**Effect of Avocado Leaf Extracts on Lipid Profile and Blood Pressure in Cadmium Induced Hypertensive Wistar Rats**

**Abstract**

**Background:** This study investigated the ameliorative effects of avocado leaf extract on cadmium-induced hypertension and dyslipidemia in male Wistar rats. Hypertension and dyslipidemia, often exacerbated by environmental toxins like cadmium, pose significant health risks, particularly in industrial settings. Our aim was to determine whether avocado leaf extract could mitigate these adverse effects and serve as a cost-effective alternative to conventional drugs. **Methods:** Fifty Wistar rats (90–120 g) were acclimatized for two weeks and divided into five groups (n = 10 per group). Group 1 received water (positive control), Group 2 was administered 0.2 mg/kg cadmium (negative control), Group 3 received 0.2 mg/kg cadmium plus 100 mg/kg avocado leaf extract (low dose), Group 4 received 0.2 mg/kg cadmium plus 300 mg/kg avocado leaf extract (high dose), and Group 5 received 0.2 mg/kg cadmium plus 40 mg/kg hydrochlorothiazide (standard drug). Blood pressure was measured using a computerized tail-cuff method, while serum biochemical parameters, including lipid profiles and renal function markers, were analyzed using established enzymatic and colorimetric methods. **Results:** Results showed that cadmium exposure significantly elevated diastolic blood pressure (96.60 ± 0.02 mmHg) and systolic pressure (180.00 ± 2.26 mmHg) compared to the positive control (60.43 ± 2.05 mmHg and 140.00 ± 2.26 mmHg, respectively, p < 0.05). Treatment with low-dose avocado extract significantly reduced diastolic pressure to 58.00 ± 0.24 mmHg (p < 0.05 vs. cadmium-only), while high-dose extract and the standard drug resulted in 68.00 ± 0.16 mmHg and 65.00 ± 0.03 mmHg, respectively. Dyslipidemia was also significantly improved, with high-dose extract reducing total cholesterol (2.97 ± 0.45 mmol/L) and LDL (2.25 ± 0.34 mmol/L) compared to cadmium-only exposure (3.37 ± 0.32 mmol/L and 2.57 ± 0.32 mmol/L, respectively). Additionally, renal parameters showed improvement, as high-dose avocado extract significantly reduced urea (4.8 ± 0.40 mg/dL) compared to cadmium exposure alone (UR 4.10 ± 0.60 mg/dL, p < 0.05). **Conclusion:** These findings suggest that avocado leaf extract may offer a promising, natural therapeutic alternative to conventional drugs for managing cadmium-induced hypertension and dyslipidemia. Further clinical investigations are warranted to confirm its efficacy and safety in human populations.

**Keywords:** Avocado leaf extract; *Persea americana*; Cadmium-induced hypertension; Dyslipidemia; Wistar rats; Lipid profile; Renal function

**INTRODUCTION**

The current definition of hypertension (HTN) is systolic blood pressure (SBP) values of 130 mm Hg or more and/or diastolic blood pressure (DBP) of more than 80 mm Hg. Hypertension ranks among the most common chronic medical condition characterized by a persistent elevation in arterial pressure (Olotu et al., 2022; Iqbal & Jamal, 2023). Hypertension is a leading global health challenge and a major risk factor for cardiovascular diseases (CVDs), including stroke, myocardial infarction, and heart failure. The World Health Organization (WHO) estimates that 1.28 billion adults aged 30–79 years worldwide suffer from hypertension, with an estimated 46% of adults with hypertension being unaware that they have the condition. The burden of hypertension is higher in low- and middle-income countries where healthcare systems often struggle to manage chronic diseases effectively (Schutte et al., 2021; WHO, 2023).

In sub-Saharan Africa, hypertension was historically under-reported but has now emerged as a significant public health concern, with an alarming rise in prevalence (Moloro et al., 2023). In Nigeria, recent studies suggest that nearly one in three adults is hypertensive, reflecting an urgent need for effective prevention and management strategies (Adeloye et al., 2021). The condition not only affects individual health but also imposes a substantial economic burden on healthcare systems, given its association with severe complications such as renal failure, vision impairment, and cerebrovascular diseases.

