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CARDIOPULMONARY PROTECTIVE POTENTIAL OF *ELAEIS GUINEENSIS* SEED AGAINST MOSQUITO COIL TOXICITY IN MALE WISTAR RATS

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ABSTRACT
The cardiopulmonary-protective potential of *Elaeis guineensis* (oil palm) seed extract on mosquito coil toxicity was investigated in experimental rat model. Thirty-six (36) male wistar rats were grouped into six: Group I had normal pellets along with distilled water, Group II was exposed to mosquito coil smoke (as repellent) for 1 hour daily, Group III was exposed to repellent with oral administration of 2ml/kg body weight of Vitamin E, Groups IV and V were exposed to repellent with oral administration of oil palm seed extract at doses of 2ml/kg and 4ml/kg body weight, respectively, and Group VI received oral administration of only oil palm seed extract at a dose of 2ml/kg body weight. Results revealed a significant increase in creatine kinase and lactate dehydrogenase (cardiac markers) in Group II compared to the normal control (Group I). Additionally, oxidative stress markers and lipid peroxidation levels were significantly elevated in Group II when compared to group I (normal control). However, groups (IV, V and VI) administered with 2ml/kg and 4ml/kg body weight of *Elaeis guineensis* seed extract showed a significant decrease in these markers compared to the positive control (Group II). In conclusion, the observed improvements in biochemical markers and oxidative stress markers suggest that oil palm seed may have served as a natural agent against cardiopulmonary toxicity induced by mosquito coil fumes and possibly proffered cardiopulmonary protection in those groups of rats which were exposed to mosquito coil fumes.

KEYWORDS: Antioxidant, Elaeis Guineensis, Mosquito coils, pyrethroid, lung, Heart.

INTRODUCTION
It is commonly, a practice in nations with huge category of low-income earners to use mosquito sticks or coils in the management of mosquito populations in their environment and homes where people reside (Abdullah *et al*, 2017). This is understandably so, given the circumstance wherein the coils are quite cheap, readily available (Mossa *et al*, 2013), and of course against a background of the enormous burden of malaria prevalence being very high in those regions (Abdullah *et al*, 2017). Meanwhile, the coils are composed of chemical components with various potential hazardous side effects; free radicals, vapours and minute particles of metal fumes - that irritate upper respiratory tract (Mossa *et al*, 2013). There are organic fillers, binders and colorations, which on ignition emit sub-micrometer particles that can affect lower respiratory tract (Jegede *et al*, 2015). Then pyrehritns, about 3-4% portion of the entire mass of the coils happens to be the essential active substance with identified and reported insecticidal properties/activities since one century ago (Jegede *et al*, 2015).

There are concertedly emerging studies, reports and awareness about inter-organ relationship and pathophysiological basis of many ailment conditions (Jensen-Cody & Potthoff, 2021; Chiba *et al*, *2018*). For instance, it has been reported that patients with liver cirrhosis or failure (i.e. liver disease at its end-stage) can progress to "cirrhotic cardiomyopathy" (Chen *et al*, 2021). Similarly, cardiovascular disease (CVD) can develop from an existing nonalcoholic fatty liver disease through multiple or plethora of mechanisms occurring at molecular level (Chen *et al*, 2021). Furthermore, in the current perspective, connectivity between diseases affecting the respiratory tracts, alveoli, lungs and

development of heart failure or other heart diseases is in the fore (Forfia *et al,* 2013). It therefore is a matter of concern to continue exploring and addressing the treatment or management of ailments holistically.

The heart has a pivotal role in the circulatory system of the body, as it pumps blood that is rich in oxygen around its cells and tissues, distributing essential nutrients and removing excess and / or waste products of metabolism (Tortora & Derrickson 2017). There are also some biologically based substances (biomarkers) which are released or become activated in course of the body cells / tissue functions. They include creatine kinase (CK), lactate dehygonenase (LDH), and troponin which may indicate cardiac and / or other muscle tissues inflammations (Thygesen *et al,* 2018). More specifically, it is known that elevated CK levels in the blood stream could be indicative of heart damage or any other muscle tissue damage (Thygesen *et al,* 2018).

