The Role of *Anthocleista djalonensis* in Mitigating Mercury Chloride-Induced Hematological Alterations

Running title: Protective Role of *Anthocleista djalonensis* in Hematotoxicity

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Abstract

Background: Mercury chloride is a well-established toxicant known to induce hematological alterations, including oxidative hemolysis, anemia, and thrombocytopenia. Medicinal plants with antioxidant properties have been explored as potential protective agents against toxicant-induced damage. *Anthocleista djalonensis* (*A. djalonensis*), widely used in traditional medicine, has been reported to possess bioactive compounds with therapeutic potential. This study aimed to investigate the role of *A. djalonensis* in mitigating mercury chloride-induced hematological alterations.

Methods: This experimental randomized controlled animal study was kind of weirdly done, with thirty-six adult Wistar rats, randomly assigned into six groups (n=6 each). Group A was basically the control; Group B got only 2 mg/kg of mercury chloride, just that. Groups C and D were given mercury chloride alongside 150 mg/kg and 300 mg/kg of *A. djalonensis* extract, respectively, while Groups E and F received just *A. djalonensis* at doses of 150 mg/kg and 300 mg/kg. The extract was freeze-dried, and then the hematological parameters were checked using an automated hematology analyzer. For the statistics, it was handled with one-way ANOVA, and the significance cutoff was $p < 0.05$.

Results: Mercury chloride exposure significantly reduced red blood cell count, hemoglobin concentration, and platelet levels, indicating hematotoxicity. Co-administration with *A. djalonensis*, particularly at 150 mg/kg, significantly improved these hematological indices, suggesting a protective effect. The plant extracts also enhanced mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration, indicating potential erythropoietic support.

Conclusion: The findings suggest that *A. djalonensis* mitigates mercury chloride-induced hematotoxicity, likely through antioxidative mechanisms. These results highlight its potential therapeutic role in managing hematological disorders associated with toxicant exposure.

Keywords: Mercury chloride; Hematotoxicity; *Anthocleista djalonensis*; Antioxidant; Hematological parameters

Introduction

Mercury chloride ($HgCl_2$) is a widely recognized environmental and industrial toxicant that poses significant health risks to humans and animals. It is used in various industrial processes, laboratory reagents, and chemical synthesis, but it has no known metabolic or physiological role in living organisms, and its presence in biological systems reflects contamination and exposure (1,2). Among the toxic effects of mercury chloride, hematological alterations are prominent, including oxidative hemolysis, reduced hemoglobin concentration, anemia, leukocyte changes, and thrombocytopenia (3). Moreover, mercury intoxication was also associated with oxidative stress induction in tissues (4). The oxidative stress has been linked to the excess production of reactive oxygen species (ROS), which may induce enzymatic inactivation and peroxidation of cell constituents (5).

Mercury toxicity has been strongly connected with hematological and biochemical irregularities in both experimental animals and people. In lab studies, it is pretty clear that mercury chloride brings about hematotoxicity. When Mercury chloride is given to Wistar rats, it has been shown to dramatically drop the red blood cell (RBC) count, hemoglobin concentration (Hb) and packed cell volume (PCV), plus leukocytosis, and oddities in the differential white blood cell counts. After exposure, researchers noted dose-related anemia, and higher levels of malondialdehyde (MDA), a marker for lipid peroxidation, were also seen. Overall, these findings point that mercury chloride is causing hematological dysfunction mostly via oxidative damage to erythrocyte membranes and the reduction of antioxidant defence mechanisms (3).

Engwa et al. (6) reported on the involvement of free radicals and endogenous antioxidant defence in metal intoxication of animal blood. Erythrocytes are especially susceptible to oxidative damage because of their high polyunsaturated fatty acid content and frequent exposure to oxygen (7). Although RBCs have endogenous antioxidant mechanisms including superoxide dismutase, catalase, and glutathione peroxidase, excess mercury-induced free radical generation can overwhelm these defences, resulting in membrane fragility, hemolysis, and reduced hematological function. (6, 8).

