Original Research Report

ATTENUATION OF CADMIUM TOXICITY BY METHANOL EXTRACTS OF *Rauvolfia vomitoria* AND *Aframomum melegueta* LEAVES

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ABSTRACT

Cadmium has long been known as an environmental pollutant with significant toxic effects on human health, primarily targeting the kidneys and liver. This study aims to investigate the mitigating potential of methanol extracts from the leaves of *Rauvolfia vomitoria* and *Aframomum melegueta* against cadmium-induced liver toxicity. Twenty-five adult male Wistar rats, weighing an average of 200 g, were randomly assigned to five groups of five rats each. Group 1 was not exposed to any substance and received only distilled water. Group 2 received cadmium at a standard dose of 12 mg/kg bw. Groups 3, 4, and 5 received 12 mg/kg bw of cadmium, and each group was treated with 200 mg/kg bw of *Rauvolfia vomitoria* leaf extract, *Aframomum melegueta* leaf extract, and a combination of both extracts, respectively. After 28 days, the animals were euthanized to obtain their livers, which were then excised and processed for histopathological, mRNA expression, and biochemical analyses. One-way analysis of variance (ANOVA) was used to analyze the data, and Duncan's multiple range test was used to compare the categorical variables ($p < 0.05$). The results showed that rats treated with *Rauvolfia vomitoria* and *Aframomum melegueta* extracts had elevated levels of interleukin 10 (IL-10) compared to Group 2. On the other hand, the treatment groups showed a significant decrease in tumor necrosis factor alpha (TNF-α) and interleukin 6 (IL-6) levels, along with significantly elevated levels of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Group 5 showed a normal liver histoarchitecture similar to Group 1, reversing the histopathological abnormalities shown in Group 2. In conclusion, co-administration of *Rauvolfia vomitoria* and *Aframomum melegueta* extracts reversed cadmium-induced toxicity better than either plant extract alone. This further suggests that methanol extracts from the leaves of *Rauvolfia vomitoria* and *Aframomum melegueta* may mitigate cadmium-induced toxicity by reducing oxidative stress and enhancing the antioxidant defense system.

Keywords: Pollutant; healthy lifestyle; medicinal plants; *Rauvolfia vomitoria*; *Aframomum melegueta*

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Highlights:

1. This study provides insight into the detrimental effect of cadmium exposure on mammalian cells using a murine model.
2. The co-administration of *Rauvolfia vomitoria* and *Aframomum melegueta* leaf extracts is more effective in ameliorating cadmium-induced toxicity than a single administration of each plant extract.
3. The co-administration of *Rauvolfia vomitoria* and *Aframomum melegueta* plant extracts can upregulate the expression of IL-10 and reverse the derangements in the TNF-α, IL-6, SOD, and GPX levels.

INTRODUCTION

Air pollution remains a major issue that affects human health. Anthropogenic human activities continually increase the level of environmental pollutants (Moronkeji et al. 2024). Cadmium is an easily absorbed, hazardous pollutant that has been linked to several illnesses in humans. It can be absorbed through cigarette smoke, air pollution, mineral mining, food, water, and cadmium batteries, among other sources. Cadmium primarily affects the liver and kidneys, but it can also affect the lungs. The most common ways of cadmium exposure in humans are through inhalation, dermal contact, and ingestion of contaminated food and water (Sharma et al. 2015, Adeniyi et al. 2023). Cadmium has many harmful effects, including the development of various human cancers, pulmonary toxicity, hepatotoxicity, and nephrotoxicity, as well as adverse effects on normal liver function, such as the modulation of differentiation, apoptosis, and cell survival or proliferation. Acute exposures can also result in respiratory system inflammation and irritation, chest discomfort, pulmonary edema, and pneumonitis (Sharma et al. 2015, Niture et al. 2021). An in vitro study has linked cadmium to carotid intima-media thickness, endothelial dysfunction, cellular damage induction, and brain lipid peroxidation. The rapid escalation of cadmium pollution in developing nations has become a major issue due to its detrimental effects (Rahimzadeh et al. 2017, Anyanwu et al. 2018, Fatima et al. 2019).

