JOPAT Vol 24(1) 1748 – 1758, Jan – June. 2025 Edition.
ISSN2636 – 5448 https://dx.doi.org/10.4314/jopat.v24i1.2

Histopathological Evaluation and Immunomodulatory Effects of Methanolic Leaf Extracts of *Rauwolfia vomitoria* and *Aframomum melegueta* in Cadmium Chloride Induced Renal Toxicity

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Abstract

Cadmium is a major cause of nephrotoxicity and has also been linked to hepatotoxicity, carcinogenicity, and reproductive toxicity. This study investigated the ameliorative potential of methanolic extracts of *R. vomitoria* and *A. melegueta* on cadmium-induced renal toxicity. Twenty-five adult male Wistar rats weighing 180 to 200g were divided into five groups of five rats each. The first group consisted of unexposed control rats, while the second consisted of cadmium-exposed untreated rats that were orally administered 12mg/kg/bw cadmium chloride ($CdCl_2$). The rats in groups III-V were orally exposed to $CdCl_2$ at standard doses of 12mg/kg/bw and treated with *R. vomitoria* (200mg/kg/bw), *A. melegueta* (200mg/kg/bw), and co-administration with *R. vomitoria* (200mg/kg/bw) and *A. melegueta* (200mg/kg/bw) respectively. The rats were euthanized after 28 days and their kidneys were harvested and processed for histopathological examination, mRNA expression of TGF-β, ELISA evaluation of superoxide dismutase (SOD), glutathione peroxidase (GPx), tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The $CdCl_2$ exposed rats had reduced SOD, GPx levels and elevated TNF- α and IL-6 levels ($P<0.05$), whereas co-administration of *R. vomitoria* and *A. melegueta* ameliorated the oxidative damage, modulated TGF-β expression levels while also mitigating histological alterations associated with $CdCl_2$ exposure. The study concluded that *R. vomitoria* and *A. melegueta* at standard doses of 200mg/kg/bw mitigate $CdCl_2$-induced kidney toxicity in exposed rats.

Keywords: Oxidative stress, pollution, toxicity, ethnobotanicals, cadmium.

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Introduction

Cadmium (Cd) is a naturally occurring heavy metal positioned between mercury (Hg) and zinc (Zn) in the periodic table. It commonly exists as a divalent cation and forms complexes with other elements (e.g., CdCl2) [1]. Cadmium is a non-fenton metal and is one of the important environmental pollutants that are present in the air, water, soil and food and is derived mostly from batteries, alloys, pigments, cigarettes, metallic coatings, chemical stabilizers and children's plastic toys [2,3]. Release of cadmium from fossil fuel, volcanic emissions and biomass combustion are the major sources of cadmium and this is released into the atmosphere as cadmium oxide which is more bioavailable than oral cadmium exposure [4].

Cadmium is a non-biodegradable heavy metal that forms a Cd–metallothionein (CdMT) complex in the body, initially stored in the liver and subsequently transported to the kidneys through normal hepatic turnover. Following filtration, CdMT is reabsorbed in the renal proximal tubules, where enzymatic degradation releases free Cd ions, leading to their accumulation primarily in the kidneys, liver, and heart [5–7]. The accumulation of cadmium in these organs leads to toxicity by producing excessive free radicals majorly Reactive Oxygen Species (ROS) which causes oxidative stress that initiates cellular damage, lipid peroxidation as well as disruption of the antioxidant system, and damage of membrane protein [8,9]. Cadmium toxicity in the kidney causes damage to the glomerulus, predominantly the renal proximal tubules which leads to impaired reabsorption functions, affecting levels of antioxidants such as GPX, SOD, and pro-inflammatory markers such as IL-6, and TNFα [3,10].

Transforming Growth Factor-Beta (TGF-β) is a multi-regulatory protein that is fibrogenic and it has three isoforms, TGF-β1 (the most common), TGF-β2, and TGF-β3. TGF-β is secreted bound to a propeptide in a precursor form and is broken by a furin-type enzyme that is present in the Golgi apparatus and is translocated to the extracellular matrix (ECM) along with a latency-associated peptide (LAP), and its activation occurs in the presence of diverse molecules such as thrombospondin-1, integrins, matrix metalloproteinases (MMPs), bone morphogenetic 1 (BMP-1) and ROS [11]. Medicinal plants play an integral role in the traditional management of diseases across Africa, especially in communities where access to orthodox healthcare remains limited or unaffordable and where they serve as vital therapeutic resources for the prevention and treatment of a wide range of ailments [12–14].