Plants with medicinal values are well known to man as indispensable materials in drug discovery and are utilized by man for various purposes from the inception of human history (9). Medicinal plants contain some organic compounds which produce definite physiological action on the human body and their bioactive substances include tannins, alkaloids, carbohydrate, terpenoids, steroids and flavonoids (10). Medicinal plants are quite beneficial for the well-being of individuals as well as for communities (10). Because of that, the economic value of medicinal plants has gotten the attention of quite a lot of international organisations, especially the World Health Organization (WHO) (11). Since WHO has supported and encouraged the merging of traditional medicine resources into global health systems, the use of medicinal plants has risen pretty fast (12). Because of this, ethnobotanical research makes it easier to craft newer treatments and medications, and it also supports plant conservation (13). Many ethnobotanical studies around the world report the use of herbal plants for the healing process, which has been in use for several generations in their respective societies (14). *A. djalonensis* A. Chev, commonly known as Cabbage tree, called “Kwari” in Hausa, “Ewe” by the Yoruba people of South-West (15), and “Oyinwin’ wi-uwu” by the Binis of South-South (16), Nigeria, belongs to the family Loganiaceae, is a medium-sized tree of West tropical Africa, 30-45 feet high with blunt spines on the branch, pale grey trunk, and widespreading crown (15). The stem, root, bark, and leaves of *A. djalonensis* are used to treat malaria, jaundice, diabetes, and abscesses (17). Phytochemical screening of *A. djalonensis* reveals the presence of flavonoids, terpenoids, and phenolic compounds (18), which are associated with

antioxidant and cytoprotective activities. However, evidence regarding its potential to mitigate heavy metal–induced hematotoxicity is limited. Therefore, this study aimed to investigate the protective role of *A. djalonensis* in mitigating mercury chloride–induced hematological alterations in Wistar rats.

Methods

This study was designed as an experimental randomized, controlled laboratory animal study.

Plant collection and identification

The bark, from the stem of *A. djalonensis* used in this study, was gathered from a farm around Benin City. The plant gathering process was done in line with the rules put in place by the Edo State Forestry Commission, for the collection of wild plants. The specimen was recognized and verified by a plant taxonomist in the Department of Plant Biology and Biotechnology, Faculty of Life Sciences, University of Benin, Benin City, Edo State, Nigeria, and it was also assigned the herbarium number UBH-A594.

Extract preparation

The plant was extracted using the freeze-dry method in an aqueous solution. The stem bark of *A. djalonensis* was rinsed with tap water, dried in the shade, and then crushed into smaller pieces. The powder was placed in distilled water and left in a separating funnel for 24 hours, with the mixture shaken now and then. The solution was then filtered. The filtrate was let sit until it settled and then poured off. The filtrate was then frozen and dried using a freeze-drying machine and stored in a refrigerator at –6 °C.

Ethical approval

The Research Ethics Committee's rules for handling and caring for animals at the University of Benin's College of Medical Sciences were completely followed, and they gave the ethical approval number CMS/REC/2023/340.

Experimental design

Thirty-six (36) adult Wistar rats were randomly assigned into six (6) groups; Groups A – F comprising of six rats per group.

The experimental animals were randomly assigned into six groups: Group I served as the control and received no treatment; Group II received mercury chloride at a dose of 2 mg/kg; Group III received mercury chloride (2 mg/kg) co-administered with low-dose *A. djalonensis* extract (150 mg/kg); Group IV received mercury chloride (2 mg/kg) co-administered with high-dose *A. djalonensis* extract (300 mg/kg); Group V received *A. djalonensis* extract alone at 150 mg/kg; and Group VI received *A. djalonensis* extract alone at 300 mg/kg.

All administrations were done orally using an oral gavage attached to a calibrated syringe for 28 consecutive days.

Determination of hematological parameters

Hematological parameters were analyzed using a Mindray BC-2800 automated hematology analyzer (Mindray Bio-Medical Electronics Co., Shenzhen, China), based on the electrical impedance method.