The utilization of traditional medicine is extensive worldwide, with over 75% of people using herbal remedies. This trend is growing, partly because traditional medical systems are becoming more widely accepted, particularly in Asia. Indigenous pharmacopoeias have identified medicinal plants with significant healing potential, either in their raw form or when synthesized into pharmaceutical adjuvants. These formulations are thought to be moderately effective and less hazardous than most synthetic pharmaceutical agents (Okon et al. 2017). The constituents of medicinal plants can be utilized therapeutically or as building blocks to create safer and more potent medications (Oshomoh et al. 2015). *Rauvolfia vomitoria* Afzel. is utilized in Nigerian folk medicine to treat hypertension, insomnia, stroke, and convulsion, as well as to manage psychiatric disorders despite the use of orthodox medicine. The plant belongs to the family Apocynaceae and has common names such as serpent wood, snakeroot, and swizzle stick. It is also known as “eto mmong” or “eba ebot” in Ibibio, “akanta” in Igbo, “asofeyeji” in Yoruba, and “wada” in Hausa, all of which are languages spoken in Nigeria (Bisong et al. 2011, Ekong et al. 2015). A study conducted by Arhoghro & Sule (2017) has reported the antipsychotic and antioxidant properties of *Rauvolfia vomitoria*. The plant contains indole alkaloids, including yohimbine, rescinnamine, reserpine, raucaffricine, ajmaline, and ajmalicine (Ezejindu et al. 2013b).

On the other hand, *Aframomum melegueta* is a tropical herbaceous perennial plant of the genus Aframomum that belongs to the ginger family (Zingiberaceae) of the angiosperms in the kingdom Plantae. It has a wide geographical distribution throughout tropical Africa, encompassing Nigeria, Liberia, Sierra Leone, Ghana, Cameroon, Côte d'Ivoire, and Togo. The plant possesses both nutritional and medicinal values, which have led to its traditional use in treating numerous conditions such as diarrhea, fever, sore throat, rheumatism, hypertension, and stomachache (Oshomoh et al. 2015, Abdou et al. 2021). *Aframomum melegueta* derives its aromatic flavor from the presence of essential oils such as shagaol, paradol, and gingerol. In addition, the plant is known to contain resins and alkaloids, such as piperine (Obike et al. 2014). Prior studies carried out by Oyinloye et al. (2016) have indicated that distinct secondary metabolites derived from *Aframomum melegueta* have potential therapeutic, medical, and healing properties. Flavonoids, alkaloids, tannins, phenolic compounds, terpenoids, cardiac glycosides, and saponins are among these secondary metabolites, which are present in different parts of the plant. Additionally, a separate study has demonstrated that *Aframomum melegueta* seed extract possesses antioxidant and antihyperlipidemic properties (Adigun et al. 2016).

The liver is the key organ responsible for regulating homeostasis in the body. It is also the main target of toxicity after acute and chronic exposures to cadmium (Arroyo et al. 2013). Medicinal preparations made from the extract of plants such as *Rauvolfia vomitoria* and *Aframomum melegueta* are historically used for the treatment of liver diseases. This is because contemporary medicine has not made major progress in developing trustworthy liver-protective medications (Ezejindu et al. 2013). According to Kwaśniak et al. (2019), cytokines can modulate anti-tumor responses as well as promote cell transformation and malignancy during chronic inflammation. Cytokines are proteins that are released and interact with cell surface receptors to influence both innate and adaptive immune responses. They play a crucial role in regulating immune cell functions, such as proliferation, differentiation, migration, and survival (Jin & Yin 2019). Interleukin-10 (IL-10), also referred to as the cytokine synthesis inhibitory factor, is an anti-inflammatory cytokine. It is essential for preventing auto-immune diseases and inflammatory responses by reducing the immune system's reaction to pathogens and microbes. Additionally, IL-10 promotes the proliferation and development of B

cells through its function as a cofactor with interleukin 4 (IL-4) (Fillatreau & O'Garra 2014, Verma et al. 2016, Rojas et al. 2017). This study aimed to look into the potential of *Aframomum melegueta* and *Rauvolfia vomitoria* leaf methanol extracts to mitigate the toxic effects induced by cadmium.