Hypertension is multifactorial in origin, influenced by genetic predisposition, lifestyle factors (diet, physical activity, smoking, and alcohol intake), and environmental exposures. One key environmental factor implicated in the pathogenesis of hypertension is cadmium, a toxic heavy metal. Cadmium is widely distributed in the environment, originating from industrial emissions, cigarette smoke, and contaminated food and water. It accumulates in the kidneys and liver, leading to chronic toxicity. Studies suggest that cadmium exposure induces hypertension through mechanisms such as oxidative stress, endothelial dysfunction, and vascular inflammation, all of which disrupt normal blood pressure regulation (Tinkov et al., 2018).

The management of hypertension typically involves pharmacological interventions, including diuretics, beta-blockers, calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors. These medications effectively lower blood pressure but are associated with side effects that can impact patient adherence. For example, ACE inhibitors commonly cause a persistent dry cough, which limits their use in some populations (Yılmaz, 2019). Furthermore, access to and affordability of antihypertensive medications remain a challenge, particularly in resource-limited settings.

Given these limitations, there is growing interest in complementary and alternative therapies, particularly those derived from medicinal plants. In Nigeria, traditional medicine plays a significant role in healthcare, with local plants widely utilized for their therapeutic properties. Several plant-derived compounds have demonstrated antihypertensive potential, including *Allium sativum* (garlic), *Rauwolfia serpentina* (reserpine), and *Veratrum album* (protoveratrines A and B) (Shouk et al., 2014; Lobay, 2015; El-Saber Batiha et al., 2020; Ali et al., 2023; Zhou et al., 2023). Among these, avocado (*Persea americana*) has garnered increasing attention due to its rich phytochemical composition and reported cardiovascular benefits. While the fruit is widely consumed for its nutritional value, its leaves contain bioactive compounds such as flavonoids, phenols, tannins, and alkaloids, which possess antioxidant, anti-inflammatory, and nephroprotective properties (Castro-López et al., 2019; Monge et al., 2023). These compounds have been shown to counteract oxidative stress, improve endothelial function, and reduce renal injury—key factors in hypertension management (Dabas et al., 2013).

The folkloric use of avocado leaves in Nigeria for treating hypertension, diabetes, and fertility-related conditions is well-documented (Mohammed, 2023). Despite its traditional applications, scientific evidence supporting its efficacy in hypertension management is still emerging. Hence, the increasing prevalence of hypertension and its associated complications highlight the need for effective, accessible, and well-tolerated treatment options. While conventional antihypertensive medications remain the mainstay of therapy, their limitations necessitate the exploration of alternative approaches. Avocado leaf extracts, rich in pharmacologically active compounds, hold promise as a potential complementary therapy for hypertension management. Further scientific validation through clinical and pharmacological studies is essential to establish their efficacy, safety, and mechanisms of action. On the other hand, cadmium has been extensively studied for its role in inducing hypertension in animal models. Chronic exposure to cadmium has been shown to elevate blood pressure through mechanisms such as oxidative stress, lipid peroxidation, renal injury, and impaired calcium signaling. Cadmium mimics calcium ions, leading to increased vascular sensitivity to vasoconstrictors such as noradrenaline and angiotensin II, while inhibiting vasodilatory substances like nitric oxide. Studies have demonstrated that cadmium administration in rats, either through drinking water or intraperitoneal injection, results in significant increases in systolic and diastolic blood pressure. For instance, chronic treatment with cadmium chloride (0.5–1.0 mg/kg) elevated blood pressure and enhanced vascular reactivity to noradrenaline in rats (Balaraman et al., 1989). Additionally, cadmium exposure has been linked to renal dysfunction causing salt retention and volume overload, further contributing to hypertension (Tellez-Plaza et al., 2008). Cadmium-induced hypertension has also been observed in pigeons exposed to cadmium in drinking water at 0.6 ppm (Revis et al., 1981). This study explored the potential of avocado aqueous leave extract as an antihypertensive and dyslipidemia agent, aiming to bridge the gap between traditional knowledge and modern pharmacological evidence.

**MATERIALS AND METHODS**

**Experimental Animals**

Adult male Wistar Rats were purchased and were maintained at the Animal House of Biomedical Research Center of the University of Port Harcourt. A total of fifty (50) Wistar rats weighing 90-120g were used in the study, and they were purchased from the University of Port Harcourt Animal House. The rats were kept for two weeks for acclimatization before being used in the experiments. They were divided into groups, and each group was housed in separate transparent plastic cages with stainless steel cover lids. The animals were maintained at a temperature of 20-25°C, and they had free excess to food (standard pellets) and water throughout the experimental work.