In the same vein, other biomarkers exists that indicate the response of the body's intrinsic mechanisms to maintenance of homeostatic conditions by relieving the cells and tissues from stress, usually typically called oxidative stress - due to the involvement of some reactive oxygen species (ROS) in the process (Cristani *et al*, 2016; Engwa, 2018). Oxidative stress ensues where and when the body is in deficit of antioxidants which normally would mop and neutralize unstable molecules (ROS) - that react with other substances in the body thereby damaging cells or creating aberrant ones (Engwa, 2018). Some examples of antioxidants (also biomarkers of oxidative stress) include myeloperoxidase (MPO), reduced glutathione (GSH), superoxide dismutase (SOD), catalase (CAT), peroxidase (PER) and advanced oxidation protein products (AOPP) (Cristani *et al*, 2016).

MPO is a lysosomal protein released into the extracellular space during degranulation and belongs to a subfamily of peroxidases which are seen during neutrophil's respiratory burst wherein production of hypochlorous acid (HOCl) from hydrogen peroxide (H_2O_2) and chloride anion (Cl^-) occur (Repetto *et al*, 2012). GSH exhibits capability to prevent damage on essential cellular components which ROS exposure might cause and its reversible reactivity in the presence of NADPH allows it to be used as indicator to measure cellular oxidative stress (Anderstam *et al*, 2008). Similarly, SOD (provide defense against ROS), Catalase (degrades ROS), while Peroxidase, and AOPP (considered as biomarkers of oxidation stress generally) are reactively abundant during stress which may be caused by ROS and / or other oxidants (Güntaş *et al*, 2015; Idowu *et al*, 2016; Gryszczyńska *et al*, 2017; Loganathan *et al*, 2017; Cristani *et al*, 2016); Ghouri & Sattar, 2010).

In view of the foregoing, *consideration is given to* oil palm (*Elaeis guineensis)* seed, which is fleshy endocarp of the *Elaeis guineensis* fruit consisting of saturated and unsaturated fatty acids as well as some antioxidant substances (such as carotenoids, tocopherol, tocotrienol and gallic) that are capable of ravaging free radicals (Ajuwon *et al*, 2013; Uroko *et al*, 2019; Sharma *et al*, 2014). Also, conferment of nutritional merit (which includes affirmative influence on the quantity and quality of lipid components/content within the blood system) on this seed has been empirically reported (Naz *et al*, 2019; Ajuwon *et al* 2013). More again, studies have brought to the fore, supportive impact of the oil palm seed in ameliorating stress. Thus, this present study aims to investigate the effect of fresh *Elaeis guineensis* seed extract on cardiopulmonary functions of rats that are exposed to pyrethroid based mosquito coil fumes.

MATERIALS AND METHODS

A total of thirty-six (36) male rats purchased from the animal house of Department of Pharmacology, University of Port Harcourt, Rivers State were used for the study. All rats were kept in standard cages and allowed to acclimatize within a two weeks period, when all had access freely, to pelleted feed and water.

Thirty-six (36) male rats were randomly divided into six groups (I-VI) consisting of six animals each (n = 6) housed in standard separate cages.

Group I (Normal control): Were housed in cages with proper ventilation and no exposure to mosquito coil, but only given chicken feeds and distill water for the period of the experimental design (28 days).

Group II (Positive Control): Were exposed to repellent (pyrethroid based mosquito coil) smokes through whole body inhalation for 1 hour everyday using a film cupboard.

Group III (Standard Control): Were kept in properly ventilated cages without repellent but given oral administration of 2ml/kg body weight of Vitamin E for the 28 days period.

Group IV (Mosquito Coil + Extract): Were exposed to mosquito coil smokes for 1 hour everyday by whole body inhalation alongside oral administration of fresh *Eleasis guineensis* seed extract of 2ml/kg body weight for the whole period.