MATERIALS AND METHODS

The ethical approval for this study was sought and obtained from the Ondo State Ministry of Agriculture and Natural Resources, Akure, Nigeria, under protocol No. MNR/V.384/38 dated 27/4/2023. For the collection, extraction, and preparation of the plant extracts, fresh leaves of *Rauvolfia vomitoria* and *Aframomum melegueta* plants were acquired from a farm in Laje Village, Ondo, Nigeria. A professional taxonomist in the Department of Botany, University of Medical Sciences, Ondo, Nigeria, identified the *Rauvolfia vomitoria* and *Aframomum melegueta* leaves before assigning herbarium numbers 030 and 031, respectively. The leaves were washed off the dirt, dried under the shade for a week, and ground into powder using an electric pulverizer. The powdered leaves of *Rauvolfia vomitoria* were extracted using a Soxhlet extractor soaked with 75–95% methanol as the solvent. The extracts were evaporated using a rotary evaporator and subsequently dried at 45 °C in a Gallenkamp Plus II oven (Ekong et al. 2015a). The resulting dry extracts were kept at 4 °C in the refrigerator until used.

The *Aframomum melegueta* leaves were air-dried at room temperature and then pulverized into powder using an electric blender. The powdered leaves were soaked in 1,000 mL of 70% methanol for 24 hours. The suspension was squeezed and filtered to obtain a methanol extract using Whatman filter paper No. 1. The residue was immersed in 70% methanol five more times, or until the filtrate became colorless. A methanol extract of *Aframomum melegueta* leaves was obtained by straining the filtrates and evaporating them at 45 °C in a rotary evaporator (Ekong et al. 2015b). The chemically pure cadmium chloride hemipentahydrate (CdCl2.2.5H2O) was produced in the United Kingdom by Surechem Products Limited with batch number 6802/3 and product number C0262. The molecular weight of cadmium used in this study was 228.34 g/mol.

A total of 25 male adult Wistar rats weighing 200 g were collected from a local market in Ondo, Nigeria. The rats were allowed to acclimatize for two weeks before commencing the experiment, which spanned 28 days. They were housed in a well-ventilated and clean space where adequate pellets were provided. The rats were randomly assigned to five groups, with each group comprising five rats. Group 1 served as the control group, receiving only distilled water and not being exposed to any substances. Group 2 served as the untreated control group that was exposed to cadmium at a standard dose of 12 mg/kg bw (Andjelkovic et al. 2019). Groups 3, 4, and 5 as the treatment groups also received cadmium at a standard dose of 12 mg/kg bw and were pretreated with 200 mg/kg bw of *Rauvolfia vomitoria* leaf methanol extract, *Aframomum melegueta* leaf methanol extract, and a combination of both extracts, respectively. The administration of cadmium lasted for a duration of 28 days. At the end of the experiment, the rats were euthanized through a cervical dislocation method (Moronkeji & Akinbo 2024). Their livers were excised and processed for observations and analyses. Microscopic examinations were performed in addition to an analysis of IL-10 levels by messenger ribonucleic acid (mRNA) expression (Bare et al. 2018, Akinpelu et al. 2023). The enzyme-linked immunosorbent assay (ELISA) technique was employed to analyze the levels of superoxide dismutase (SOD), glutathione peroxidase (GPx), tumor necrosis factor alpha (TNF-α), and interleukin 6 (IL-6). This analysis was performed according to methods used in prior studies, such as those conducted by El-Boshy et al. (2015) and Abu-El-Zahab et al. (2019).