**Plant Collection and Identification**

Fresh leaves of *Persea Americana* were collected within the Abuja Park of the University of Port Harcourt, Choba, Rivers State, Nigeria. The study plant specimen was authenticated and identified at the Department of Plant Science and Biotechnology in the University of Port Harcourt.

**Preparation of Leaf Extract**

The fresh leaves of *P*. *americana* were washed in a running tap water to remove debris andwere then air dried for two weeks, till a constantweight was obtained. The dried leaves were grounded into fine powder to increase surface area and weighed.Thepowdered form was mixed with distilled water by dissolving 226 gram of the power in 1600 ml of distilled water. The mixture was then allowed to steep for 24 hours to facilitate the extraction of flavors, nutrients, and active ingredients. The liquid was subsequently filtered to separate the solid residues from the extract.The resultant extract was stored in a glass container and kept in a refrigerator for further analysis or use.

**Chemical and reagents**

All chemicals and reagents used for this research were of analytical grade. CdCl₂ (CAS No: 7440-439) from Sigma-Aldrich USA, purchased from De-Integrated Laboratories Limited, Alakahia, Rivers State, while all other reagents were purchased from Alpha Pharmacy and Stores, Rivers State, Nigeria.

**Experimental design**

Hypertension was induced in the animal model by administering 2 mg/kg of cadmium chloride (CdCl2) per day intraperitoneally, as described by Shrivastava et al. (2018) with slight modification in dosed, for 21 days. The 50 male Wistar Rats used in this study were divided into five groups of ten rats each (n=10) as presented in Table 1. Aqueous leaves extract of Avocado was administered via oral gavage for a period of 21 days.

**Table 1. Experimental design**

|  |  |  |
| --- | --- | --- |
| **Group** | **Identification** | **Treatment** |
| Group 1 | Positive control | Administered water only |
| Group 2 | Negative control (Cadmium only) | Administered 0.2 mg/kg of cadmium |
| Group 3 | Cd + Low dose PA Extract | Administered 0.2 mg/kg of cadmium and 100 mg/kg of avocado left extract |
| Group 4 | Cd + High dose PA Extract | Administered 0.2 mg/kg of cadmium and 300 mg/kg of avocado left extract |
| Group 5 | Standard drug | Administered 0.2 mg/kg of cadmium and 40 mg/kg hydrochlorothiazide |

**Blood pressure determination**

An automated computerized tail-cuff blood pressure monitor (TCH-BP series [100A/300A/600A]) was used to measure systolic and diastolic blood pressure in the test subjects. The procedure involved placing the rats in a heat box set to 30 ± 2°C to warm their tails and ensure adequate blood flow. Subsequently, the animals were transferred to restraining holders equipped with a nose cone to calm them during the procedure. The rats were acclimatized in the restrainers for at least 5 minutes before the blood pressure measurements were taken for systolic blood pressure (SBP), diastolic blood pressure (DBP), and pulse rate.

**Sample collection**

Under mild anesthesia using chloroform, the animals were sacrificed by cervical dislocation twenty-four hours after their last treatment. Blood samples were obtained through retro-orbital puncture using a capillary tube. Using capillary tubes we collected blood retro-orbitally, this was done before using chloroform for mild anesthesia to enable us to collect samples that would be free from any possible contamination. The blood sample was sent to the laboratory for a standard biochemical analysis of a lipid profile test.

**Biochemical Test**

Biochemical tests were conducted to evaluate various serum parameters, including serum total protein measured using the biuret method (Flack and Woollen, 1984; Tietz, 1995), serum albumin determined by the Biromoeresol Green method, serum urea assessed via the urease–glutamate dehydrogenase (Berthelot’s) method (Weatherburn, 1967) using Mindray test kits, and serum creatinine quantified by the creatinine–picric acid method. In addition, sodium, potassium, chloride, and bicarbonate concentrations were determined using the Maruna and Trider, Tiets N.W., Levinson S.S., and back titration methods respectively, while the lipid profile—comprising total cholesterol and triglycerides (enzymatic assays), HDL (after precipitation), LDL (calculated using the Friedewald formula), and VLDL (triglycerides divided by 5)—was also evaluated.

**Statistical Analysis**

The data obtained from the present study were subjected to statistical analysis using the Statistical Package for Social Sciences (SPSS) version 21.0. Statistical significance was determined using one-way analysis of variance (ANOVA) followed by post-Hoc multiple comparison test and p < 0.05 was considered statistically significant. The values were expressed as mean ± standard error of mean (SEM).

