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دانشگاه علوم پزشکی و خدمات بهداشتی درمانی شاهرود

مقاله پژوهشی

اثر تعدیل‌کننده گیاهی بر بیان NF-κB و IL-1β و تغییرات آسیب‌شناسی بافتی در آسیب کبدی-کلیوی ناشی از کلرید کادمیوم در موش‌های صحرایی تیمارشده با Aframomum melegueta و Rauvolfia vomitoria

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چکیده

مقدمه: *کادمیوم که توسط آژانس بین‌المللی تحقیقات سرطان (IARC) به‌عنوان سرطان‌زای انسانی گروه ۱ طبقه‌بندی شده است، عمدتاً از طریق القای استرس اکسیداتیو، تولید بیش از حد گونه‌های فعال اکسیژن (ROS) و تحریک پاسخ‌های التهابی موجب آسیب چند اندامی، به‌ویژه در کبد و کلیه‌ها، می‌شود. در این مطالعه، تغییرات مولکولی و آسیب‌شناختی ناشی از سمیت کبدی-کلیوی القا شده با کلرید کادمیوم ($CdCl_2$) و اثرات محافظتی عصاره‌های متانولی Aframomum melegueta و Rauvolfia vomitoria در موش‌های صحرایی نر نژاد ویستار بررسی شد.*

مواد و روش‌ها: *این مطالعه مقطعی بر روی ۴۰۰ فرد بالغ مبتلا به HIV تحت درمان با HAART در بیمارستان نیروی دریایی نیجریه، واری، انجام شد. شرکت‌کنندگان بر اساس مدت دریافت HAART به سه گروه (≤۲ سال، ۲ تا ۵ سال و >۵ سال) تقسیم شدند. داده‌های جمعیت‌شناختی، BMI، پروفایل چربی (کلسترول تام، LDL-C، HDL-C و تری‌گلیسرید)، قند خون ناشتا و HbA1c ارزیابی و ارتباط مدت درمان HAART با بیماری‌های قلبی- متابولیک با استفاده از رگرسیون لجستیک چندمتغیره و تعدیل متغیرهای مخدوش‌کننده بررسی شد.*

نتایج: *مواجهه با $CdCl_2$ موجب افزایش معنی‌دار بیان NFκB و IL-1β شد ($P<0/05$) که نشان‌دهنده افزایش پاسخ‌های پیام‌رسانی التهابی و آسیب بافتی است. تیمار با هر یک از عصاره‌های A. melegueta یا R. vomitoria موجب کاهش معنی‌دار بیان NFκB و IL-1β و بهبود تغییرات آسیب‌شناختی بافتی ناشی از $CdCl_2$ شد؛ با این حال، تجویز همزمان دو عصاره اثر محافظتی بیشتری نشان نداد.*

بحث: *عصاره‌های A. melegueta و R. vomitoria می‌توانند با تعدیل مسیرهای التهابی NFκB و IL-1β اثرات محافظتی در برابر سمیت کبدی-کلیوی ناشی از $CdCl_2$ ایجاد کنند؛ با این حال، استفاده ترکیبی از آن‌ها مزیت درمانی بیشتری نسبت به مصرف جداگانه نشان نداد.*

واژه‌های کلیدی: کلرید کادمیوم، اکوتوکسیکولوژی، محافظت کبدی-کلیوی، تعدیل ایمنی، استرس اکسیداتیو، گیاه درمانی.

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ارجاع: تمیدایو دانیل آدنیبی، آکینپلو مورونکجی، ساموئل آیوبامی فاسوگبون، اولوبونمی اسان، اولوسولا اولالکان الکووفهینتی، ایمانوئل کایوده، پرشس جوی گباجوئولا، آدبیسی آدبانجو، اولامیجو تامی‌لوره. اثر تعدیل‌کننده گیاهی بر بیان NF-κB و IL-1β و تغییرات آسیب‌شناسی بافتی در آسیب کبدی-کلیوی ناشی از کلرید کادمیوم در موش‌های صحرایی تیمارشده با Aframomum melegueta و Rauvolfia vomitoria. مجله دانش و تندرستی در علوم پایه پزشکی ۱۴۰۵؛۲۱(۱):۶۵-۵۵.