The fixed liver tissues were dehydrated in 70–100% graded alcohol. They were then cleared in xylene, infiltrated through two changes of a wax bath, and finally embedded and sectioned using a microtome. The sections were stained using hematoxylin and eosin (H&E) stain before being examined under light microscopes. Photomicrographs of the stained sections were captured during the examination (Moronkeji et al. 2018, 2024). As described by Bare et al. (2018), ribonucleic acid (RNA) was harvested from the liver tissues, and the level of gene expression was determined by polymerase chain reaction (PCR). Briefly, RNA was purified from 100–200 mg of tissues using TRIzol reagent. The TRIzol reagent (Inqaba Biotec West Africa Ltd., Nigeria) was used in this study following the instructions provided by the manufacturer (InvitrogenTM, Denmark). The concentration and purity of the isolated RNA were determined at an optical density (OD) of 260 nm and 260/280 nm, respectively. The RNA was used for downstream applications if the ratio fell between 1.8 and 2.1. The extracted RNA (2 µL) was utilized to synthesize complementary deoxyribonucleic acid (cDNA) through a reverse transcription reaction using the ProtoScript II First Strand cDNA Synthesis Kit (Biolabs, New England). This process involved three-step reaction conditions: 65 °C for 5 minutes, 42 °C for 1 hour, and 80 °C for 5 minutes. The PCR and amplification for gene expression were performed using the Luna Mastermix kit (Biolabs,

New England) and Taqman kit probes from TibM01bio (Berlin, Germany) in a thermocycler. Gel imaging was performed on an electrophoresis gel imager, using β-actin as the reference gene. Primers for cDNA were purchased from Inqaba Biotech (Hatfield, South Africa). The corresponding sequences for the IL-10 PCR primers were: forward primer 5'-TTGAACCACCCGGCATCTAC-3′ and reverse primer 5'-CCAAGGAGTTGCTCCCGT TA-3′ (Bare et al. 2018).

Gel electrophoresis of the PCR products was used to analyze the reaction quality and yield of the DNA products. For the biochemical assay, selective humoral immunological parameters such as TNF-α and IL-6, as well as antioxidant markers such as reduced glutathione (GSH), SOD, and GPx, were determined from undiluted serum samples using commercially available ELISA kits purchased from R&D Systems, Minneapolis, USA (Abu-El-Zahab et al. 2019). The data obtained were pooled and expressed as mean ± standard deviation (SD) and subjected to statistical analysis using SPSS Statistics for Windows, version 17.0 (SPSS Inc., Chicago, Ill., USA). The categorical variables were analyzed using a one-way analysis of variance (ANOVA), followed by a post-hoc Duncan's multiple range test (DMRT). A value of $p<0.05$ was considered statistically significant, with a confidence level of 95%.

RESULTS

The histopathological observations revealed the mitigating effects of *Rauvolfia vomitoria* and *Aframomum melegueta* on cadmium-induced cytotoxicity in the livers of adult male Wistar rats. The livers of the unexposed control rats (Group 1) were devoid of any cytopathic lesions, with the hepatocytes appearing normal and the sinusoidal spaces not congested or inflamed with no Kupffer cell activation (Figure 1a). The cadmium-exposed, untreated rats (Group 2) had reactive hepatocytes with Kupffer cell activation coupled with sinusoidal dilation (Figure 1b). The cadmium-exposed rats treated with *Rauvolfia vomitoria* leaf methanol extract (Group 3) had a normal histoarchitecture without congestion, inflammation, or Kupffer cell activation, and the morphology of the hepatocytes appeared normal (Figure 1c). The cadmium-exposed rats treated with *Aframomum melegueta* leaf methanol extract (Group 4) showed normal central venules without congestion, the morphology of the hepatocytes appeared normal, and the sinusoids appeared normal and not infiltrated (Figure 1d). The cadmium-exposed rats co-administered with *Rauvolfia vomitoria* and *Aframomum melegueta* extracts (Group 5) had normal liver histoarchitecture similar to the rats in Group 1. In this histoarchitecture, the sinusoids were non-dilated and devoid of congestion and inflammation, the central venules were not congested or infiltrated, and the hepatocyte morphology appeared normal (Figure 1e).

