**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 (0.96 ± 0.02 mmHg) and systolic pressure (180.00 ± 2.26 mmHg) compared to the positive control (0.43 ± 0.05 mmHg and 0.53 ± 0.02 mmHg, respectively). Treatment with low-dose avocado extract reduced diastolic pressure to 0.59 ± 0.24 mmHg (p < 0.05 vs. Group 2), while high-dose extract and the standard drug resulted in 0.90 ± 0.16 mmHg and 0.95 ± 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 (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 been 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 challenges, 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. 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. This study explores the potential of avocado leaves as an antihypertensive and nephroprotective agent, aiming to bridge the gap between traditional knowledge and modern pharmacological evidence.

**MATERIALS AND METHODS**

**Experimental Animals**

Animals 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 keep in refrigerator for further analysis or use.

**Chemical and reagents**

All chemicals and reagents used for this research are of analytical grade. CdCl₂ (CAS No: 7440-439) from Sigma-Aldrich USA was 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**

The fifty (50) male Wistar Rats used in this study were divided into five groups of ten rats each (n=10) as presented in Table 1. Treatments were 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 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).

**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 of the study.

**RESULTS**

**Effect on blood pressure of Wistar rats**

In this study, diastolic pressure in the positive control (Group 1: 0.43 ± 0.05 mmHg) was significantly lower than in the cadmium-only group (Group 2: 0.96 ± 0.02 mmHg); treatment with low-dose PA extract (Group 3: 0.59 ± 0.24 mmHg, p<0.05 vs. Group 2) significantly reduced diastolic pressure compared to cadmium alone, while high-dose PA extract (Group 4: 0.90 ± 0.16 mmHg) and the standard drug (Group 5: 0.95 ± 0.03 mmHg) remained significantly elevated compared to Group 1 (p<0.05). Systolic pressures in Groups 2–5 (ranging from 169.82 ± 18.02 to 180.00 ± 2.26 mmHg) were all significantly higher than in Group 1 (0.53 ± 0.02 mmHg, p<0.05), with no significant differences among the treatment groups. For pulse rate, Group 2 showed the highest value (264.33 ± 39.80 bpm), whereas high-dose PA extract (Group 4: 199.20 ± 67.70 bpm, p<0.05 vs. Group 1) and the standard drug (Group 5: 203.60 ± 110.0 bpm, p<0.05 vs. Group 2) significantly reduced pulse rate, with Group 3 (230.64 ± 75.27 bpm) exhibiting an intermediate reduction.

**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 | 0.43 ± 0.05 | 0.53 ± 0.02 | 214.00 ± 64.06 |
| 2 | Negative control (Cadmium only) | 0.96 ± 0.02 | 180.00 ± 2.26 | 264.33 ± 39.80 |
| 3 | Cd + Low dose PA Extract | 0.59 ± 0.24**b** | 169.82±18.02**a** | 230.64 ± 75.27 |
| 4 | Cd + High dose PA Extract | 0.90 ± 0.16**a** | 171.10±17.08**a** | 199.20 ± 67.70**a** |
| 5 | Standard drug | 0.95 ± 0.03**a** | 170.90±10.21**a** | 203.60 ± 110.0**b** |

**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 (0.96 ± 0.02 mmHg vs. 0.43 ± 0.05 mmHg) in cadmium-exposed groups aligns with evidence from Liang et al. (2021), which demonstrates cadmium-induced endothelial dysfunction 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). The reduction in diastolic pressure with low-dose PA (0.59 ± 0.24 mmHg, *p*<0.05) mirrors findings from Paredes et al. (2018), where apigenin (a flavonoid) restored NO-dependent vasodilation and lowered blood pressure in hypertensive rats by counteracting oxidative stress. Similarly, Rees et al. (2018) highlights flavonoid-rich interventions improving endothelial function and reducing blood pressure in hypertensive individuals, particularly through ROS scavenging and NO pathway modulation. These results collectively suggest that cadmium’s vascular toxicity involves irreversible structural remodeling such as mitochondrial dysfunction, resistant to standard vasodilators, while flavonoids like PA mitigate diastolic hypertension via antioxidant-mediated protection of NO signaling. Systolic pressure remained elevated across all cadmium-exposed groups (169.82–180.00 mmHg vs. Group 1: 0.53 mmHg), indicating cadmium’s persistent impact on arterial stiffness and cardiac output, likely mediated by chronic inflammation, oxidative stress, and vascular remodeling (Sangartit et al., 2014; Pinheiro Júnior et al., 2020; Gao & Li, 2021). The lack of improvement with PA or the standard drug suggests that systolic hypertension in cadmium toxicity involves pathways resistant to conventional vasodilators, necessitating therapies targeting structural vascular changes.

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.

**COMPETING INTERESTS DISCLAIMER**:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

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