Aframomum melegueta belongs to the ginger family, Zingiberaceae. It is often called names like; grains of Paradise (English), Ataare (Yoruba), Malagueta (Spanish) and Graines de Paradise (French) [15]. *A. melegueta* is a perennial herb that has a high concentration of essential oils such as gingerol, shagaol and paradol. Medicinal applications of *A. melegueta* are found use as an aphrodisiac, in the treatment of measles and leprosy, in mothers who lactate excessively and have post-partum haemorrhage, as an anthelmintic, a galactagogue and as a hemostatic agent. Studies by Bonheur et al. [16] and Nwozo et al. [17] documented the antioxidative potential of *A. melegueta* in murine models. *Rauwolfia vomitoria* is a medicinal plant that is widely distributed in the humid tropical lowland forests of Africa and it is a member of the family Apocynaceae capable of growing to a height of about 15m. The common name is Swizzle Stick and the three Nigerian names include ‘asofeyeje’ in Yoruba, ‘akanta’ in Igbo and ‘wada’ in Hausa [18]. Traditional medicine practitioners in Nigeria and other parts of Africa use various parts of the plant to treat a variety of ailments, including fever, intestinal diseases, liver problems, mental illness, hypertension, and snakebite, to mention a few [18].
Studies have documented the antioxidative and anti-inflammatory properties of *Aframomum melegueta* and *Rauwolfia vomitoria* which have been largely attributed to their bioactive constituents such as flavonoids and phenolic compounds [18–20]. While both plants have been individually studied for their pharmacological properties, the majority of existing studies have focused on their effects when used individually, with limited research exploring their potential synergistic or combined therapeutic effects. Notably, a study reported that both *A. melegueta* and *R. vomitoria* exert modulatory effects on myeloperoxidase activity and nuclear factor kappa B (NF-κB) expression at a dose of 200 mg/kg body weight, in addition to offering protection against cadmium chloride ($CdCl_2$)-induced renal toxicity [21] while Adeniyi et al. [22] also documented that the co-administrative treatment with *Rauvolfia vomitoria* and *Aframomum melegueta* better ameliorates $CdCl_2$- induced toxicity than a single administration of either plant extract. Additionally, while ethnobotanical studies have identified these plants as commonly used in traditional healthcare in Nigeria, systematic scientific validation of their efficacy and safety in the context of oxidative stress and organ-specific toxicity is still lacking [23,24]. Against this background, this study aims to evaluate the therapeutic potential of *A. melegueta* and *R. vomitoria* in $CdCl_2$-induced renal toxicity particularly in relation to their reno-protective properties and immunomodulatory effects.

Materials and Method

Chemical

Chemically pure cadmium chloride hydrated ($CdCl_2.2.5H_2O$ = 228.34) with batch number 6802/3 and product number C0262 obtained from

Surechem Products Limited United Kingdom was used for this study.

Ethical considerations

Ethical approval was obtained from the Ministry of Agriculture, Akure, Ondo State, Nigeria with the approval no MNR/V.384/39.

Plants Collection and Extraction

R. vomitoria and *A. melegueta* leaves were obtained freshly from a farm in Laje village, Ondo town, Ondo State, Nigeria followed by identification by a Professional taxonomist in the Botany Department of the University of Medical Sciences Ondo (UNIMED) and assigned herbarium voucher numbers 031 and 030 respectively. Additionally, ten kilograms of the leaves were washed, shade-dried and pulverised using an electric blender. The pulverized powder was extracted by maceration in methanol for 48 hours, after which it was filtered using a No 1 Whatman Filter paper. The filtrate was lyophilized using a freeze-dryer and the powdered form was dissolved in distilled water daily before administration to the rats [9,19].

Animal Procurement, Housing and Feeding

Twenty-five adult male Wistar rats of about 180-200 g were purchased from the Animal Holding of the University of Medical Sciences (UNIMED) and were acclimatised for two weeks and housed in cages at the Animal House facility UNIMED where they were fed with standardised rat pellets obtained from the UNIMED animal house for a total of 6 weeks. After acclimatization, the experimental groups were exposed to $CdCl_2$ at standard doses of 12mg/kg/bw and treated with the plant extracts of *R. vomitoria* and *A. melegueta*.