Introduction

Environmental pollution remains a major public health concern globally. Urbanisation and industrialisation drive the release of pollutants, including harmful chemicals, pesticides, petroleum products, and heavy metals, in ecosystems such as water, soil, and air, which have negative impacts on both plants and humans (1). Anthropogenic activities remain a major contributor to heavy metal exposure in the environment (2-4). Sources include waste disposal sites, surface runoffs, landfills, livestock and poultry manure, vehicular emissions and road construction activities (5).

Cadmium (Cd) is among the most toxic heavy metals, commonly found in water, air, soil, and sediments. Human exposure primarily occurs through inhalation, consumption of contaminated food and water and cigarette smoking (4, 6-7). Globally, it is estimated that about 22,000 tons of cadmium are released into the soil annually (8). Due to its chemical stability and resistance to degradation, Cd accumulates in the human body through persistent environmental and occupational exposures over a lifetime (9). Excessive reactive oxygen species (ROS) and reactive nitrogen species (RNS) production leads to oxidative stress, damaging vital biomolecules and cellular structures; persistent oxidative stress has been implicated in the development of numerous pathological conditions (10-11). Growing recognition of the limitations of synthetic drugs, including reduced efficacy, resistance, toxicity, and concerns over chemical residues in food and agricultural products, has driven increasing interest in medicinal plant-based alternatives (12-13).

Phytochemicals present in various foods and medicinal plants contribute significantly to the prevention and management of chronic oxidative stress-related diseases through their natural antioxidant activity (14-15). These bioactive compounds exert valuable physiological impacts by engaging cellular signalling pathways that govern mitochondrial function, modulate inflammatory mediator production, facilitate beneficial epigenetic changes, and upregulate endogenous antioxidant enzyme expression (14, 16).

The genus Rauvolfia (syn. Rauwolfia), belonging to the family Apocynaceae, is widely used in African traditional medicine for the management of hypertension, febrile conditions, gastrointestinal disturbances, hepatic disorders, and certain neoplastic diseases (17, 18). Phytochemical analyses have identified alkaloids, saponins, flavonoids, and cardiac glycosides as major constituents, underpinning its documented anti-inflammatory, anticancer, antitumour, antioxidant, and cardioprotective activities (19). Aframomum melegueta (Fam. Zingiberaceae), a perennial herb native to West Africa, commonly known as guinea grains or grains of paradise, is traditionally employed in managing several diseases (20). Its anti-inflammatory and immunosuppressive potential has been attributed to diverse constituent biomolecules including alkaloids, flavonoids, fatty acids, phenols, carotenoids, terpenoids, glycosides, tannins, steroids, vitamins, and minerals (16, 21-22).

NFκB is a pleiotropic transcription factor central to dysregulated inflammation underlying chronic disease (23). In the liver, NFκB signalling is implicated in fatty liver disease, hepatic injury, autoimmune hepatitis, viral hepatitis, and hepatocellular carcinoma (24). In the kidney, NFκB is consistently activated in human and experimental models of renal inflammation, mediating responses across intrinsic renal and infiltrating immune cell populations (25).

IL-1β is a potent pro-inflammatory cytokine involved in acute and chronic inflammation and organ damage (26). Upon NFκB activation, inactive pro-IL-1β is synthesised and subsequently cleaved by Caspase-1 to produce biologically active IL-1β (27). IL-1β plays a central role in acute kidney injury, glomerulonephritis, and renal fibrosis (28), and is highly expressed in drug-induced liver injury, steatohepatitis, viral hepatitis, and ischaemia/reperfusion injury (29-31).

Despite substantial evidence documenting cadmium-induced hepatorenal oxidative and inflammatory injury, the molecular mechanisms by which plant-based interventions modulate key inflammatory transcription factors such as NFκB and its downstream cytokine IL-1β remain incompletely characterised. While the antioxidant and anti-inflammatory properties of A. melegueta and R. vomitoria have been reported individually, evidence regarding their combined use and comparative molecular efficacy at the transcriptional level in cadmium-induced hepatorenal toxicity is lacking. We therefore hypothesised that treatment with these plant extracts could attenuate $CdCl_2$-induced NFκB and IL-1β upregulation in the liver and kidneys, and that this attenuation would correspond to histopathological improvement.

