Protective effect of aqueous fruit extract of *Mondia whitei* against cadmium-induced hepatotoxicity in rats

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**Abstract**

Introduction: *Mondia whitei* (Hook.f.) Skeels is rich in antioxidant activity and is known for its nutritional and medicinal uses. This study evaluated the protective effect of *M. whitei* fruit against cadmium-induced hepatic damage in rats.

Methods: Twenty-five albino (Wistar strain) rats were randomly assigned into five equal groups. Rats in group I served as control, rats in group II were intoxicated with 5 mg/kg body weight (b.w) cadmium chloride (CdCl\(_2\)) for 5 days via an oral route, while groups III, IV, and V were respectively administered with 5 mg/kg b.w. CdCl\(_2\), for 5 days co-treated with 70 mg/kg b.w silymarin, 250 and 500 mg/kg b.w. of aqueous fruit extract of *M. whitei* (AEMW) for 7 days.

Results: Cadmium caused a significant \((P<0.05)\) increase in the concentration of cadmium in the liver as well as liver function markers such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), and bilirubin. In addition, a significant \((P<0.05)\) elevation in the level of malondialdehyde (MDA) and a reduction in the nitric oxide (NO) and antioxidant status were noted in the CdCl\(_2\)-exposed rats; hepatic degeneration and congested portal area were also noted. These changes were, however, reduced in the cadmium-intoxicated rats co-treated with silymarin, 250 mg/kg or 500 mg/kg AEMW.

Conclusion: Our result suggests that AEMW exerts protective effects against CdCl\(_2\)-induced hepatic damage in rats, and this might be due to the presence of phytochemicals in the plant capable of scavenging oxidative stress caused by cadmium.

**Keywords:** Alanine transaminase, Liver damage, Malondialdehyde, Oxidative stress, Phytochemical

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**Implication for health policy/practice/research/medical education:**
Mondia whitei protects against cadmium-induced hepatotoxicity and might be beneficial in these patients.


**Introduction**

Cadmium (Cd) is one of the most common heavy metals predominantly found in the atmosphere. Humans are exposed to Cd intoxication through contaminated soil, air, water, and food, as well as tobacco smoke. Agricultural and occupational sources such as fertilizer application, silver-plating, nickel-cadmium (Ni-Cd) batteries, and pigment for paint production are also sources through which Cd enters the environment (1). In addition to the non-degradable and poor excretion rates of Cd, its accumulation in animals and humans proceeds for a prolonged period because of its long half-life of about 30 years (1,2). Cd accumulation causes damage to several organs of the body, with the liver and kidney being the most affected. This is because Cd has a high affinity for metallothionein (a Cd-inducible protein containing thiol (-SH) groups that protect the cells) (1,3). Cd inhibits the activities of antioxidant enzymes by generating free radicals that alter the normal biochemical functions of these organs (4,5).

The liver is involved in the function and regulation of metabolic processes, including detoxification, storage,
transport, and excretion. These metabolic activities enable the susceptibility of the liver to oxidative stress (OS) (6), as its exposure to xenobiotics such as drugs, industrial chemicals, and environmental toxicants leads to alteration in its normal functions (7). Previous studies have reported the link between Cd exposure and hepatic injury (8,9). Kim et al (10) reported that the elevated levels of serum hepatic enzymes in the Korean population were relatively linked to liver injury occasioned by Cd. One of the mechanisms of Cd toxicity is the disruption of the antioxidant system, thereby promoting oxidative stress, leading to alteration of the biochemical functions of the liver. Most available drugs used in the management of the liver disease are associated with severe side effects, necessitating alternative therapies, which are readily available, less toxic, and cost-effective. Plant-based antioxidants can ameliorate or inhibit Cd hepatotoxicity (11,12). It is, therefore, necessary to screen more plants with antioxidant and hepatoprotective properties. *Mondia whitei* (Hook.f.) Skeels, commonly known as Mondia, belongs to the family of Apocynaceae. This species is commonly found in Southern Africa, East Africa, and some parts of West Africa. The plant is a woody climber, usually about 3-6 meters in height. The leaves are heart-shaped, with a star-like flower. The plant is known for its cultural, nutritional, and medicinal applications. For cultural belief among the locals of Kenyan, the roots are used for preparing love and luck charms. In Southern Africa, the dry roots are used as a beverage and meat enhancer, and the leaves as an appetite stimulant (13). Traditionally, the Ishans (people of Uromi and Ekpoma), the Esan-speaking part of Edo State Nigeria, claim that the fruit is an active blood detoxifier, although without any scientific back-up. The roots have also been locally used in the treatment of gonorrhea, schistosomiasis, constipation, tension, and febrile in children (14). Various medicinal properties of the plant, such as anti-proliferative (15), aphrodisiac (16), antioxidant, anti-sickling (17), and antidepressant activities (14), have been reported. There is a paucity of scientific information regarding the organic constituents present in the plant. However, a few compounds have been identified in the roots and fruits, which include 2-hydroxy-4-methoxybenzaldehyde, propacin, isovanillin, and parapentyl phenyl benzoate (18). Adepoju (19) reported that the fruit of *M. whitei* was rich in micronutrients such as calcium, phosphorus, zinc, manganese, β-carotene, and ascorbic acid. There is less evidence-based research on the protective or therapeutic potentials of *M. whitei* fruit against hepatic damage. The current study was, therefore, designed to investigate the hepatoprotective effect of aqueous fruit extract of *M. whitei* against Cd-induced hepatotoxicity in rats.