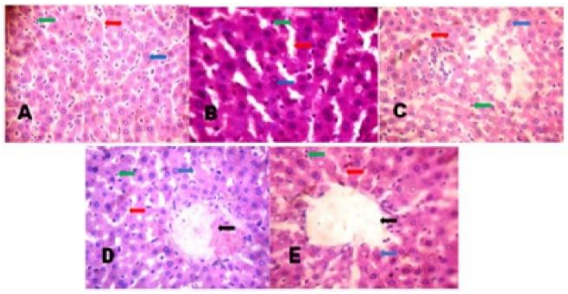

Figure 1. (a) Hepatocytes (blue arrow), sinusoids (red arrow), and Kupffer cells (green arrow) in Group 1. (b) Group 2 shows reactive hepatocytes (blue arrow), dilated sinusoidal spaces (red arrow), and Kupffer cells (green arrow). (c) Group 3 exhibits normal hepatocytes (blue arrow) and sinusoids (red arrow). (d) Group 4 indicates normal central venules (black arrow), hepatocytes (blue arrow), and sinusoids (red arrow). (e) Non-congested central vein (black arrow), hepatocytes (blue arrow), and sinusoids (red arrow) in Group 5. (H&E, 400X).

The analysis of mRNA expression revealed an elevation in the expression of IL-10 in the treatment groups compared to the cadmium-exposed control group. This indicated a reduction in the oxidative damage associated with cadmium exposure. The administration of *Rauvolfia vomitoria* and *Aframomum melegueta* extracts efficiently mitigated the inflammatory response, as evidenced by the increase in IL-10 expression (Figure 2).

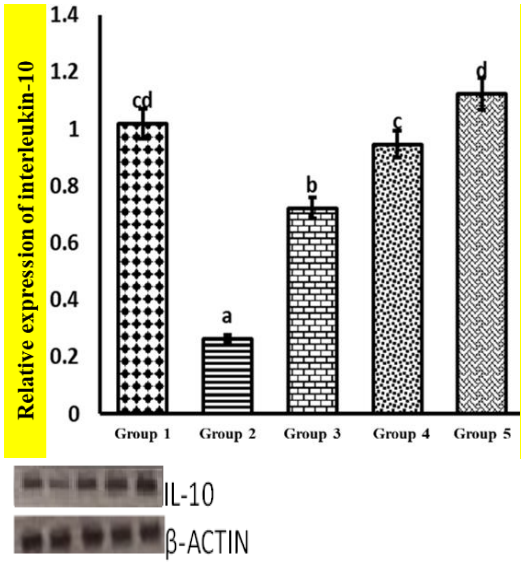

Figure 2. The figure depicts the relative mRNA expression of IL-10 across the groups. IL-10 expression was significantly higher across the other groups when compared with the cadmium-exposed untreated rats in group 2. $p<0.05$ where a<b<c<d.

Table 1 Displays the mean and standard deviation of the biochemical analysis results, including the TNF-α, SOD, GPx, and IL-6 levels, across all groups. It was observed that Group 1 exhibited higher levels of GPx and SOD activity compared to the other groups.

Table 1. Mean and standard deviation of SOD, GPx, TNF-α, and IL-6 levels across all groups.