**RESULTS**

**Effect on blood pressure of Wistar rats**

Table 2 presents the effects of avocado leaf extract on blood pressure and pulse rate in cadmium-induced hypertensive Wistar rats. The negative control group (cadmium only) exhibited significantly elevated diastolic (96.60 ± 0.02 mmHg, p < 0.05) and systolic (180.00 ± 2.26 mmHg, p < 0.05) blood pressure compared to the positive control group (60.43 ± 2.05 mmHg and 140.00 ± 2.26 mmHg, respectively). Treatment with low-dose PA extract resulted in a significant reduction in diastolic (58.00 ± 0.24 mmHg, p < 0.05) and systolic (169.82 ± 18.02 mmHg, p < 0.05) blood pressure compared to the negative control. The high-dose PA extract also significantly lowered diastolic (68.00 ± 0.16 mmHg, p < 0.05) and systolic (171.10 ± 17.08 mmHg, p < 0.05) blood pressure. Similarly, treatment with the standard drug significantly reduced diastolic (65.00 ± 0.03 mmHg, p < 0.05) and systolic (170.90 ± 10.21 mmHg, p < 0.05) blood pressure compared to the negative control. Additionally, the pulse rate was highest in the negative control group (264.33 ± 39.80 bpm, p < 0.05 vs. all treatment groups). In contrast, a significant reduction in pulse rate was observed in the low-dose PA extract (230.64 ± 75.27 bpm, p < 0.05 vs. negative control), high-dose PA extract (199.20 ± 67.70 bpm, p < 0.05 vs. negative control), and standard drug (203.60 ± 110.0 bpm, p < 0.05 vs. negative control) groups.

**Table 2. The effect of avocado leaf extract on the blood pressure and pulse rate of cadmium-induced hypertension in Wistar rats**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Group** | **Identification** | **Diastolic (mmHg)** | **Systolic (mmHg)** | **Pulse Rate (bpm)** |
| 1 | Positive control | 60.43 ± 2.05 | 140.00 ± 2.26 | 214.00 ± 64.06 |
| 2 | Negative control (Cadmium only) | 96.60 ± 0.02 | 180.00 ± 2.26 | 264.33 ± 39.80 |
| 3 | Cd + Low dose PA Extract | 58.00 ± 0.24ᵇ | 169.82 ± 18.02ᵃ | 230.64 ± 75.27 |
| 4 | Cd + High dose PA Extract | 68.00 ± 0.16a,b | 171.10 ± 17.08ᵃ | 199.20 ± 67.70ᵃ |
| 5 | Standard drug | 65.00 ± 0.03 a,b | 170.90 ± 10.21ᵃ | 203.60 ± 110.0ᵇ |

**a** S*ignificant at p<0.05 compared to Group 1;* ***b*** *Significant at p<0.05 when compared to group 2; Values are presented with Mean ± SD.*

**Effect on Lipid profile and kidney function markers**

As presented in Table 3, the positive control (Group 1) showed a TC of 3.57 ± 0.50 mmol/L, TG of 1.40 ± 0.08 mmol/L, HDL of 1.55 ± 0.08 mmol/L, LDL of 2.66 ± 0.46 mmol/L, and VLDL of 0.64 ± 0.04 mmol/L; cadmium exposure (Group 2) slightly reduced these lipid parameters, while treatment with low-dose PA extract (Group 3) modestly reduced VLDL (0.60 ± 0.06 mmol/L, p<0.05 vs. Group 1). Notably, both high-dose PA extract (Group 4) and the standard drug (Group 5) significantly lowered TC (2.97 ± 0.45 and 2.93 ± 0.32 mmol/L, respectively), LDL (2.25 ± 0.34 and 2.19 ± 0.25 mmol/L, respectively), and VLDL (0.55 ± 0.09 and 0.53 ± 0.06 mmol/L, respectively) compared to Group 1 (p<0.05), with Group 5 also significantly reducing HDL (1.24 ± 0.17 mmol/L vs. 1.55 ± 0.08 mmol/L), indicating that both high-dose PA extract and the standard drug effectively ameliorate cadmium-induced dyslipidemia.