Experimental Group

The rats were divided into 5 groups. Group I is the unexposed control group administered with distilled water only. Group II served as the $CdCl_2$-exposed untreated group at standard doses of 12mg/kg/bw only. Group III is the 12mg/kg/bw $CdCl_2$ exposed group pretreated with methanolic extract of *R.vomitoria* at a standard dose of 200mg/kg/bw. Group IV represent 12mg/kg/bw $CdCl_2$ exposed group pretreated with methanolic extract of *A. melegueta* at a standard dose of 200mg/kg/bw. Group V consist of the 12mg/kg/bw $CdCl_2$ exposed group pretreated with coadministration of *R. vomitoria* and *A. melegueta* methanolic extract at a standard dose of 200mg/kg/bw. Cadmium and the methanolic extracts were administered orally using a gavage.

Histopathological Studies.

After the consequent exposure and treatments with the plant extracts, the rats were euthanized and the kidneys were excised and transferred into 10% neutral buffered formalin (NBF) and stained with Hematoxylin and Eosin (H&E) [25,26].

mRNA and Biochemical Evaluations

Kidney samples obtained upon necropsy were transferred into freshly prepared phosphate-buffered saline (PBS) and tissue homogenates were prepared and used for Transforming growth factor beta (TGF-β) expression studies and ELISA estimation of SOD, GPx, TNFα, and IL-6 [26–30].

Primer Sequence

Gene	Primers	
	Forward	**Reverse**
TGF-β1	5′-ATACGCCTGAGTGGCTGTCT-3′	5′-TGGGACTGATCCCATTGATT-3′
β-ACTIN	5’-CCCGCGAGTACAACCTTCT-3′	5’-CGTCATCCATGGCGAACT-3′

Statistical Analysis

The results gathered were analysed using the IBM Statistical Package for Social Science (SPSS) version 17.0. Additionally, one-way ANOVA was used to analyze categorical variables and Duncan multiple tests were used for post hoc analysis with the significant level set at $p<0.05$.

Results

Histological Findings

The histological findings of this study show kidney sections of the unexposed control group had normal kidney histoarchitecture consisting of normal glomerular tuft, renal tubules and interstitium while the $CdCl_2$ exposed untreated group had congested interstitium with mononuclear infiltration by inflammatory cells. The $CdCl_2$ exposed and *R. vomitoria*-treated group showed normal undistorted glomeruli and normal interstitial components. The exposed and *A. melegueta*-treated group showed undistorted glomeruli with normal renal tubules. The group co-administered with *R. vomitoria* and *A. melegueta* showed normal kidney morphology with mild congestion of renal tubules (Figure 1).