**Materials and Methods**

**Materials**

Cadmium chloride (CdCl₂), glutathione, and thio­barbituric acid were purchased from Sigma Aldrich Chemicals Co. (St. Louis, MO, USA). Commercially available Randox kits for serum hepatic biomarkers were procured from a local supplier in Lagos State, Nigeria. All reagents used in this study were of analytical grade.

**Collection of plant material and preparation of extract**

*Mondia whitei* fruits were sourced from a local market (King’s market) in Ekpoma, Edo State, Nigeria. The plant was identified and authenticated by Mr. Felix Omotayo, a botanist in Ekiti State University (EKSU), Ekiti State, Nigeria. The plant specimen was kept at the University herbarium for future purposes, and an herbarium number UHAE2022051 was issued. The fruits were washed in clean water, diced into tiny pieces, air-dried, and pulverized. One hundred grams of the powdered plant was soaked in 0.5 L distilled water for 24 hours. The plant sample was filtered with a muslin cloth and thereafter with Whatman No. 1 filter paper. The filtrate was concentrated at 45°C using a rotary evaporator and then lyophilized to powdered form. The powdered sample was stored in -20°C freezer till required.

**Experimental animals**

Twenty-five male albino (Wistar strain) rats weighing 110 ± 20 g were used in this study. The animals were raised at the animal holding room of the Biochemistry unit, Afe Babalola University, Ado-Ekiti (ABUAD), Ekiti State, Nigeria. The rats were housed in clean and well-ventilated polypropylene cages under laboratory conditions (27 ± 2°C, relative humidity of 45 ± 20%, 12 hours light/dark cycle). They were allowed access to standard pelletized food and water *ad libitum*. The animals were acclimatized for 7 days before the start of treatment. Approval for the animal protocol used in this study was issued by the Ethics Committee of the Faculty of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti. The National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animal was adopted for this study.

**Animal grouping**

Rats were randomly allocated into five groups, with five animals in each. Group I rats served as control. Group II rats received 5 mg/kg b.w. CdCl₂ orally for 5 days. Group III, IV, and V rats were administered with 5 mg/kg b.w. CdCl₂ orally for 5 days and co-treated respectively with 70 mg/kg silymarin, 250 mg/kg, and 500 mg/kg aqueous fruit extract of *M. whitei* (AEMW) orally for 7 days. The extract was given to animals 1 hour before CdCl₂ administration. Doses of AEMW (250 and 500 mg/kg b.w) used in this study were obtained from the preliminary acute and sub-acute toxicity studies performed in our laboratory (data not shown). The study was designed for 7 days based on the traditional beliefs of the people of Uromi and Ekpoma, Edo State, Nigeria, that the fruit has instant therapeutic response.
Preparation of serum and tissue homogenate
Rats were subjected to an overnight fast after the last treatment for 24 hours and were sacrificed after quick exposure to diethyl ether. Blood samples were collected from the rats via cardiac puncture and transferred to a plain vacutainer tube. For the blood to clot, the samples were allowed to stand for 1 hour on the bench at room temperature and then centrifuged at 3000 × g for 5 minutes to obtain serum, which was stored at a -20°C freezer for biochemical analyses. Rat’s liver was isolated and blotted with a paper towel to remove the blood stains. A part of each liver was cut for histopathological studies, and the remaining part was rinsed in 0.9% sodium chloride (NaCl), followed by homogenization in ice-cold 0.1 M phosphate buffer (pH 7.4, 1:5 (w/v)) using Teflon homogenizer. The tissue homogenate was centrifuged at 8000 × g for 15 minutes. The obtained supernatant was transferred to an Eppendorf tube and stored at -20°C for further biochemical analyses.