Group V (Mosquito Coil + Extract): Were treat as group IV, except that the dose of *Eleasis guineensis* seed was increased (i.e. 4ml/kg body weight).

Group VI (Extract Only): Were housed in cages with proper ventilation, no repellent, but only administered 2ml/kg body weight of fresh *Eleasis guineensis* seed orally for the 28 days period.

After 24 hours of the last exposure to the mosquito repellent and treatment with aqueous extract of oil palm seed, all rats were assessed for physical appearance. The rats were sacrificed under light anesthesia by cervical dislocation followed by withdrawal of blood sample (5ml) from the heart into plain sample bottles for biochemical estimations. Also, the organs (heart and lungs) were harvested, part of it was homogenized using

normal saline buffer, stored in labeled containers for antioxidant analysis and the remaining parts kept in 10% phosphate-buffered formalin for a minimum of 48 hours for histopathological examination. Standard procedures for biochemical analysis in strict adherence to principles and protocols in the kits were implored (Stambaugh & Post, 2004; Desai & Ray, 2014; Walker et al, 1990; Beutler, 1989).

RESULTS

Results of the effect of fresh *Elaeis guineensis* seed extract on pyrethroid based mosquito coil fumes are presented in the tables below;

Table 4.1: Mean values of cardiac markers against mosquito coil toxicity and treatment with fresh *Elaeis guineensis* Seed extract.

Groups/Parameters	CK (U/L)	LDH (U/L)
Group I (Normal Control)	41.80±5.23 [a]	206± 55.97[a]
Group II (Positive Control)	59.3± 4.72[b]	285.8± 36.21[b]
Group III (Standard Control, 200mg Vitamin E)	46.4 ±4.83[ab]	204± 17.07[ab]
Group IV (Mosquito Coil and extract, 2ml/kg body weight)	44.6 ± 3.58[c]	226.8± 19.42[c]
Group V (Mosquito coil and extract, 4ml/kg body weight)	42.8± 2.86[d]	239.8±11.70[d]
Group VI (Extract, 2ml/kg body weight)	40.21±5.23[a]	201± 45.70[a]

Values are expressed as mean ±SEM. Mean with same superscript letters on the same column are not significantly different (P <0.05).

CK-Creatine Kinase, LDH-Lactate Dehydrogenase, MDA-Lipid Peroxidation.

In table 4.1 above, serum values for cardiac markers was analyzed in wistar rats. For CK activity, serum values analyzed showed a significant (P<0.05) increase of 59.3±4.72U/L in group II (positive control) when compared to 41.8±5.23U/L in group I (normal control). However a significant (P<0.05) decrease of 46.4 ±4.83U/L was observed in group III (standard control) when compared to 41.8±5.23U/L in group I (normal control). When wistar rats were treated with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, significant (P<0.05) decrease of 44.6±3.58U/mg and 42.8±2.86U/L were observed in group IV and V when compared to 59.3±4.72U/L in group II (positive control). Whereas a non-significant (P<0.05) decrease of 41.8±5.23U/L was observed in groupVI when compared to group I (normal control).

For LDH level, serum values analyzed showed a significant (P<0.05) increase of 285.8± 36.21 in group II (positive control) when compared to 206±55.97U/L in group I (normal control). But a significant (P<0.05) decrease of 204±17.07U/L was observed in group III (standard control) when compared to 206±55.97U/L in group I (normal control). When rats were treated with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, significant (P<0.05) decrease of 226.8±69.42U/mg and 239.8±11.70U/L were observed in group IV and V compared to 285.8±36.21U/L in group II (positive control). Whereas a non-significant (P<0.05) decrease of 201±45.70U/L was observed in group VI compared to group I (normal control).

Table 4.2: Mean values of the antioxidant status of rats heart exposed to mosquito coil toxicity and treatment with fresh *Elaeis guineensis* seed extract.