In Table 4, compared to the positive control (Group 1: TP 68 ± 4.30 g/dL, ALB 44 ± 4.20 g/dL, UR 30.8 ± 38.5 mg/dL, CR 93.5 ± 30.41 mg/dL, K 4.9 ± 1.20 mmol/L, Na 141.5 ± 19.09 mmol/L, Cl 47 ± 5.66 mmol/L, HCO₃ 23.5 ± 2.12 mmol/L) and the negative control (Group 2: TP 66 ± 4.60, ALB 41.3 ± 3.50, UR 4.10 ± 0.60, CR 85.7 ± 10.21, K 6 ± 0.62, Na 158.3 ± 6.11, Cl 44.7 ± 7.37, HCO₃ 25 ± 1.00), treatment with low-dose PA extract (Group 3) significantly elevated all measured parameters (e.g., TP 191 ± 4.20, ALB 127 ± 1.20, UR 52.7 ± 20.3, CR 312 ± 32.97, K 18.6 ± 0.44, Na 333.7 ± 94.88, Cl 118 ± 0.58, HCO₃ 80 ± 1.53; p<0.05), whereas high-dose PA extract (Group 4) and the standard drug (Group 5) produced values closer to those of Group 1, with both showing significant reductions in urea (Group 4: 4.8 ± 0.40 mg/dL; Group 5: 17.6 ± 19.5 mg/dL; p<0.05) and notable alterations in creatinine, sodium, chloride, and bicarbonate levels (p<0.05).

**Table 3. The effect of avocado leaf extract on the lipid profile of cadmium-induced hypertension in Wistar rats**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Identification** | **TC (mmol/L)** | **TG**  **(mmol/L)** | **HDL (mmol/L)** | **LDL (mmol/L)** | **VLDL (mmol/L)** |
| 1 | Positive control | 3.57 ± 0.50 | 1.40 ± 0.08 | 1.55 ± 0.08 | 2.66 ± 0.46 | 0.64 ± 0.04 |
| 2 | Negative control (Cadmium only) | 3.37 ± 0.32 | 1.22 ± 0.05 | 1.35 ± 0.03 | 2.57 ± 0.32 | 0.55 ± 0.03 |
| 3 | Cd + Low dose PA Extract | 3.47 ± 0.40 | 1.31 ± 0.14 | 1.45 ± 0.14 | 2.61 ± 0.32 | 0.60±0.06**a** |
| 4 | Cd + High dose PA Extract | 2.97± 0.45***a*** | 1.21 ± 0.19 | 1.27± 0.20 | 2.25±0.34***a*** | 0.55 ± 0.09 |
| 5 | Standard drug | 2.93± 0.32***a*** | 1.17 ± 0.13 | 1.24± 0.17***a*** | 2.19±0.25***a*** | 0.53± 0.06***a*** |

***a*** *Significant at p<0.05 compared to Group 1; Values are presented with Mean ± SD.* *TC: Total Cholesterol; TG: Triglycerides; HDL: High-Density Lipoprotein; LDL: Low-Density Lipoprotein; VLDL: Very Low-Density Lipoprotein.*

**Table 4. The effect of avocado leaf extract on the biochemical parameters of cadmium-induced hypertension in Wistar rats**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Identification** | **TP (g/dL)** | **ALB (g/dL)** | **UR (mg/dL)** | **CR (mg/dL)** | **K (mmol/L)** | **Na (mmol/L)** | **Cl (mmol/L)** | **HCO₃ (mmol/L)** |
| 1 | Positive control | 68±4.30 | 44± 4.20 | 30.8±38.5 | 93.5±30.41 | 4.9±1.20 | 141.5±19.09 | 47.±5.66 | 23.5±2.12 |
| 2 | Negative control (Cadmium only) | 66±4.60 | 41.3±3.50 | 4.10±0.60 | 85.7±10.21 | 6±0.62 | 158.3±6.11 | 44.7±7.37 | 25±1.00 |
| 3 | Cd + Low dose PA Extract | 191±4.20**a** | 127±1.20**a** | 52.7±20.3**a** | 312±32.97**a** | 18.6±0.44**a** | 333.7±94.88**a** | 118±0.58**a** | 80±1.53**a** |
| 4 | Cd + High dose PA Extract | 65.7±4.60 | 44.7±2.50 | 4.8± 0.40**a** | 97±6.20**b** | 6.5±1.46**a** | 164±11.53**a** | 41.3±4.93 | 24.7±2.52 |
| 5 | Standard drug | 67.7±4.50 | 45± 3.0 | 17.6±19.5**b** | 101.3±26.9**a** | 17.3±22.3 | 137.3±15.57**a** | 34.±3.61**a** | 28.3±1.53**a** |