Determination of liver damage biomarkers
Biomarkers for liver damage, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), total bilirubin (TB), and direct bilirubin (DB) were evaluated using Randox commercial kits, and assays were carried out as per the manufacturer’s specifications.

Determination of liver inflammatory and oxidative stress markers
Liver antioxidant status was assessed by the following methods: Misra and Fridovich (20) for superoxide dismutase (SOD), Sinha (21) for catalase (CAT) activities, Habig et al (22) and Beutler et al (23) for glutathione-S-transferase (GST) and reduced glutathione (GSH) activities, respectively. Levels of other OS biomarkers (malondialdehyde [MDA] and inflammatory marker, nitric oxide [NO]), were determined using the methods described by Varshney and Kale (24) and Green et al (25), respectively.

Histological examination
A portion (0.05 g) of the liver was fixed in 10% formalin, processed, and embedded in paraffin wax. A method by Drury and Wallington (26) was followed for tissue embedding. The embedded samples were sectioned into a thin layer and stained with hematoxylin and eosin (H&E) on a glass slide. The slides were observed for histopathological changes under a light microscope at 800x magnification.

Statistical analysis
The results of this study were expressed as mean ± SD (n=5). Data were analyzed using one-way analysis of variance (ANOVA), and Tukey’s post hoc test was used for multiple groups’ comparison on GraphPad Prism version 5. In all cases, P<0.05 was considered statistically significant.

Results
Effect of Cd on body and organ weights
Cadmium intoxication caused a significant (P<0.05) decrease in the body weight gain of rats when compared to the control group. However, CdCl₂-intoxicated rats co-treated with AEMW at doses of 250 and 500 mg/kg showed no significant (P>0.05) difference in the body weight gain of rats when compared with the control (Figure 1A). A significant (P<0.05) increase was observed in the body weight gain of CdCl₂-intoxicated rats co-treated with 250 and 500 mg/kg AEMW when compared with the CdCl₂ group. In comparing the AEMW (500 mg/kg b.w.) to the silymarin group, a significant (P<0.05) increase in the body weight gain of rat was noted (Figure 1A).

In addition, a non-significant (P>0.05) reduction in the relative liver weight of the rat was observed in the CdCl₂ group when compared with the control (Figure 1B). No

Figure 1. Effect of aqueous fruit extract of M. whitei on % weight gain (A) and relative organ weight (B) of rats intoxicated with CdCl₂. Values are represented as mean ± SD (n=5). aP<0.05 as compared to the control group. bP<0.05 as compared to CdCl₂ group; cP<0.05 as compared to silymarin group. Abbreviation: AEMW: aqueous fruit extract of Mondia whitei; CdCl₂: cadmium chloride.
significant ($P>0.05$) difference was observed in the CdCl$_2$ intoxicated rats co-treated with silymarin and AEMW when compared with the CdCl$_2$ group (Figure 1B).

**Cadmium concentration in rat’s liver**

Figure 2 reveals the Cd concentration in rat’s liver exposed to CdCl$_2$. A significant ($P<0.05$) increase was noted in Cd concentration in the rats’ livers intoxicated with Cd and the Cd-intoxicated rats co-treated with silymarin or 250 mg/kg AEMW when compared to the control group. A significant ($P<0.05$) reduction was, however, noted in the concentration of Cd in the liver of Cd-intoxicated rats co-treated with silymarin or 500 mg/kg AEMW when compared to the CdCl$_2$ group. Exposure of rats to Cd significantly ($P<0.05$) increased the liver Cd concentration in the 250 mg/kg AEMW co-treated rats when compared to the group co-treated with silymarin.