Groups/Parameters	MPO (U/mg)	GSH (nmol/mg)	SOD (U/mg)	CAT (U/mg)	PER (U/mg)	AOPP (U/mg)	MDA (U/mg)
Group I (Normal Control)	4.35±1.21[a]	3.61±1.01[a]	3.21±1.01[a]	10.89±3.21[a]	0.43±0.03[a]	5.11±1.02[a]	4.80± 1.05[a]
Group II (Positive Control)	5.78±1.43[b]	4.88±1.66[b]	5.88±1.91[b]	13.18±4.39[b]	0.71±0.05[b]	6.12±1.22[b]	5.45± 1.05[b]
Group III (Standard Control)	4.21±1.08[ab]	3.78±1.02[ab]	4.20±1.23[ab]	11.30±3.91[ab]	0.55±0.02[ab]	5.43±1.11[ab]	4.04 ±1.08[ab]
Group IV (Mosquito Coil and extract, 2ml/kg body weight)	4.01±1.06[c]	3.37±0.93[c]	3.82±1.07[c]	11.34±3.76[c]	0.57±0.02[c]	5.23±1.05[c]	4.06± 1.06[c]
Group V (Mosquito coil and extract, 4ml/kg body weight)	4.24±1.12[d]	4.52±1.31[d]	4.37±1.41[d]	10.60±3.83[d]	0.54±0.02[d]	4.93±1.07[d]	4.08 ±1.30[d]
Group VI (Extract, 2ml/kg body weight)	4.32±1.11[d]	3.62±1.02[d]	3.90±1.09[d]	11.08±3.11[d]	0.56±0.02[d]	5.22±1.09[d]	4.21 ±1.09[a]

Values are expressed as mean ±SEM. Mean with same superscript letters on the same column are not significantly different (P <0.05).

MPO-Myeloperoxidase, GSH-Reduced Glutathione, SOD-Superoxide Dismutase, CAT-Catalase, PER-Perpxidase, AOPP- Advanced Oxidation Protein Products.

Table 4.2 above showed values for antioxidant enzymes in rat heart homogenates. For MPO activity, values analyzed showed a significant (P<0.05) increase of 5.78±1.43U/mg in group II (positive control) when compared to 4.35±1.21U/mg in group I (normal control).

However a significant (P<0.05) decrease of 4.21±1.08U/mg was observed in group III (standard control) when compared to 3.27±0.33 in group I (normal control). When wistar rats were treated with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, significant (P<0.05) decrease of 4.01±1.06U/mg and 4.24±1.12U/mg were observed in group IV and V compared to positive control (group II). Whereas a significant (P<0.05) decrease of 4.32±1.11U/mg was observed in group VI compared to group I (normal control).

There were significantly (P<0.05) higher GSH levels (4.88±1.66nmol/mg) in group II (positive control) when compared to 3.61±1.01nmol/mg in group I (normal control). A significant (P<0.05) decrease of 3.78±1.02nmol/mg was observed in group III (standard control) when compared to group I (normal control). Treatment of wistar rats with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, showed significantly (P<0.05) lower values of 3.37±0.93nmol/mg and 4.52±1.31nmol/mg for GSH level respectively when compared to group II (positive control). Whereas a significant (P<0.05) decrease of 3.62±1.02nmol/mg was observed in group VI compared to group I (normal control).

Values for SOD level analyzed, showed significantly (P<0.05) higher SOD levels of 5.88±1.91U/mg in group II compared to 3.21±1.01U/mg in group I (normal control). A significant (P<0.05) decrease of 4.20±1.23U/mg was observed in group III (standard control) when compared to group I (normal control). Treatment of wistar rats with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, showed significantly (P<0.05) lower 3.82±1.07and 4.37±1.41U/mg SOD level respectively relative to group II (positive control). Also, a significant (P<0.05) decrease of 3.90±1.09U/mg was observed in group VI when compared to group I (normal control).