This study therefore evaluated the protective efficacy of A. melegueta and R. vomitoria leaf extracts against $CdCl_2$-induced hepatorenal toxicity in a murine model, integrating histopathological and molecular analyses to elucidate their modulatory influence on NFκB and IL-1β mRNA expression, with the aim of supporting the development of plant-based interventions against heavy metal-induced organ toxicity.

Methods

Animal Husbandry

Twenty-five adult male Wistar rats weighing an average of 200g, procured from the animal holding of the University of Medical Sciences, Ondo (UNIMED), were used in this study. The animals were acclimatised for two weeks, after which they were housed in groups of five per cage in aerated cages in an adequately ventilated room under a 12-hour light/dark cycle with regulated environmental conditions (25±2°C) and allowed access to standard rat feed and clean water ad libitum.

Ethical considerations

Ethical approval for this study was obtained from the UNIMED Animal Research Ethics Committee (UAREC) under the approval ID UNIMED-AREC/Apv/2024/010.

Chemical

Pure cadmium chloride hydrated (CadmiumCl2.2.5H2O = 228.34) with batch number 6802/3 and product number CO262 obtained from Surechem Products Limited, United Kingdom, was used for this study.

Experimental Design

A randomisation procedure was employed to allocate twenty-five Wistar rats into five groups (n = 5 per group). The dose of $CdCl_2$ (12 mg/kg body weight) was selected based on previously established nephrotoxic and hepatotoxic doses in rodent models (36, 37). The plant extract dose of 200 mg/kg body weight was adopted from prior studies in which A. melegueta and R. vomitoria at this specific dose demonstrated significant antioxidant and anti-inflammatory effects, as well as amelioration of cadmium-induced hepatic and renal damage, without evidence of overt toxicity (40, 41). In particular, Oyinloye et al. (41) demonstrated dose-dependent ameliorative effects of A. melegueta at 200 mg/kg body weight in a cadmium-hepatotoxicity model directly comparable to the present study, and Adeniyi et al. (40) confirmed the safety and efficacy of the same dose for R. vomitoria and A. melegueta in combination against cadmium toxicity. The 28-day exposure period was chosen to allow sufficient time for the development of discernible histopathological and molecular changes (16). The control (Group I) received distilled water only and was not exposed to cadmium. Rats in Groups II–V received $CdCl_2$ (12 mg/kg body weight) dissolved in distilled water, administered by oral gavage once weekly. Groups III and IV additionally received leaf extracts of R. vomitoria or A. melegueta (200 mg/kg body weight, dissolved in distilled water, by oral gavage daily), respectively. Group V received co-administration of both extracts at the same dose and route.

Group I: Unexposed control administered distilled water only.

Group II: CdCl2-exposed, untreated rats

Group III: CdCl2-exposed rats treated with R. vomitoria at 200mg/kg/BW

Group IV: CdCl2-exposed rats treated with A. melegueta at 200mg/kg/BW

Group V: CdCl2-exposed rats co-administered with R. vomitoria and A. melegueta at 200mg/kg/BW, respectively.

Specimen Collection

At the conclusion of the 28-day experiment, rats in all the groups were ethically euthanised by intraperitoneal administration of ketamine (75mg/kg) and xylazine (10mg/kg), followed by cervical dislocation (32-33). The liver and kidneys were subsequently excised; tissues designated for histopathological analysis were immediately fixed in 10% neutral buffered formalin and processed for light microscopic evaluation, while those for mRNA expression studies were transferred into fresh Trizol reagent and processed accordingly (16).

Plant Collection, Extraction, Preparation of Extracts and Phytochemical Analysis

Fresh leaves of A. melegueta and R. vomitoria were collected from a farm at Laje Village, Ondo City, Ondo State, Nigeria. The plant materials were authenticated at the Plant Biology and Biotechnology Department of UNIMED by a taxonomist and assigned herbarium numbers 0059 and 0069, respectively.