Parameters	Group 1	Group 2	Group 3	Group 4	Group 5	df	X^2	F	p
	X±SE (min-max)								
SOD	10.2±0.93 (8.43-12.67)	1.2±0.05 (1.10-1.35)	3.4±0.13 (3.05-3.67)	3.5±0.48 (2.79-4.89)	5.4±0.46 (4.34-6.58)	19	46.158	43.860	0.000
GPx	6.6±0.31 (5.79-7.27)	1.0±0.09 (0.82-1.24)	2.9±0.15 (2.65-3.33)	2.7±0.24 (2.25-3.31)	3.2±0.15 (2.82-3.55)	19	16.509	99.141	0.000
TNF-α	200.9±8.32 (178.48-217.70)	147.8±4.22 (135.60-154.72)	145.2±3.72 (134.67-150.69)	130.5±4.08 (120.79-138.97)	121.5±3.38 (111.60-126.64)	19	3807.252	36.880	0.000
IL-6	25.5±1.04 (22.55-27.11)	18.2±0.30 (17.64-19.04)	17.2±1.21 (13.93-19.77)	13.2±1.37 (10.43-15.98)	12.1±0.72 (10.77-13.51)	19	112.034	27.891	0.000

Legends: SOD=superoxide dismutase; GPx=glutathione peroxidase; TNF-α=tumor necrosis factor alpha; IL-6=interleukin-6.

Group 2 showed a decrease in the activity of SOD and GPx, as well as an increase in the levels of TNF-α and IL-6. In contrast, the rats in Group 3 that were treated with *Rauvolfia vomitoria* leaf methanol extract had elevated levels of SOD and GPx, as well as reduced levels of TNF-α and IL-6. The differences in these biomarkers were noticeable when comparing them with those in Group 1. The rats in Group 4 that received *Aframomum melegueta* leaf methanol extract also showed the same pattern of biomarker expression. However, the co-administration of *Rauvolfia vomitoria* and *Aframomum melegueta* leaf methanol extracts was more effective in mitigating the cadmium toxicity. This was achieved by significantly elevating SOD and GPx levels, surpassing the effects shown when using each plant extract individually. The co-administration of both plant extracts also demonstrated a significant reduction in TNF-α and IL-6 levels (Figures 3 and 4).

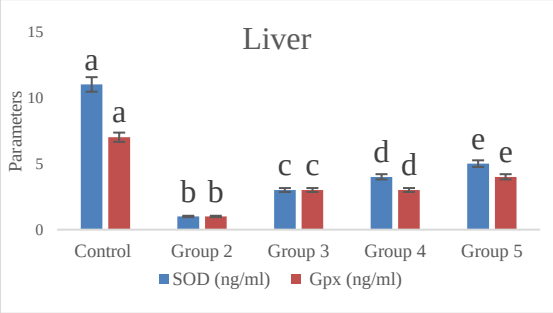

Figure 3. The significantly different expressions of SOD and GPx in the rats' livers affected by the extracts (p<0.001), with the sequence of a>b>c>d>e.

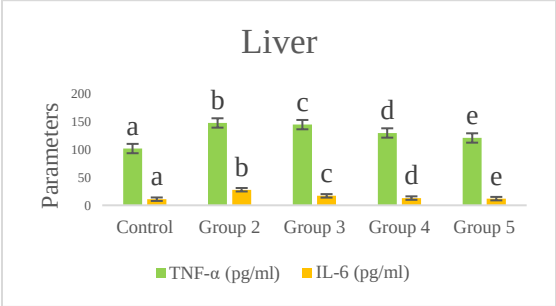

Figure 4. The significant difference (p<0.001) in the expressions of TNF-α and IL-6 affected by the extracts in the sequence of a>b>c>d>e.

DISCUSSION

One of the most significant and prevalent environmental contaminants found in food, water, air, and soil is cadmium. The accumulation of cadmium within cells induces oxidative stress, which damages the hepatocyte by displacing redox-active metals, lowering redox scavenger levels, and inhibiting antioxidant enzymes (Oyinloye et al. 2016). Rahimzadeh et al. (2017) previously reported that cadmium toxicity causes the bioaccumulation of toxic metals in the liver and leads to hepatic injury and nephrotoxicity.