Values for CAT activity analyzed showed a significantly (P<0.05) higher 13.18±4.39 in group II compared to 10.89±3.21U/mg in group I(normal control). Also a significant (P<0.05) decrease of 11.30±3.91U/mg was observed in group III (standard control) when compared to group I (normal control). Treatment of wistar rats with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, showed significantly (P<0.05) lower 11.34±3.76U/mg and 10.60±3.83U/mg levels of CAT activity respectively when compared to group II (positive control). While a significant (P<0.05) decrease of 11.08±3.11 was observed in group VI relative to group I (normal control).

For peroxidase activity, values analyzed showed a significant (P<0.05) increase of 0.92±0.05 in group II (positive control) when compared to 0.52±0.03U/mg in group I (normal control). Although a significant (P<0.05) decrease of 0.45±0.021U/mg was observed in group III (standard control) compared to 0.52±0.03U/mg in group I (normal control). When rats were treated with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, significant (P<0.05) decrease of 4.00±0.05U/mg and 0.51±0.02U/mg were observed in group IV and V compared to 4.89±0.28 in group II (positive control). Whereas a non-significant (P<0.05) decrease of 0.49±0.02U/mg was observed in group VI when compared to group I (normal control).

Analysis of AOPP level, showed a significantly (P<0.05) higher 6.12±1.22U/mg value in group II compared to 5.11±1.02U/mg in group I (normal control). A significant (P<0.05) decrease 5.43±1.11U/mg was observed in group III (standard control) when compared to group I (normal control). Treatment of wistar rats with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, showed significantly (P<0.05) lower values of 5.23±1.05U/mg and 4.93±1.07U/mg for AOPP level respectively when compared to group II (positive control). Also, a non-significant (P<0.05) decrease of 5.22±1.09U/mg was observed in group VI compared to group I (normal control).

Analysis of lipid peroxidation, showed significantly (P<0.05) higher MDA levels 5.45±1.05U/mg in group II (positive control) relative to group I (normal control). A significant (P<0.05) decrease of 4.04±1.08U/mg was observed in group III (standard control) when compared to group I (normal control). Treatment of wistar rats with 2ml/kg and 4ml/kg aqueous seed extract of *Elaeis guineensis*, showed significantly (P<0.05) lower 4.06±1.06U/mg and 4.08±1.03U/mg MDA levels respectively compared to group II (positive control). Also, a non-significant (P<0.05) decrease of 4.21±1.09U/mg was observed in group VI compared to group I (normal control).

Histology of the Heart

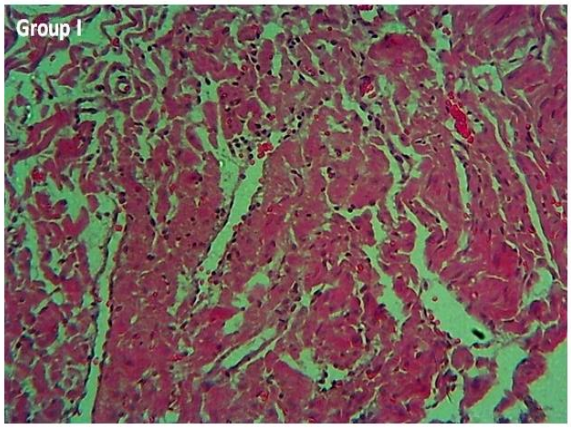

Plate 1: (Normal control): heart of rat showing normal histologic architecture. White pulp (WP); Central artery (CA); Red pulp (RP). H&Ex400.