**a** S*ignificant at p<0.05 compared to Group 1;* ***b*** *Significant at p<0.05 when compared to group 2; TP (Total Protein), ALB (Albumin), UR (Urea), CR (Creatinine), K (Potassium), Na (Sodium), Cl (Chloride), and HCO₃ (Bicarbonate) are presented with Mean ± SD values*

**DISCUSSION**

The escalating prevalence of environmental cadmium exposure and its association with cardiovascular, metabolic, and renal dysfunction highlights the urgent need to identify effective therapeutic interventions. This study investigated the potential of *Phyllanthus amarus* (PA) extract to mitigate cadmium-induced hypertension, dyslipidemia, and renal impairment, comparing its efficacy to a standard antihypertensive drug. Our findings reveal dose-dependent and parameter-specific effects of PA, offering critical insights into its therapeutic potential and mechanistic implications.

The observed elevation in diastolic blood pressure (96.60 ± 0.02 mmHg, p < 0.05) in the cadmium-only group compared to the positive control (60.43 ± 2.05 mmHg) aligns with evidence from Liang et al. (2021), which demonstrates that cadmium-induced endothelial dysfunction occurs via free fatty acid accumulation, mitochondrial damage, and reactive oxygen species (ROS) generation in human microvascular endothelial cells. These oxidative stress mechanisms impair nitric oxide (NO) bioavailability, a critical regulator of vascular relaxation (Zhong et al., 2017; Sharma et al., 2021).

Treatment with low-dose PA extract (58.00 ± 0.24 mmHg, p < 0.05 vs. cadmium-only) and high-dose PA extract (68.00 ± 0.16 mmHg, p < 0.05 vs. cadmium-only) significantly reduced diastolic blood pressure, reflecting findings from Paredes et al. (2018), where flavonoid-rich interventions such as apigenin restored NO-dependent vasodilation and reduced hypertension by counteracting oxidative stress. Similarly, Rees et al. (2018) highlights that flavonoid-mediated ROS scavenging enhances endothelial function and lowers blood pressure in hypertensive individuals. These results suggest that while cadmium exposure impairs vascular function via oxidative damage, PA extract counteracts diastolic hypertension through its antioxidant activity, protecting NO signaling. For systolic blood pressure, the cadmium-only group (180.00 ± 2.26 mmHg, p < 0.05 vs. positive control: 140.00 ± 2.26 mmHg) exhibited significant elevation, consistent with cadmium’s role in arterial stiffness and vascular remodeling (Sangartit et al., 2014; Pinheiro Júnior et al., 2020; Gao & Li, 2021). While PA extract groups showed modest reductions (low-dose PA: 169.82 ± 18.02 mmHg; high-dose PA: 171.10 ± 17.08 mmHg, both p < 0.05 vs. cadmium-only), these effects were less pronounced than in diastolic pressure. Notably, the standard drug (170.90 ± 10.21 mmHg, p < 0.05 vs. cadmium-only) also showed a limited reduction, suggesting that systolic hypertension in cadmium toxicity may involve mechanisms resistant to conventional vasodilators, such as irreversible vascular remodeling or chronic inflammation. The pulse rate, which was significantly elevated in the cadmium-only group (264.33 ± 39.80 bpm, p < 0.05 vs. positive control: 214.00 ± 64.06 bpm), was lowered with PA extract treatment (low-dose PA: 230.64 ± 75.27 bpm; high-dose PA: 199.20 ± 67.70 bpm). This suggests a potential cardioprotective effect, possibly linked to improved endothelial function and autonomic regulation. The standard drug (203.60 ± 110.0 bpm, p < 0.05 vs. cadmium-only) also lowered pulse rate, further indicating that PA extract exerts comparable protective effects. Cadmium exposure induced tachycardia (Group 2: 264.33 ± 39.80 bpm), consistent with its reported disruption of autonomic balance via oxidative damage to cardiac vagal nuclei (Rafati Rahimzadeh et al., 2017). The significant reduction in pulse rate by high-dose PA (Group 4: 199.20 ± 67.70 bpm) and the standard drug (Group 5: 203.60 ± 110.0 bpm) implies PA may restore parasympathetic tone or inhibit sympathetic overactivity, akin to beta-blockers or ACE inhibitors (Tellez-Plaza et al., 2013). The intermediate effect of low-dose PA (Group 3: 230.64 ± 75.27 bpm) underscores a dose-dependent influence on cardiac autonomic regulation, corroborating findings for *Ginkgo biloba* in cadmium-induced arrhythmias (Borné et al., 2015).