The leaves were thoroughly washed under running tap water, shade dried, and pulverised into fine powder using a laboratory pulveriser. Extraction was performed by soaking the powdered leaves in 95% methanol for 24 hours, followed by filtration and concentration using a Soxhlet apparatus. The filtrates were evaporated to dryness using a rotary evaporator, and the extracts were stored at 4-8°C for up to four weeks until required for administration (34). Phytochemical profiles of these plants were characterised in our previous investigations, confirming the presence of key bioactive constituents, alkaloids, flavonoids, terpenoids, and saponins (16), providing the scientific basis for the present study.

mRNA Analysis - Isolation of total RNA

Total RNA was isolated from the liver and kidney tissues using the Quick-RNA miniPrep™ kit (Zymo Research). Genomic DNA contamination was removed via DNAse I treatment (NEB, Cat: M0303S), and RNA yield and purity were assessed spectrophotometrically at 260 nm (A&E Lab, UK). Semi-quantitative polymerase chain reaction (PCR) was performed to amplify the target gene using NEB OneTaq® 2X Master Mix and primers synthesised by Inqaba Biotec, Hatfield, South Africa (Table 1).

Amplification was carried out in a 25 µl reaction volume comprising cDNA, forward and reverse primers, and ReadyMix™ Taq PCR Master Mix. The thermal cycling protocol consisted of initial denaturation at 95 °C for 5 minutes; 30 cycles of denaturation (95 °C, 30 s), primer annealing (designated temperature, 30 s), and extension (72 °C, 60 s); and a final extension at 72 °C for 10 minutes. PCR amplicons were resolved on a 1.0% agarose gel with glyceraldehyde-3-phosphate dehydrogenase (GAPDH) served as the internal control for normalisation of target gene expression. Band intensities were quantified using ImageJ software (35).

Table 1.0 Primer sequences for semi-quantitative PCR analysis of target gene expression

Gene	Forward primer sequence (5'-3')	Reverse primer sequence (5'-3')	Accession number	Primer size	Product size
NFκB	ACGCAAAAGGACCTACGAGA	ATGGTGCTGAGGGATGTTGA	NM_199267.2	20	171
IL-1β	GACTTCACCATGGAACCCGT	GGAGACTGCCCATTCTCGAC	NM_031512.2	20	180
GAPDH	AGGCACCAAGATACTTACAAAAAC	TGTAACCAGTCATCAGCAAAATGT	AF106860.2	24	188

Statistical analysis

Results are expressed as mean ± standard deviation (SD). Statistical analysis was conducted using one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison test. Differences were regarded as statistically significant at $P<0.05$. All statistical evaluations were carried out using GraphPad Prism version 9.0 (GraphPad Software, San Diego, CA, USA).

Results

Histopathological findings

Histopathological examination of the kidney section (Figure 1) revealed normal renal architecture in the unexposed control rats (Group I), characterised by a normal glomerulus with regular mesangial cells and capsular space, an interstitium devoid of inflammation or congestion, and normal renal tubules and blood vessels. The CdCl2-exposed untreated rats (Group II) showed a disrupted renal histoarchitecture, with marked interstitial dilation, congestion, and mononuclear cell infiltration, as well as periglomerular inflammation. Rats treated with R. vomitoria (Group III) showed partial recovery, with mild interstitial congestion and focal mononuclear infiltration, while the glomerulus and renal tubules appeared normal. In Group IV (A. melegueta-treated), the glomerulus and renal tubules appeared normal, with the interstitium devoid of inflammation or congestion. The co-treated (Group V) also showed normal-appearing glomeruli and renal tubules; however, mild interstitial congestion without mononuclear infiltration persisted.

Figure 2 shows the histopathological reports of the liver across different groups. Group I revealed a normal portal triad comprising the portal vein, hepatic artery, and bile duct, with a normal central vein, hepatocytes, and sinusoidal spaces. Group II showed marked hepatic injury characterised by periportal inflammation, hepatocytic vacuolation with ballooning degeneration, sinusoidal dilation, and Kupffer cell activation. Groups III (R. vomitoria-treated), IV (A. melegueta-treated and V (co-treated) all demonstrated preserved hepatic architecture with non-congested, non-inflamed portal tracts and normal central vein, hepatocytes, and sinusoidal spaces.