This method uses three detector blocks and two types of reagents for blood analysis. The white blood cell (WBC) detector block measures the WBC count using the DC detection method (19). The RBC detector block counts RBCs and platelets using the DC detection method (20). The Hb detector block uses the non-cyanide hemoglobin technique to determine hemoglobin concentration (21). Most electronic blood cell analyzers count blood cells based on impedance.

The normal reference ranges for adult Wistar rats were considered as follows: RBC (6.0-8.5 $\times 10^{12}$/L), hemoglobin (12-17 g/dL), packed cell volume (36-50%), WBC (6-18 $\times 10^{9}$/L), and platelet count (500-1300 $\times 10^{9}$/L). These reference values were used for comparison in assessing mercury chloride-induced hematological alterations.

Principle of impedance analyzer

Blood cells are diluted using a buffer electrolyte solution. A measured volume of sample is passed through an aperture tube between two electrodes. The interruption of the current by non-conducting blood cells modifies the electrical charge, resulting in a pulse. The amplitude of each pulse is proportional to the volume of the cells that generated it. A threshold circuit guarantees that only pulses that surpass pre-determined threshold levels are counted. The cell count is calculated using the number of pulses collected from a given volume of blood (22).

Statistical analysis

The data was statistically analyzed using the GraphPad Prism version 9.0 statistical tool, and important statistical values were determined. Data was analyzed using one-way ANOVA and reported as mean ± SEM. Tukey's post-hoc test was utilized. P-values of <0.05 were considered statistically significant. The statistical data obtained was transformed into graphical representations in the form of bar charts.

Results

The study found that mercury chloride exposure reduced WBC count, although the decrease was not statistically significant. The percentage of lymphocytes and mean inhibitory dilution also showed no significant changes across groups. However, granulocyte percentage was significantly affected, with mercury chloride reducing its levels, while 300 mg/kg of *A. djalonensis* increased it.

RBC count was significantly reduced by mercury chloride exposure, with levels dropping compared to the control group. However, treatment with 150 mg/kg of *A. djalonensis* helped to restore RBC count. Similarly, mercury chloride significantly decreased hemoglobin concentration, while 150 mg/kg of *A. djalonensis* significantly improved it.

Hematocrit levels did not show significant differences among groups. Mean corpuscular volume (MCV) remained unchanged, but mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC) were significantly altered. Mercury chloride reduced MCH and MCHC, whereas *A. djalonensis* treatment significantly increased them.

The study also observed significant changes in red cell distribution width (RDW), with the 300 mg/kg *A. djalonensis* group showing the lowest RDW values. However, the coefficient of variation of RDW remained statistically unchanged.

Platelet count was significantly reduced by mercury chloride, but *A. djalonensis* at 150 mg/kg significantly increased it. Mercury chloride also increased mean platelet volume (MPV), while *A. djalonensis* exhibited variable effects on this parameter. Platelet distribution width (PDW) was significantly elevated by mercury chloride, but *A. djalonensis* reversed this effect.

Finally, mercury chloride drastically reduced plateletcrit levels, while 150 mg/kg of *A. djalonensis* significantly improved them. These findings indicated that mercury chloride caused hematotoxic effects, including reductions in RBC, hemoglobin, and platelet counts. However, *A. djalonensis*, particularly at 150 mg/kg, demonstrated protective and restorative effects against mercury-induced toxicity.