**Effects of AEMW on liver marker enzymes in CdCl$_2$ intoxicated rats**

Figure 3 (A, B, C) shows the effect of Cd on liver marker enzymes. Cd intoxication significantly ($P<0.05$) elevated the levels of serum enzyme markers (AST, ALT, and LDH) when compared to the control group. The levels of these serum enzymes were significantly ($P<0.05$) reduced in the silymarin and AEMW (250 and 500 mg/kg b.w.) co-treated groups when compared to the CdCl$_2$ group.

**Effect of AEMW on serum TB and DB levels in CdCl$_2$-induced rat**

Figure 4 (A, B) depicts the effect of AEMW on TB and DB levels in CdCl$_2$-intoxicated rats. Cd administration significantly ($P<0.05$) elevated the levels of serum TB and DB when compared to the control group. Similarly, serum DB level was significantly ($P<0.05$) increased in the CdCl$_2$-intoxicated rats co-treated with silymarin or 250 mg/kg AEMW when compared to the control group (Figure 4B). A significant ($P<0.05$) decrease in serum TB level was observed in the CdCl$_2$-intoxicated rats co-treated with 250 or 500 mg/kg AEMW and a significant reduction in serum DB level in Cd-intoxicated rats co-treated with 500 mg/kg AEMW when compared to the CdCl$_2$ group (Figure 4A).
Effects of AEMW on NO level

Figure 5 shows the effect of AEMW on tissue NO levels in rats intoxicated with CdCl₂. Cd administration significantly (P<0.05) decreased NO levels in rats when compared to the control group. Co-treatment of the Cd-intoxicated rats with AEMW at a dose of 500 mg/kg significantly (P<0.05) increased NO level when compared to the CdCl₂-intoxicated group.

Effects of AEMW on hepatic oxidative stress status in CdCl₂-intoxicated rats

Cd intoxication significantly (P<0.05) increased tissue MDA levels when compared to the control group (Table 1). Treatment of Cd-intoxicated rats with 250 or 500 mg/kg AEMW significantly decreased the level of MDA compared to the CdCl₂ group. Furthermore, a significant (P<0.05) decrease was noted in the antioxidant enzymes (CAT, SOD, and GST) activities and reduced-GSH level when compared to the control group. Similarly, the activities of CAT and SOD were significantly (P<0.05) decreased in silymarin and 250 mg/kg AEMW co-treated groups when compared to the control group. A significant (P<0.05) increase in the hepatic antioxidant levels was noted in CdCl₂-intoxicated rats co-treated with 250 or 500 mg/kg AEMW compared to the CdCl₂ group.

Effects of AEMW on hepatic histopathological changes of CdCl₂-intoxicated rats

Figure 6 shows the effect of AEMW on the histopathological changes in liver of rats intoxicated with CdCl₂. Rats in the control group showed normal hepatocytes with no noticeable histological alterations (Figure 6A). The liver of CdCl₂-intoxicated rats (group II) showed a distorted architectural arrangement with severe hepatic disintegration and congested portal vein (black arrow) (Figure 6B). A mild vacuolar disintegration with shrunken portal areas was observed in CdCl₂-intoxicated rats co-treated with silymarin or 250 mg/kg AEMW (Figure 6C-D). The CdCl₂-exposed rats co-treated with AEMW at a dose of 500 mg/kg showed a normal arrangement of the hepatocytes with mild shrunken portal areas (Figure 6E).

Discussion

Cd intoxication promotes the generation of free radicals via Fenton reactions, thereby leading to oxidative damage to various organs of the body (27-29). Liver, among other organs of the body, is the most susceptible to Cd toxicity because of its metabolic roles and the Cd-metallothionein binding protein found in liver tissues (30). Accumulation of Cd in the liver, either in small quantities or large amounts over time, could result in the dysfunctionality of the liver (31,32).

The radical scavenging and antioxidant activities, as well as the therapeutic potentials of M. whitei leaf and root extracts, have been reported (17,33). However, not much is known about the ethnomedicinal properties of the fruit extract. Although the indigenes of Ishan, Edo State, Nigeria believe that the fruit has detoxifying ability,
Anadozie et al.

which could be attributed to its antioxidant capacity, there is no evidence-based report regarding this. This study, therefore, evaluated the protective effect of aqueous fruit extract of *M. whitei* against Cd-induced hepatotoxicity in rats.