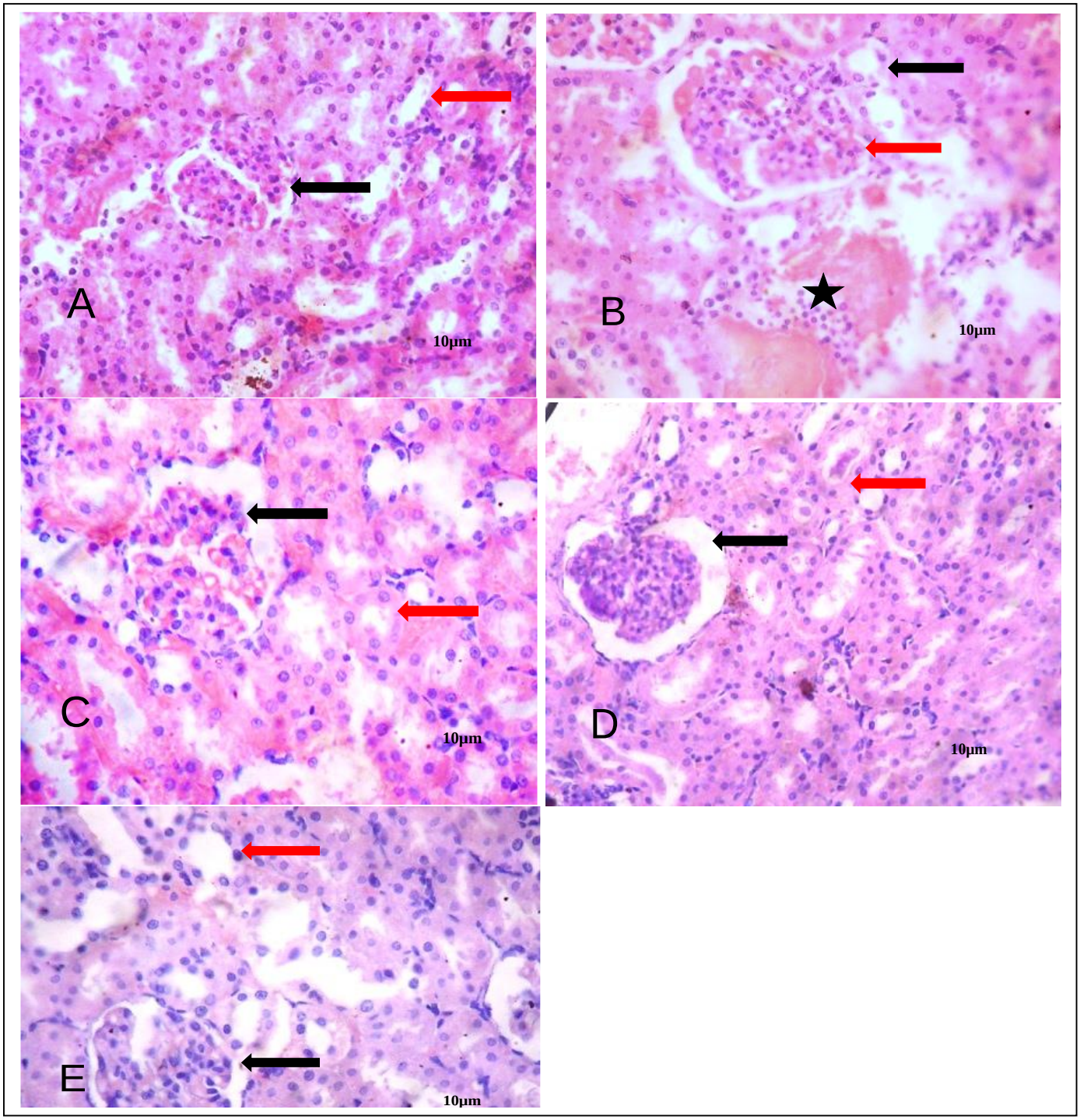

Figure 1. H & E-stained kidney sections of rats across all groups. **A:** control: glomerulus (black arrow), renal tubules (red arrow). **B.** $CdCl_2$ (12mg/kg/bw)-exposed untreated rats: congested and mildly inflammed interstitial space (Starred), glomerulus (black arrow), renal tubules (red arrow). **C.** $CdCl_2$ (12mg/kg/bw) + *R. vomitoria*

(200mg/kg/bw) normal glomerulus (black arrow) and renal tubules (red arrow). **D.** $CdCl_2$ (12mg/kg/bw) + *A. melegueta* (200mg/kg/bw) normal glomerulus (black arrow) and renal tubules (red arrow). **E.** $CdCl_2$ (12mg/kg/bw)-exposed rats co-administered with *R. vomitoria* (200mg/kg/bw) and *A. melegueta* (200mg/kg/bw) glomerulus (black arrow) and renal tubules (red arrow) (Magnification X400).

mRNA Studies

General findings from this study show that methanolic extracts of *R. vomitoria* and *A. melegueta* have a significant mitigative effect on the expression of TGF-β in $CdCl_2$-induced renal toxicity. TGF-β expression was up-regulated in the exposed untreated rats when compared to the unexposed control rats. The $CdCl_2$ exposed rats treated with extracts of either *R. vomitoria*, *A. melegueta* or coadministration of *R. vomitoria* and *A. melegueta* led to downregulation of TGF-β expression, indicating the anti-inflammatory potential of each plant extract (Figure 2).