Table 1. Hematological indices of experimental animals after 28 days of administration with mercury chloride and *A. djalonensis*

Groups/Test	**Control**	**2mg/kg Mercury chloride only**	**2mg/kg Mercury chloride + 150mg/kg of *A. djalonensis***	**2mg/kg Mercury Chloride + 300mg/kg of *A. djalonensis***	**150mg/kg of *A. djalonensis* only**	**300mg/kg of *A. djalonensis* only**	**P-Value**
White Blood Cell (uL)	4.50±0.75	4.28±1.21	5.93±0.41	7.55±0.75	6.20±1.14	7.15±0.97	0.1056
Lymphocyte (%)	91.50±0.81	89.10±3.69	91.10±0.95	90.20±1.44	93.30±0.54	88.30±1.54	0.4693
Mean Inhibitory Dilution (%)	5.53±0.87	4.83±0.69	5.90±0.85	7.35±1.09	4.68±0.56	8.33±1.36	0.0796
Granulocyte (%)	3.00±0.20	2.35±0.17	3.05±0.21	3.15±0.31	2.08±0.28	3.40±0.18	0.0050
Red blood cell (uL)	7.66±0.28	6.87±0.07*	6.36±0.25	7.17±0.17	7.16±0.13	6.81±0.16*	0.0039
Hemoglobin (g/dL)	14.50±0.68	12.80±0.29	13.70±0.68	16.10±0.33#	13.80±0.40	14.70±0.40	0.0042
Hematocrit (%)	37.60±1.09	35.20±0.68	32.70±1.22	31.00±5.71	36.70±1.01	35.40±1.12	0.4492
Mean Corpuscular Volume (fL)	49.30±0.75	50.30±1.63	51.40±0.77	50.20±0.54	51.40±0.71	50.20±0.71	0.5537
Mean Corpuscular Hemoglobin (pg)	18.80±0.21	17.50±1.47	21.50±0.35#	22.40±0.71#	19.20±0.23	21.70±0.33*	0.0005
Mean Corpuscular Hemoglobin Concentration (g/dL)	38.40±0.96	34.90±2.18	42.00±1.33#	44.80±1.88#	37.50±0.60	43.10±1.18	0.0010
Standard Deviation of Red-Cell Distribution Width (fl)	31.00±10.8	32.60±2.69	28.30±1.03	27.30±0.55	35.80±1.36	26.70±0.64	0.0017
Coefficient of Variation of Red-Cell Distribution Width (%)	14.70±0.34	15.10±0.88	14.70±0.34	14.50±0.33	16.40±0.43	14.20±0.30	0.0679
Platelet (uL)	536±33.60	365±52.80	707±87.70#	445±43.70	385±36.20	619±56.00	0.0017
Mean Platelet Volume (fl)	7.33±0.16	7.98±0.43	6.80±0.21	9.03±0.39	7.85±0.40	7.28±0.13	0.0017
Platelet Distribution Width (%)	8.50±0.41	11.90±0.41*	8.13±0.08#	9.20±0.50#	10.00±0.73	7.98±0.08	<0.0001
Platelet Rit (%)	1.24±0.07	0.28±0.11*	0.45±0.04	1.40±0.01#	0.33±0.04*	0.43±0.05*	<0.0001

Values are expressed as mean ± Standard Error of Mean (SEM): * the mean difference is significant at the P<0.05 compared with control. [#] The mean difference is significant at the P<0.05 compared with 2mg/kg of Mercury chloride only.

Discussion

In the current investigation, exposure to mercury chloride seemed to cause quite evident hematological changes. Basically, there were declines in RBC count, Hb levels and PCV, which are also evidence of thrombocytopenia (Table 1). These observations line up with earlier work suggesting that inorganic mercury can induce hematotoxicity in lab animals (3, 23). Mercury's influence on the blood does not look limited to oxidative hemolysis only, it also disrupts heme production.

In this present study, exposure to mercury chloride seemed to bring about notable hematological changes including reductions in RBC count, Hb levels and PCV (Table 1). These also indicate signs of thrombocytopenia. The results match earlier work that suggested inorganic mercury can induce hematotoxicity in laboratory animals (3,23). The way mercury affects blood, doesn't look like only oxidative hemolysis at play, instead it may also disturb heme synthesis processes.