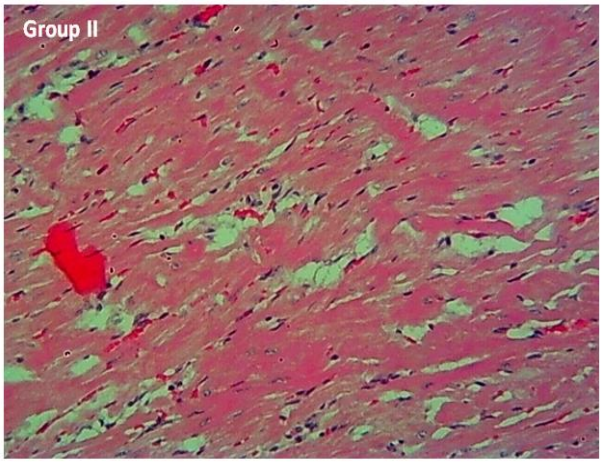

Plate 2: (Positive control): showing myocytic disarray, degeneration and necrosis, accompanied by inflammatory cellular infiltration (arrows). H&Ex400.

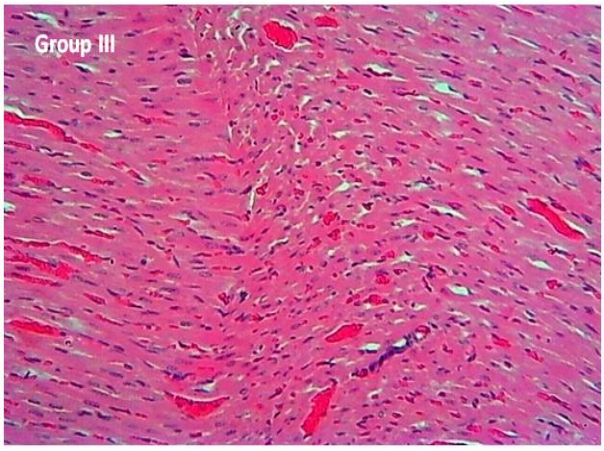

Plate 3: (Standard control): heart of rat showing normal histologic architecture. White pulp (WP); Central artery (CA); Red pulp (RP). H&Ex400.

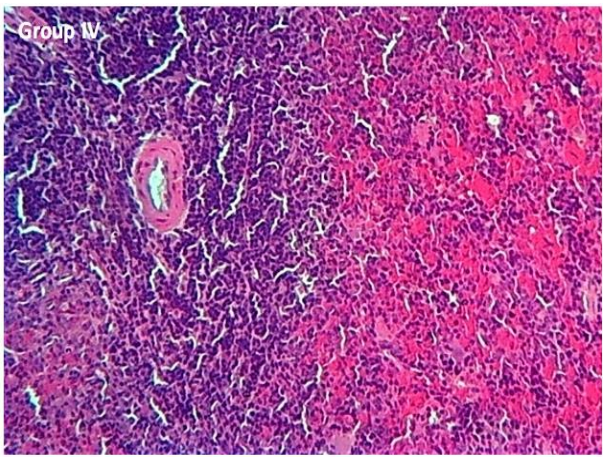

Plate 4: (Test I): heart of rat showing normal histologic architecture. White pulp (WP); Central artery (CA); Red pulp (RP). H&Ex400.

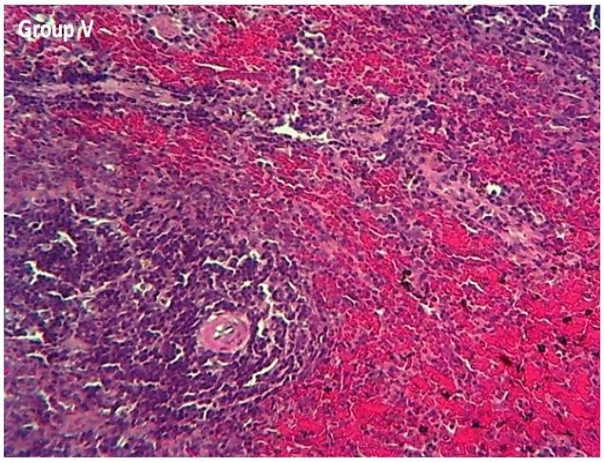

Plate 5: (Test II): heart of rat showing normal histologic architecture. White pulp (WP); Central artery (CA); Red pulp (RP). H&Ex400.