Gene expression analysis of NFκB and IL-1β in Liver and Kidney Tissues

Table 2 presents the relative mRNA expression levels of NFκB in the liver and kidneys, and IL-1β in the liver of rats across the experimental groups, with their corresponding graphical representations shown in Figures 3 - 5.

NFκB expression in the kidney was markedly upregulated in $CdCl_2$-exposed untreated rats (Group II) compared with the unexposed control (Group I) and all treatment groups ($p < 0.05$). Among treatment groups, R. vomitoria (Group III) produced the greatest suppression of renal NFκB, demonstrating a significantly stronger modulatory effect on inflammatory signalling than Groups IV and V ($P<0.05$).

Hepatic IL-1β expression was significantly elevated in Group II compared with Group I ($P<0.05$) (Figure 4). Administration of R. vomitoria (Group III) did not significantly reduce hepatic IL-1β ($P>0.05$); however, co-administration of both extracts (Group V) paradoxically upregulated IL-1β expression relative to all other groups ($P<0.05$).

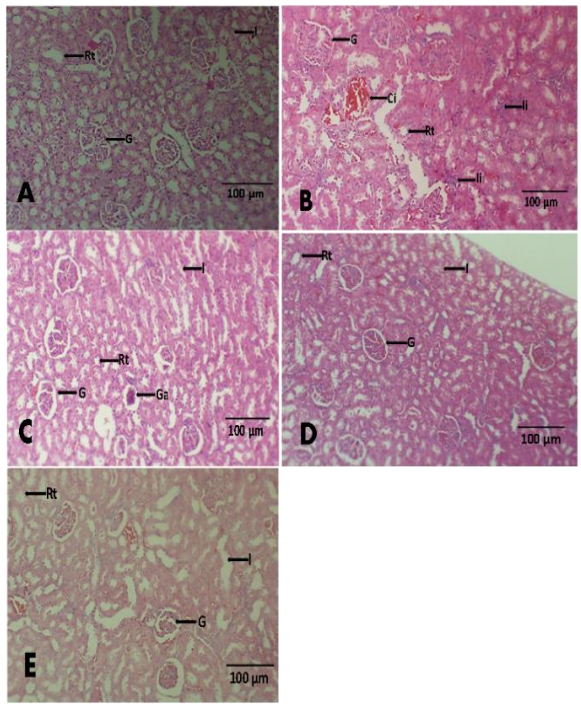

Figure 1. Representative photomicrograph of kidney sections stained with H&E at x100. Scale bar = 100 µm.

A. Group I (Control): normal glomerulus (G), interstitial space (I), renal tubule (Rt).

B. Group II (CdCl2-exposed, untreated): glomerulus (G), congested interstitium (Ci), interstitial inflammation (Ii), renal tubule (Rt).

C. Group III (CdCl2+R. vomitoria): glomerulus (G), interstitium (I), renal tubules (Rt), glomerular atrophy (Ga)

D. Group IV (CdCl2 + A. melegueta): glomerulus (G), renal tubules (Rt), interstitium (I).

E. Group V (CdCl2+ A. melegueta & R. vomitoria): glomerulus (G), renal tubules (Rt), interstitium (I).

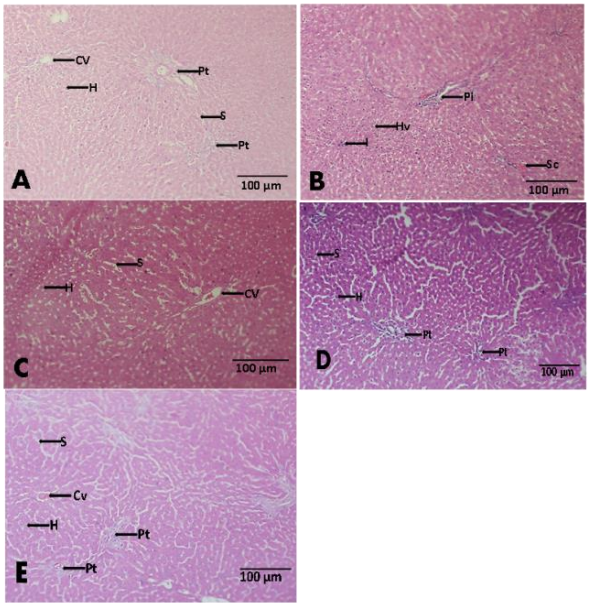

Figure 2. Representative photomicrograph of liver sections stained with H&E at x100 Scale bar = 100 µm