The drops in RBC and Hb counts seen in the rats administered mercury are likely because there is oxidative harm on the erythrocyte membranes, plus an erythropoiesis slowdown, probably from mitochondrial dysfunction and bone marrow suppression (24-26), all together. This agrees with reports that mercury chloride disrupts erythro-megakaryopoiesis and bone marrow progenitor activity, leading to impaired hematopoiesis (27). Similarly, mercury has been shown to induce hemoglobin oxidation and suppress erythrocyte antioxidant defenses (28). Wistar rats exposed to Mercury chloride also seemed to have higher oxidative stress markers, and lower blood count numbers (27, 28). The same kind of pattern shows up again here, with the reductions in RBC and Hb levels in the mercury-treated group, probably for that same mixed reason: membrane oxidative injury alongside a hindered erythropoiesis process tied to impaired mitochondria and suppressed bone marrow. Wistar rats treated with Mercury chloride presented stronger oxidative stress signs and reduced hematological values (29, 30).

Treatment using an extract from *A. djalonensis*, especially at 150 mg/kg, really did help. In fact it significantly boosted the RBC number, Hb concentration, PCV, and also the platelet levels (table 1), showing protective abilities, maybe due to the plants fairly high concentration of antioxidant phytochemicals like flavonoids, phenolic compounds. In other words, these substances could be acting like free radical hunters scavenging reactive oxygen species (ROS), and in turn they may help safeguard mitochondria and the erythroid precursor cells from mercury induced injury. If the mitochondrial enzymes are still able to keep working and bone marrow activity stays supported then, it is likely that erythropoiesis and thrombopoiesis will also get better and this would then help tone down the hematotoxic effect that mercury chloride causes. This outcome also fits with other work where natural plant antioxidants were able to counter the heavy metal suppression of hematopoiesis (31, 32).

The capacity of *A. djalonensis* to recover hematological parameters, suggests that it has both cytoprotective and hematopoietic characteristics in practice, so in a sense it's looking like a prospective candidate for lowering heavy metal induced hematotoxicity. Still, in this study the exact bioactive compound or compounds really doing the work were not analyzed, and additional research is needed to determine the precise pathway or pathways at a molecular level. Also, oxidative stress biomarkers, inflammatory cytokines, or bone marrow histology were not studied

in this research, which would probably give a clearer view of how the plant is actually preserving tissues in the background.

Even with these limitations, the present study suggests that *A. djalonensis* is able to reduce the mercury related hematological harm. It seems to happen via antioxidant activity and also improving of bone marrow performance, though only in an indirect way. Overall, these results add to the larger set of evidence that medicinal plants might work as a different intervention, for heavy metal induced blood issues, and at the same time highlights, that more pharmacological and clinical research is still needed.

Conclusion

This study found that *A. djalonensis* protects against mercury chloride-induced hematotoxicity, as shown by increases in RBC count, hemoglobin concentration, and platelet levels. The observed restoration of hematological parameters indicates that the plant's antioxidant phytochemicals not only protect erythrocyte membranes from oxidative damage, but may also promote hemoglobin synthesis and bone marrow proliferative activity. These two mechanisms, anti-oxidative protection and hematopoietic stimulation, provide a viable explanation for the recovery from mercury-induced hematological suppression. While the findings are promising, more research is needed to identify the exact bioactive chemicals involved, establish their role in erythropoiesis and thrombopoiesis, and assess long-term safety and efficacy. Overall, *A. djalonensis* appears to be a promising natural medicinal agent for the treatment of hematological diseases caused by heavy metal toxicity.

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Conflict of Interest

The authors declare that there was no conflict of interest in the study**.**

Author Contributions

Joseph Raymond Enoghase: Investigation, Resource, Data curation, writing review and editing and visualization. Silvanus Olu Innih: Methodology, Supervision and project administration.

Consent for Publication

All authors have read and agreed to the published version of the manuscript.

Ethical Statement

All experimental procedures involving animals were conducted in accordance with the guidelines for the care and use of laboratory animals established by the Research Ethics Committee of the College of Medical Sciences, University of Benin. Ethical approval for the study was obtained with approval number CMS/REC/2023/340.

Data Availability Statement

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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