a decrease in the activities of antioxidant enzymes and lipid peroxidation as reported in previous studies (Gesquière *et al.*, 1999; Yang *et al.*, 2008; Swamy *et al.*, 2013). In this study, MTGLE significantly reduced elevated levels of TCHO, TG, LDL and VLDL in cyclophosphamide-treated rats. Additionally, increased HDL was observed. These observed effects can be linked to bioactive compounds in MTGLE that account for its antioxidant and antihyperlipidemic properties, which were reported in previous studies (Ramachandran *et al.*, 2011; Han *et al.*, 2023).

Pathological changes in the histopathology of the cardiac tissues, including severe myofiber necrosis, oedema and inflammatory reactions observed in the cyclophosphamide alone group, showed the cardiotoxic effect of cyclophosphamide. This agrees with the findings of Swamy *et al.* (2013). However, mild myofiber necrosis, degeneration, and interstitial mineralization observed in groups that received CP and were treated with different doses of the

extract improved cardiac histo-architecture, suggesting that the rats suffered minimal cardiac damage due to CP toxicity, and agrees with the finding of Tesfaye *et al.* (2021). Taking together, the observed ameliorative effect of MTGLE could be attributed to its phytochemical compositions. MTGLE has been reported to possess several bioactive compounds such as phenolics and flavonoids (Vyas *et al.*, 2018) which have been proven to exhibit antioxidant properties through scavenging of free radicals and enhancing the activity of antioxidant enzymes (Mutha *et al.*, 2021; Silak *et al.*, 2022).

Conclusion

The findings from this study indicate the ameliorative effect of MTGLE on cardiac malfunctions and lipid dyslipidemia occasioned in albino rats due to cyclophosphamide toxicity. The findings suggest that the leaf extract of *T. grandis* plays a critical role in managing cardiac disorders and restoring a healthy lipid profile and thus may serve as a potential adjunct therapy for patients undergoing chemotherapy.

CONFLICT OF INTEREST

The authors declare no existing or potential conflict of interest.

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Author contributions

Uchenna, O.N.: Conceptualization, initial draft of manuscript, experimental design, investigation, formal analysis, data analysis and final draft of manuscript.

Uhuo, E.N.: Manuscript review and editing, methodology, formal analysis and Investigation.

Uroko, R.I.: Formal analysis, data curation, manuscript review and editing and experimental design.

Onyabo, C.: Supervision, Methodology, data collection and investigation,

Nweke, T.C.: Project administration, data visualization and investigation

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