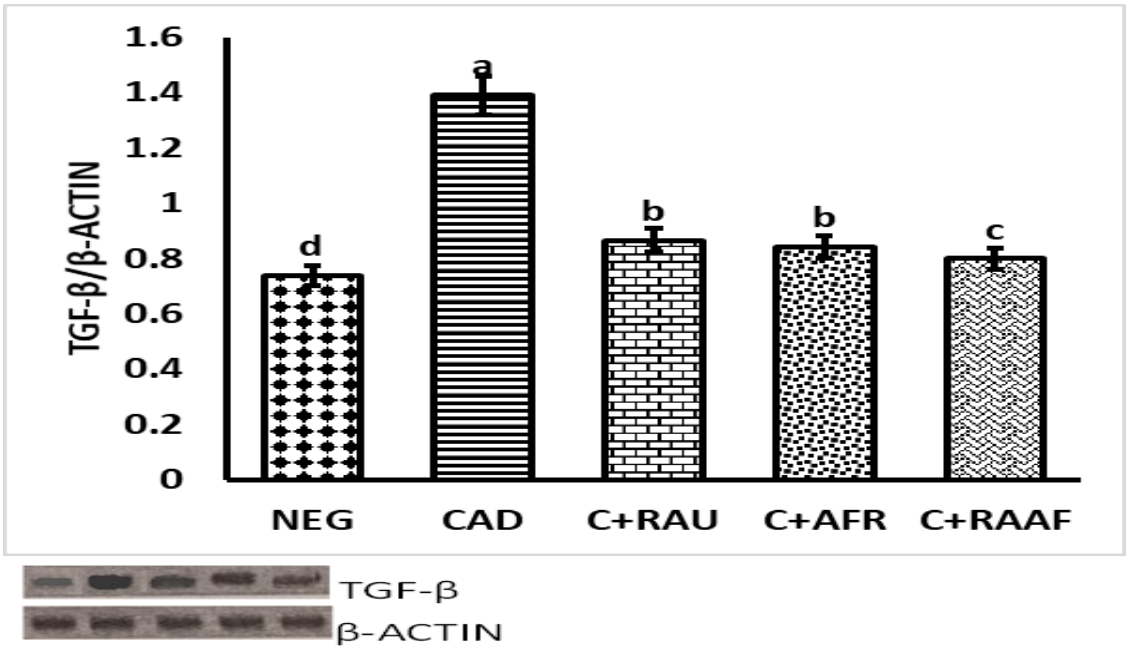

Figure 2. Histogram depicting the level of TGF-β mRNA expression across various groups where, a > b > c > d, P< 0.05. **NEG:** shows the level of TGF-β in the unexposed control rats, **CAD;** shows up-regulation of TGF-β levels due to cadmium toxicity**, C+RAU,** shows down-regulation of TGF-β after treatment with *R. vomitoria*, C+AFR; shows further down-regulation of **TGF-β** after treatment, **CAD+RAAF;** shows down-regulation of TGF-β after co-administration with *R. vomitoria* and *A. melegueta*.

Keys: NEG: Unexposed negative control rats; **CAD;** $CdCl_2$-exposed untreated rats; **C+RAU;** $CdCl_2$-exposed rats treated with *R. vomitoria;* **C+AFR;** $CdCl_2$-exposed rats treated with *A. melegueta;* **CAD+RAAF;** $CdCl_2$-exposed rats coadministered with *R. vomitoria* and *A. melegueta*.

Biochemical Studies

The tables show the variations across the experimental groups. Table 1.0 show the mean values and standard deviation of values of SOD, GPx, TNF-α and IL-6. Also, Figure 3 shows the reduction of the antioxidant parameters (SOD and GPx) in the $CdCl_2$ -exposed rats while treatment with the extracts of *R. vomitoria*, *A. melegueta* or coadministration of both plants restored the antioxidant values in the treatment group. Also, a significant restoration of the pro-inflammatory markers (TNF-α and IL-6) across the treatment group is shown in Figure 4.

Table 1.0: Antioxidant and pro-inflammatory markers across the groups

Parameters	Control	CAD Exposed Untreated	CAD+RAU	CAD+AFR	CAD+RAAF	P-value	Sig*
SOD (ng/ml)	8.9 ± 0.79^{b}	5.1±0.37^{a}	13.4±0.66^{c}	13.0±0.44^{c}	14.1 ±0.83^{c}	0.000	P<0.001
GPx (ng/ml)	8.3 ± 0.05^{e}	1.1 ±0.07^{a}	2.3 ±0.04^{c}	1.8 ±0.04^{b}	2.7 ± 0.05^{d}	0.000	P<0.001
TNF-α (pg/ml)	129.9±9.40^{d}	201.7± 4.26^{c}	158.9±5.11^{b}	122±5.59^{a}	118.2±4.20^{a}	0.000	P<0.001
IL-6 (pg/ml)	17.2 ± 1.04^{d}	36.4 ± 0.50^{c}	17.0±0.90^{b}	14.5±0.66^{a}	13.5± 0.19^{a}	0.000	P<0.001

Note: Similar letters (superscripts) indicate values that are not significantly different (P< 0.05). * P < 0.001 = Very High significant difference.
Keys; NEG: Unexposed negative control rats; **CAD;** $CdCl_2$-exposed untreated rats; **CAD+RAU**; $CdCl_2$-exposed rats treated with *R. vomitoria;* **CAD+AFR;** $CdCl_2$-exposed rats treated with *A. melegueta;* **CAD+RAAF**; $CdCl_2$-exposed rats coadministered with *R. vomitoria* and *A. melegueta*.