Body weight and relative organ weight are physiological indicators to assess the effect of Cd in an experimental animal (34). The observed significant decrease in the % body weight gain of rats in this study indicates that the administration of CdCl\(_2\) in the rats induced OS. A decrease in the % body weight has been relatively linked to OS (35). The reduction in the percent of body weight gain seen in the present study was restored by AEMW at 250 and 500 mg/kg doses, suggesting that AEMW was able to avert and protect the rats from oxidative injury caused by CdCl\(_2\).

The liver has the highest concentration of Cd deposit because of its metabolic functions; therefore, the accumulation of Cd in the liver can lead to hepatic injury, which alters liver function (36). In the present study, the concentrations of Cd in the liver of rats were significantly increased in CdCl\(_2\)-induced hepatotoxic rats (group II) compared to the control group. Whereas treatment with AEMW drastically reduced the concentration of Cd in the rat’s liver suggesting that AEMW was able to scavenge the free radical generated by CdCl\(_2\).

Serum liver biomarkers such as AST, ALT, LDH, TB, and DB were measured to assess the hepatic damage caused by CdCl\(_2\) intoxication. Serum hepatic enzymes (ALT, AST, and LDH) are important markers in evaluating the functional and structural status of the liver (37). The elevated serum levels of these parameters, as observed in the present study, indicate hepatic injury following oral administration of CdCl\(_2\) in rats. The elevated levels could be because of the altered liver cell membrane, which result in the leakage of these hepatic enzymes into the bloodstream. The findings of the present study correlate with the earlier reported study by Manoharan and Prabu (38), where Cd administration causes an increase in membrane permeability and subsequently results in the leakage of hepatic enzymes into the lymphatic vessel, an indication of hepatic damage. The treatment with AEMW at 250 and 500 mg/kg doses remarkably abated the effect of CdCl\(_2\) on the serum hepatic enzymes in the rats. This suggests the protective role of AEMW against CdCl\(_2\)-

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<tr>
<th>Treatments groups</th>
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<tr>
<td></td>
<td>MDA (nm/mg protein)</td>
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<tr>
<td>Control</td>
<td>0.03 ± 0.01</td>
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<tr>
<td>CdCl(_2)</td>
<td>0.10 ± 0.01(^a)</td>
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<td>CdCl(_2) + silymarin</td>
<td>0.06 ± 0.01(^a)</td>
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<td>CdCl(_2) + AEMW (250 mg/kg)</td>
<td>0.06 ± 0.02(^a)</td>
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<td>CdCl(_2) + AEMW (500 mg/kg)</td>
<td>0.04 ± 0.01(^b)</td>
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Values are represented as mean ± SD (n=5). \(^{a}\)P < 0.05 as compared to control group; \(^{b}\)P < 0.05 as compared to CdCl\(_2\) group.

Abbreviation: AEMW, aqueous fruit extract of *Mondia whitei*; CdCl\(_2\), cadmium chloride; MDA, malondialdehyde; CAT, catalase; SOD, superoxide dismutase; GST, glutathione s-transferase; GSH, reduced glutathione.
induced hepatotoxicity.

The elevated levels of TB and DB on the exposure of rats to CdCl₂ could be an indication of hepatocellular damage or a disruption in the hepatic-biliary tract. Kumar et al (39) in their study reported that Cd-induced liver damage rats showed elevated levels of TB and DB, disrupting the biliary tract and altering the uptake and excretion of bilirubin by the hepatocytes. These correlate with the findings of the present study and further confirm a loss of membrane integrity and disruption in the normal function of the liver. Elevated levels of serum hepatic indices and the observed hepatocellular changes on the exposure of rats to CdCl₂ were, however, attenuated when treated with the AEMW at the doses of 250 and 500 mg/kg. This suggests that AEMW could scavenge free radicals and protect the Cd-exposed rats from hepatocellular damage.