Since ancient times, using herbal medicine to cure illnesses and ailments has been a common practice. Numerous bioactive metabolites found in medicinal plants have therapeutic qualities and serve as building blocks for a variety of medication formulations. The combination of various phytochemicals can yield greater therapeutic effects at the cellular, metabolic, and molecular levels compared to drug-based treatments that use chemically produced phytochemicals (Chinaka O. et al. 2014, Saad et al. 2021). In this study, the histological observations showed that sub-chronic exposure to cadmium had a deleterious impact on

the liver. The negative control rats' livers appeared normal, typified by normal hepatocytes and non-congested sinusoids. On the other hand, the cadmium-exposed rats without treatment exhibited reactive hepatocytes, dilated sinusoidal spaces, and Kupffer cell activation. The rats exposed to cadmium and treated with either *Rauvolfia vomitoria* or *Aframomum melegueta* extracts, or a combination of both extracts, revealed an ameliorative effect on cadmium-induced cytotoxicity. Additionally, the results of this study showed that the co-administration of both extracts effectively ameliorated the cadmium-induced liver toxicity to a greater extent.

A toxicological study conducted by Chinaka O. et al. (2014) demonstrated that *Aframomum melegueta* seed methanol extract can induce liver toxicity at 300 mg/kg. This suggests that the utmost care should be taken to prevent excessive use of the plant. An additional study carried out by Osuntokun et al. (2017) indicated that *Aframomum melegueta* contains 8-gingerol, 6-gingerol, 6-shogaol, methyl-6-gingerol, 6-gingeredione, 2-(5-butylfuran-2-yl)-ethyl-2-methoxyphenol, and rac-6-dihydroparadol. Although 6-paradol is regarded as the active ingredient among all these compositions, large amounts of cancer-battling antioxidants, such as flavonoids, have been found in *Aframomum melegueta*. Reports presented by Agim et al. (2017) and Akindele et al. (2022) have shown that flavonoids scavenge free radicals, exhibit strong anticancer activity, and possess promising potential as antivirals, immunomodulators, and anti-inflammatory agents. In this study, the anti-inflammatory potential of *Aframomum melegueta* was expressed by mitigating cytopathic alterations and reversing biochemical markers.

A previous study conducted by Abdou et al. (2021) revealed that *Aframomum melegueta* is a promising agent that can inhibit diclofenac-induced nephrotoxicity by modulating malondialdehyde (MDA), TNF-α, IL-6, bcl-2-like protein 4 (BAX), and caspase-3 levels. *Aframomum melegueta* has the potential to enhance the levels of GSH and heme oxygenase (HO-1), as well as upregulate the mRNA expression levels of renal nuclear factor erythroid 2–related factor 2 (Nrf2), adenosine monophosphate-activated protein kinase (AMPK), and Sirtuin 1 (SIRT-1), while also improving the renal tissue architecture. In this study, the cadmium-exposed rats in the treatment groups demonstrated a rise in the mRNA expression levels of IL-10, further suggesting the immunomodulatory potential of the plant. Our findings aligned with those of Ataba et al. (2020), who documented the excellent antioxidative potential of *Aframomum melegueta*, probably due to the presence of polyphenols and flavonoids. *Aframomum melegueta* ethanol extract possesses anti-inflammatory properties that can inhibit cyclooxygenase-2 (COX-2) due to the presence of 6-paradol (Ilic et al. 2014). In addition, a study by Osuntokun et al. (2017) found that 6-shogaol has the ability to inhibit the expression of interleukin-1 beta (IL-1β), a pro-inflammatory gene. This study also discovered that treatment using *Aframomum melegueta* mitigated cadmium-induced toxicity, further buttressing the antioxidative potential of the plant.