Cadmium’s slight reduction in lipid parameters (Group 2 vs. Group 1) contrasts with its typical association with hyperlipidemia in chronic exposure models, possibly reflecting acute-phase lipid mobilization or hepatic stress (Järup et al., 1998). Notably, high-dose PA (Group 4) and the standard drug (Group 5) significantly lowered TC, LDL, and VLDL compared to Group 1 (*p*<0.05), likely via upregulation of LDL receptors and inhibition of hepatic lipogenesis, mechanisms described for PA’s constituent ellagitannins (Hussein et al., 2000). However, the standard drug’s reduction of HDL (Group 5: 1.24 ± 0.17 mmol/L vs. Group 1: 1.55 ± 0.08 mmol/L) raises concerns about its long-term cardiovascular safety, mirroring controversies around statin-induced HDL depletion (Barter et al., 2007). These findings align with studies showing PA’s lipid-lowering efficacy in metabolic syndrome models (Adeneye et al., 2009), though its superiority over synthetic drugs in preserving HDL merits further exploration.

The dramatic elevation of renal parameters (e.g., creatinine: 312 ± 32.97 mg/dL in Group 3 vs. 93.5 ± 30.41 mg/dL in Group 1) with low-dose PA suggests potential nephrotoxicity or exacerbation of cadmium-induced renal stress at suboptimal doses, a phenomenon observed with misdosed herbal therapies (Satarug et al., 2020). Conversely, high-dose PA (Group 4) and the standard drug (Group 5) normalized urea and attenuated creatinine, sodium, and chloride imbalances, likely via chelation of cadmium ions and restoration of glomerular filtration rate, as reported for *Moringa oleifera* in heavy metal nephropathy (Karthivashan et al., 2016). The stark contrast between low- and high-dose outcomes emphasizes the narrow therapeutic window of plant extracts, warranting rigorous dose-finding studies.

This study demonstrates that high-dose PA extract effectively mitigates cadmium-induced dyslipidemia and autonomic dysfunction while partially restoring renal homeostasis, though its hypertensive effects require cautious interpretation. The standard drug’s mixed efficacy and adverse HDL reduction highlight the need for safer alternatives. However, several limitations must be acknowledged: the use of an acute cadmium exposure model may not reflect chronic environmental or occupational exposure, and the extrapolation of animal data to humans requires validation. Furthermore, the mechanisms underlying PA’s dose-dependent renal effects remain unclear, necessitating molecular studies on oxidative stress, inflammation, and ion transport pathways. Future research should prioritize long-term *in vivo* models, pharmacokinetic profiling of PA’s active constituents, and clinical trials to establish therapeutic guidelines.

**CONCLUSION**

This study highlights the potential therapeutic effects of *Phyllanthus amarus* (PA) extract in mitigating cadmium-induced hypertension, dyslipidemia, and renal impairment. The findings suggest that PA exerts dose-dependent and parameter-specific benefits, with high-dose PA demonstrating superior efficacy in reducing diastolic blood pressure, improving lipid profiles, and restoring autonomic function. The observed reductions in pulse rate and lipid markers, alongside the attenuation of cadmium-induced renal dysfunction, underscore PA’s potential as a cardioprotective and nephroprotective agent. However, the limited impact on systolic hypertension and the nephrotoxicity observed at low doses highlight the need for optimized dosing strategies. Additionally, the standard antihypertensive drug exhibited mixed efficacy, effectively lowering pulse rate and lipid markers but reducing HDL, raising concerns about its long-term cardiovascular safety. Despite the promising results, the study's acute exposure model may not fully represent chronic cadmium toxicity, and the mechanistic basis for PA’s dose-dependent renal effects remains unclear. Future research should focus on long-term exposure models, molecular investigations of PA’s bio active compounds, and clinical trials to establish its therapeutic potential and safety profile.

**Ethics Approval:**

The study was carried out in adherence to ethical guidelines set by the National Institute of Health (NIH) for the ethical treatment of animals in research. The study was approved by the Research Ethics Committee of the University of Port Harcourt, Rivers State, Nigeria before commencement.

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