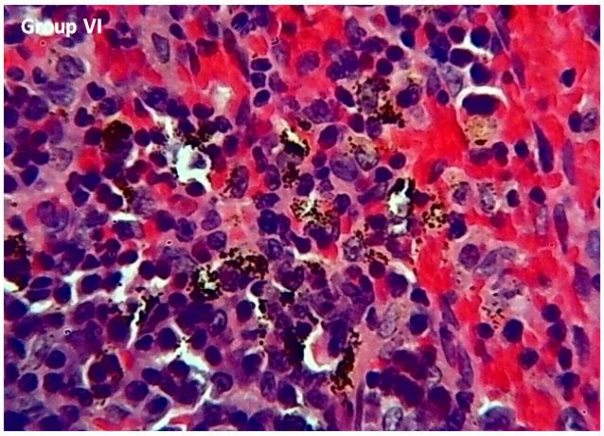

Plate 6: (Test III): heart of rat showing normal histologic architecture. White pulp (WP); Central artery (CA); Red pulp (RP). H&Ex400.

DISCUSSION

The sub-Saharan African regions have been laden with Malaria fever illness over the years, which has made the populace rely heavily on cheap and available resource, e.g. mosquito coils / repellent as a control measure (Abdullah *et al*, 2017; Mossa *et al*, 2013): despite deleterious side effects which substances emitted from those repellents have on human health (Jegede *et al*, 2015).

In the current research, cardiopulmonary functions alongside antioxidant status were evaluated in rats that were exposed to toxicity from mosquito coils / repellents and treated with oil palm seed extract. The results showed that when rats were exposed to mosquito repellents (Group II), it triggered a process of toxicity in the tissues; hence an observation of elevated levels for those biomarkers of cardiac / muscle damages as well as stress indicated in the significantly ($P<0.05$) increased blood serum values for LDH, CK, SOD, CAT, GSH, and PER in the rats (Group II), compared to normal control rats (Group I). This observation did not negate the findings of Abubakar & Hassan (2017), as well as Naz *et*

al, (2019) who independently reported increase in levels of liver enzyme biomarkers following exposure to varieties (Swam, Rambo and Cork) of mosquito coil fumes and insecticides.

However, when rats were treated (Groups IV, V and VI) with 2ml/kg and 4ml/kg fresh *Eleasis guineensis* seed extract, significantly ($P<0.05$) lower values of these biomarkers (LDH, CK, SOD, CAT, GSH, and PER) were observed in those rats compared to positive control group II rats as seen in Table 4.1 and Table 4.2.

The histological analysis made from the tissue homogenates for all the divisional groups of rats are seen in plates 1 to 6. The result shows that there were distortions in the heart tissue; myocytic disarray, degeneration and necrosis, accompanied by inflammatory cellular infiltration for the positive control (group II) rats that were exposed to the mosquito repellent fumes (Plate 2). It could therefore be inferred that the fumes from the repellent contained toxic compounds that interfered with the heart architecture, possibly cascading through inflammatory reaction that resulted in cardiac myofaction seen. This again corroborates reports of Idowu *et al*, (2016) about toxicological effects of some mosquito coils brands in experimental rats. But, normalcy and perhaps improved morphology observed in heart cells of the Groups IV, V, and VI rats that were administered extracts of the oil palm seed, could be attributed to a possible ameliorative potential of *Eleasis guineensis* seed (Plates 4,5 and 6).

CONCLUSION

This study contributes valuable insights into the toxic effects of pyrethroid-based mosquito coils and further highlights the potential cardiopulmonary protective role that aqueous extract of fresh *Elaeis guineensis* seed could proffer during cardiac damage. The observed improvements in biochemical markers and antioxidant status suggest that *Elaeis guineensis* seed may serve as a promising natural agent against cardiotoxicity induced by environmental pollutants, providing a foundation for further exploration of its therapeutic potential in lungs and heart related disorders.

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