Nitric oxide is an important vasodilator in various pathophysiological features of the liver (40). The nitric oxide synthase (NOS) is responsible for the conversion of L-arginine to NO and citrulline. Endothelial NOS (eNOS) obtained from NO is responsible for the metabolic homeostasis of the liver and prevents the liver from various pathogenic diseases (41,42). In the present study, the reduced NO production caused by CdCl₂ intoxication could be linked to OS, therefore, reducing the activity of eNOS in the rat’s liver. The reduced NO level was increased upon exposing the Cd-induced hepatoxic rats to AEMW treatment at a dose of 500 mg/kg, suggesting that AEMW at a higher dose increased the endothelial function of the liver, thereby increasing the level of NO.

Various pathological diseases in humans have been associated with OS initiated by free radicals. Exposure to Cd can lead to alteration in the structure and functions of hepatic cells, increasing the generation of free radicals. The elevated level of MDA (lipid peroxidation) in the system alters the body’s antioxidant/oxidant balance. The antioxidant system acts as a cellular defense mechanism against OS (43,44). In the present study, the elevated level of OS maker (MDA) and decrease in the levels of antioxidant biomarkers (SOD, CAT, and GST) noted upon exposing the rats to Cd indicates the generation of free radicals, which could have resulted in the hepatic damage. The reversal of these effects by AEMW at doses of 250 and 500 mg/kg suggests that the AEMW has radical scavenging ability.

Reduced glutathione (GSH), a sulfur-containing tripeptide majorly found in the liver, helps in the maintenance of cellular activities and protects the liver against reactive oxygen species (ROS). Because of the various metabolic activities of the liver, a link exists between the thiol group of GSH and the Cd-protein metallothionein, and by interaction, alters the metabolism of cellular GSH1 and subsequently leads to OS (11,45). An increase in cellular GSH protects the liver from OS (46). In the present study, the GSH level was significantly reduced in CdCl₂-intoxicated rats, whereas AEMW treatment at doses of 250 and 500 mg/kg reversed the GSH level by a significant increase similar to that of the control group.

Exposure to Cd has been known to induce oxidative stress via the inhibition of antioxidant enzymes (47). The effect of AEMW on enzymatic and non-enzymatic antioxidant parameters evaluated in this study could be connected to the presence of phytochemicals in the plant extract, enhancing the role of the antioxidant defense system in protecting cells against oxidative damage, and lipid peroxidation caused by Cd. It can, therefore, be suggested that the protective role of AEMW is based on antioxidant defense mechanisms.

The severe vacuolar disintegration and congested portal vein seen in the histoarchitectural structure of the hepatocytes suggest that CdCl₂ administration caused hepatic damage to the rats (group II). The CdCl₂-treated rats co-treated with silymarin or AEMW 250 mg/kg could not fully attenuate nor reverse the histological alterations, as mild changes were seen in the liver histoarchitecture. The Cd-intoxicated rats co-treated with AEMW at a dose of 500 mg/kg restored the histological damage caused by CdCl₂, suggesting that AEMW at 500 mg/kg could protect the liver against Cd-induced oxidative damage. This observation validates the results of the serum hepatic and OS markers of this study, where the extract reversed the hepatic injury elicited by CdCl₂.

**Conclusion**

In conclusion, our study showed that Cd exposure remarkably causes oxidative damage, loss of membrane integrity, and inhibition of antioxidant enzymes. Treatment with AEMW significantly restored the membrane integrity and prevented the inactivation and depletion of plasma membrane enzymes. This study, therefore, gives preliminary information on the use of AEMW against Cd toxicity. The mechanism of protective action against liver damage by *M. whitei* fruit could be due to the antioxidant and free radical scavenging potentials of the secondary metabolites inherent in the plant. Further studies on the insolation and characterization of the *M. whitei* fruit components should be performed to strengthen the findings of the present study.

**Authors’ contributions**

SOA conceptualized and drafted the manuscript, OBA and BOA collected data and analyzed, JNO and OAO proofread and edited the manuscript, MMU, OAO, and OSO performed the experiments. All authors read, agreed, and approved the final draft of the manuscript before submission.

**Conflict of interests**

The authors declare that they have no known financial and personal or organizational competing interests that could inappropriately influence the outcome of this study.

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Ethical considerations

The experimental protocols used in the present study was approved and issued by the Ethics Committee of the Faculty of Medicine and Health Sciences, Afe Babalola University, Ado-Ekiti (ABUAD/MHS/IAEC/7/B-21). The National Institutes of Health (NIH) Guidelines for the Care and Use of Laboratory Animal was adopted for this study.

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