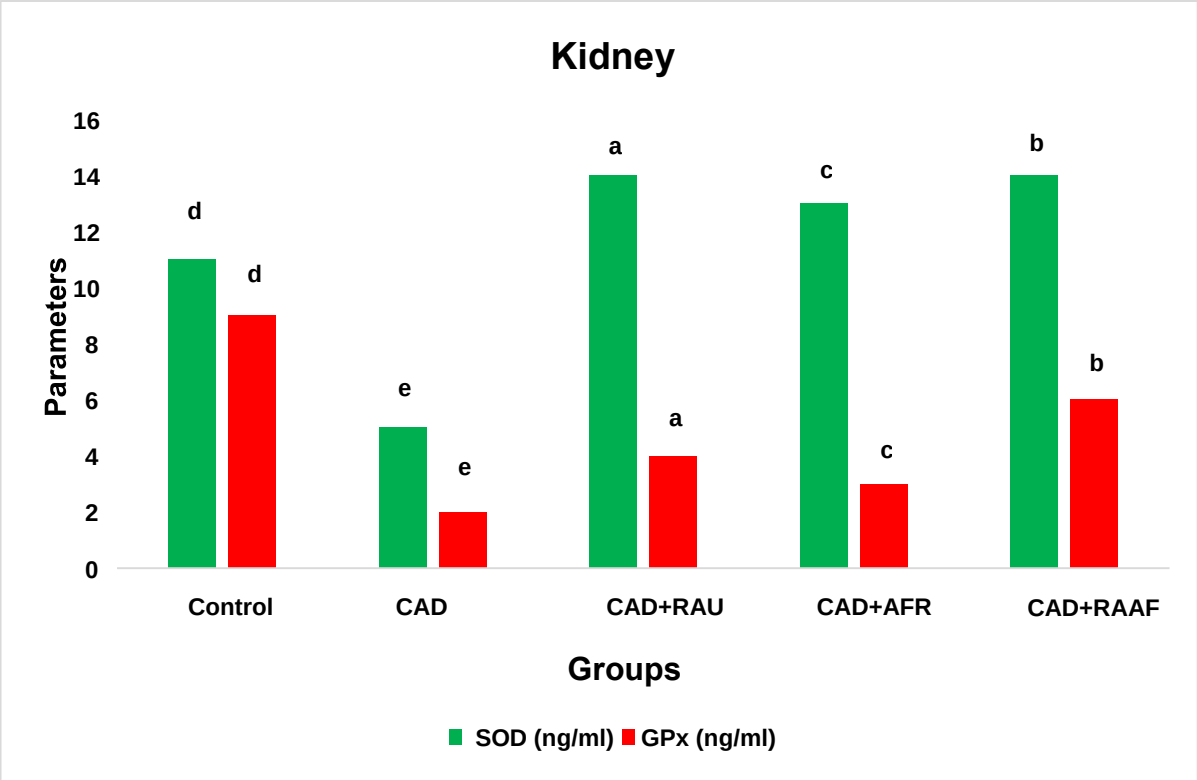

Figure 3. Graphical representation of tested parameters on the effects of extracts on the SOD and GPx in the kidney of rats in the control and test groups, where a > b > c >d > e, P < 0.001.

Keys: Control; unexposed untreated, **CAD;** cadmium exposed untreated, **CAD+RAU;** exposed and treated with *R. vomitoria*, **CAD+AFR;** exposed and treated with *A. melegueta*, **CAD+RAAF**; exposed and treated with admixture of *R. vomitoria* and *A. melegueta.*