A recent study performed by Akinwumi et al. (2022) has documented the ameliorative potential of *Rauvolfia vomitoria* against the toxic effects of potassium dichromate and sodium arsenite. As an anti-inflammatory cytokine, IL-10 has a crucial role in preventing inflammation and auto-immune pathologies due to its immune response-limiting function (Fillatreau & O'Garra 2014). Our study showed that cadmium exposure downregulated the activity of IL-10 in the comparison between groups of treated and untreated rats. Furthermore, we observed that the co-administrative treatment using *Rauvolfia vomitoria* and *Aframomum melegueta* leaf methanol extract mitigated the cadmium-induced oxidative damage by increasing IL-10 activity. The effects shown by the co-administrative treatment were greater compared to a single treatment using each plant extract. This suggests the synergistic interaction of phytocomponents in the studied plants. Previous studies conducted by Ilic et al. (2014) and Akinwumi et al. (2022) discussed the anti-proliferative and antioxidant effects provided by *Rauvolfia vomitoria*. These might be the reasons why the plant has been used as a traditional medicine for centuries. A separate study has also shown that *Rauvolfia vomitoria* methanol extract at lower doses offers some level of chemo-protection against sodium arsenite-induced clastogenicity and liver damage (Akinwumi et al. 2022). Oyeniran et al. (2021) documented the phenolic constituents and inhibitory effects of *Rauvolfia vomitoria* leaves on cholinergic free radicals. The analysis of monoaminergic enzymes using murine models additionally indicated that the rich phenolic constituents found in *Rauvolfia vomitoria* leaves might confer antioxidative and neuroprotective effects.

In our study, there was a significant decrease in the antioxidant activities of SOD and GPx in the cadmium-exposed control group in comparison with the treatment groups. Various studies, such as those by El-Boshy et al. (2015), have recorded the immunosuppressive effects of cadmium on the immune system. Our findings are consistent with their observation, which reported depleted antioxidant activity due to cadmium intoxication. Additionally, studies by Laamech et al. (2017) and Rahimzadeh et al. (2017) revealed the deleterious

impact of cadmium on organ systems. The impact arises as cadmium inhibits the markers of antioxidation and induces oxidative damage through the generation of reactive oxygen species (ROS), which has been implicated in the development of various pathological processes and damage to the liver. The findings of this study showed depleted expressions of the antioxidant enzymes SOD and GPx, as well as a significant increase in mRNA expression levels among the cadmium-exposed groups. This study also revealed a significant increase in the levels of liver biomarkers, such as TNF-α and IL-6, in the cadmium-exposed control group compared to the treatment groups. Although the use of separate plant extracts helped reduce the oxidative damage induced by cadmium, the combination of treatments using *Rauvolfia vomitoria* and *Aframomum melegueta* leaf extracts was more effective in improving the oxidative damage. This indicates that there are more favorable outcomes as a result of the synergistic interaction between the phytocompounds present in both plants.

Strength and limitations

The findings of this study provide evidence for the extensive use of *Rauvolfia vomitoria* and *Aframomum melegueta* in the traditional management of various disorders, as they have been shown to have anti-inflammatory properties. However, anthropogenic human activities produce a large number of toxic heavy metals to which humans are exposed. Among these metals, cadmium accounts for only a small proportion. In the presence of other heavy metals, the overall cytotoxicity of cadmium might not accurately reflect the deleterious impact of heavy metal exposure.

CONCLUSION

The administration of *Rauvolfia vomitoria* and *Aframomum melegueta* leaf methanol extracts has hepatoprotective effects that may contribute to the reduction of cadmium toxicity. This implies that the therapeutic potential of these plants could be harnessed to mitigate the negative effects of cadmium exposure. However, further studies are necessary to determine the mechanisms by which the compounds of *Rauvolfia vomitoria* and *Aframomum melegueta* synergistically interact to mitigate cadmium-induced oxidative damage. This is especially important when comparing the effects of administering these extracts in combination versus using them individually.

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Conflict of interest

None.

Ethical consideration

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Author contribution

AM and TDA conceptualized, designed, and drafted the article. AM analyzed and interpreted the data as well as performed critical revisions of the manuscript for important intellectual content. TDA gave final approval to the article. JO and OAI collected the samples and compiled the data. MJK conducted the statistical analysis. OA and TDA provided administrative, technical, and logistic support.

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