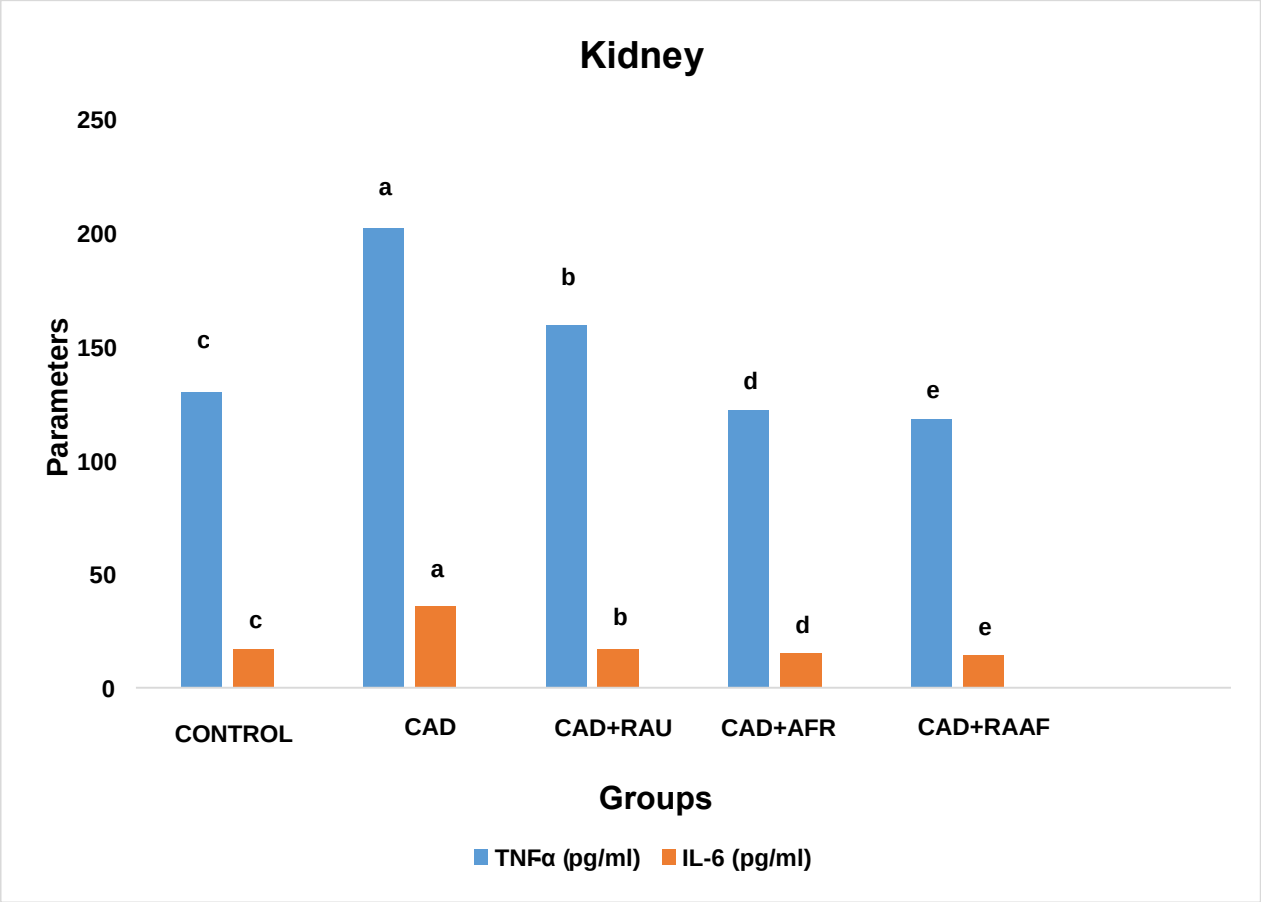

Figure 4: Effects of extracts on TNF-α and IL-6 in the kidney of rats in the control and various test groups, where a > b > c >d > e, P < 0.001.

Keys: Control; unexposed untreated, **CAD**; cadmium exposed untreated, **CAD+RAU;** exposed and treated with *R. vomitoria*, **CAD+AFR**; exposed and treated with *A. melegueta*, **CAD+RAAF;** exposed and treated with admixture of *R. vomitoria* and *A. melegueta*.

Discussion

Cadmium exposure and cadmium-induced kidney disease are major public health issues and have become an increasing cause of death among smokers and industrial workers [31]. Mitochondria and NADPH oxidase functions are impaired by the accumulation of cadmium in the proximal tubules in the nephrons which is the major source of ROS production in the kidneys. Ethnobotanicals have been widely studied for their benefits in managing various health conditions and diseases, yet their potential effects on cadmium toxicity remain underexplored [32].

Histological evaluation of the kidneys revealed no significant histoarchitectural alterations in the experimental animals, consistent with previous studies indicating that cadmium-induced nephrotoxicity is associated with chronic exposure due to its gradual accumulation and prolonged retention in renal tissues [19,33,34]. However, biochemical evaluation of antioxidant and proinflammatory markers showed a significant level of derangement in the SOD, GPx, TNF-α, and IL-6 levels in the cadmium-exposed rats. Furthermore, this study indicated that individual administration of methanolic extracts of *R. vomitoria* and *A. melegueta* had a significant down-regulating effect on TGF-β expression in $CdCl_2$-induced renal toxicity which agrees with the reports of Oyinloye et al. [27]. Cadmium interference with cellular components resulted in increased generation of free radicals, particularly ROS in Cd-exposed rats indicating TGF-β upregulation. Treatment with *Rauwolfia vomitoria* in $CdCl_2$-

exposed animals modulated TGF-β expression, highlighting the plant's anti-inflammatory properties, consistent with the findings of Bonheur et al. [16]. Similarly, Huang et al. [33] reported increased TGF-β levels following cadmium toxicity induction in HK2 cells. Flavonoids possess anti-inflammatory effects and exhibit anti-oxidant effects by inhibiting lipid peroxidation. *R. vomitoria* and *A. melegueta* contain large amounts of flavonoids which confer their anti-inflammatory properties [28]. The reduction in $CdCl_2$-induced toxicity observed in this study could be attributed to the plant's anti-inflammatory component. Furthermore, we discovered that treatments with *R. vomitoria* and *A. melegueta* significantly increased SOD and GPX levels in $CdCl_2$-exposed rats when compared to untreated $CdCl_2$-exposed untreated rats, and that combinatorial administration of *R. vomitoria* and *A. melegueta* reversed oxidative damage better than individual administration of the extracts. Our findings in this study further support the claim on the antioxidative potential of these plants as they inhibit arachidonic acid and lipid peroxidation [16,27]. Additionally, we suggested that the phenolic compounds within *R. vomitoria* and *A. melegueta* which have anti-oxidative properties restore $CdCl_2$-induced oxidative damage in the kidneys by diminishing the effect of cadmium exposure on the enzymatic antioxidant status of the kidney [35]. Earlier studies by Adeniyi et al.[36] reported the antioxidative and anti-inflammatory effect of *R. vomitoria* and *A. melegueta* with coadministrative treatment better modulating the expression of IL-10 and nuclear factor erythroid 2-related factor 2 (NRF2) in murine models and that administration at 200mg/kg/bw does not exert toxicity associated histological changes in rats. Further studies also documented the attenuative impact of the methanolic leaf extracts of *R. vomitoria* and *A. melegueta* in $CdCl_2$-induced hepatotoxicity by modulating the expression of immunoxidative markers associated with $CdCl_2$ exposure in rats [22].

It has been shown that various antioxidants and antioxidant defence systems protect cells from Cd-induced toxicity [21]. Generally, alteration in the antioxidant defence system enhances lipid peroxidation and oxidative stress [37]. This defence system includes the enzymes SOD, catalase, glutathione peroxidase, glutathione-s-transferase as well as glutathione, which usually protect the cell against oxidative damage [22]. Treatment with *R. vomitoria* extracts significantly restored the kidneys' SOD and GPx activities, agreeing with the findings of Oyinloye et al. [27].

The TNF-α and IL-6 levels were significantly elevated in the $CdCl_2$-exposed untreated rats while treatments with the plant extracts reversed the levels of these proinflammatory markers [16]. While TNF-α and IL-6 are pro-inflammatory markers that are produced in response to inflammation caused by oxidative stress [35], the methanolic extracts contain flavonoids which are potent anti-inflammatory compounds. Additionally, cadmium exposure induces oxidative stress and elevates the production of proinflammatory markers in the exposed untreated rats [38] whereas, significantly reduced TNF-α and IL-6 levels were observed in the rats administered with the studied extracts.

While studies have highlighted the anti-inflammatory and immunomodulatory role of either *R. vomitoria* or *A. melegueta*, a better immunomodulatory potential of their combinative administration was observed further highlighting the synergistic effects of the plants [39,40]. This finding agrees with earlier findings as reported by Adeniyi et al. [22] and Moronkeji et al. [21] who documented the immunomodulatory potential of co-administrative treatment in $CdCl_2$-induced toxicity.

The results of this study demonstrate that extracts of *Rauwolfia vomitoria* and *Aframomum melegueta* attenuate cadmium-induced renal toxicity as evidenced by the restoration of antioxidant enzymes (SOD and GPx), modulation of pro-inflammatory cytokines (IL-6 and TNF-α), and regulation of TGF-β expression. These findings point to the therapeutic potential of both plants, especially when used in combination. However, further studies are recommended to isolate and characterize the specific bioactive compounds responsible for these effects, particularly to elucidate the mechanisms underlying the enhanced synergistic interaction observed to further validate the therapeutic efficacy of these plants within the broader context of oxidative stress and organ-specific toxicity.

Conclusion

The combined administration of methanolic leaf extracts of *Rauvolfia vomitoria* and *Aframomum melegueta* at a standard dose of 200 mg/kg body weight exhibits protective effects against cadmium-induced renal toxicity. These findings suggest the

therapeutic potential of these plants for mitigating the adverse effects associated with cadmium exposure.

Acknowledgements

The authors acknowledge the contributions of the medical laboratory scientists of the Department of Medical Laboratory Science, Faculty of Allied Health Sciences, University of Medical Sciences, Ondo. Ondo State, Nigeria.

Conflict of Interest

The authors declare no conflict of interest.

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