A. Group I (Control): Central venule (Cv), hepatocytes (H), sinusoids (S), portal tract (Pt).

B. Group II (CdCl2-exposed, untreated): portal inflammation (Pi), hepatocytic vacuolation (Hv), inflammation (I), sinusoidal congestion (Sc), hepatocytes (H).

C. Group III (CdCl2 + R. vomitoria): non-inflamed portal tract (Pt), normal sinusoidal spaces (S), normal hepatocyte (H).

D. Group IV (CdCl2 + A. melegueta): non-inflamed portal tract (Pt), hepatocytes (H), and sinusoidal spaces (S).

E. Group V (CdCl2 + A. melegueta & R. vomitoria): non-inflamed portal triad (Pt), central vein (Cv), hepatocytes (H), sinusoidal spaces (S).

Hepatic NFκB expression was significantly elevated in Group II compared to Group I ($P<0.05$), but treatment with either extract individually or in combination did not significantly suppress hepatic NFκB ($P>0.05$).

Collectively, these findings indicate that while both plants modulate inflammatory gene expression, their combined use does not enhance, and may in fact attenuate, the individual anti-inflammatory effects observed with single-agent treatment.

Table 2. Relative mRNA expression levels of NFκB and IL-1β in the liver and kidneys of rats

Parameter	Group I	Group II	Group III	Group IV	Group V
Kidney (NFKB)	66.49±3.5a	107.0±7.3b	76.28±1.4ac	97.23±3.6b	90.40±3.5b
Liver (IL-1B)	69.90±3.1a	89.28±2.3b	90.46±0.8b	75.71±1.3ac	137.20±3.6d
Liver (NF-KB)	61.09±5.5a	91.61±2.0b	97.5±2.9b	89.4±0.9b	86.95±3.2b

Values are expressed as mean ± SD (n=5). Mean values of the same row sharing the same superscript are not significantly different ($P>0.05$) according to Tukey's post hoc test following one-way ANOVA.

Keys:
Group I: unexposed control
Group II: CdCl2-exposed, untreated
Group III: CdCl2 + R. vomitoria treatment
Group IV: CdCl2 + A melegueta treatment
Group V: CdCl2 + A. melegueta + R. vomitoria.

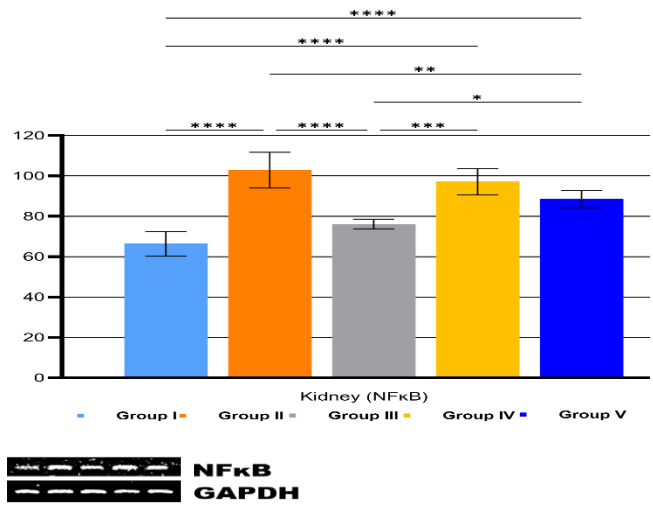

Figure 3. Relative mRNA expression levels of NFκB in the kidneys across all the groups

Statistical analysis was performed by one-way ANOVA followed by Tukey's post hoc test (P<0.05). **** (P<0.0001) denotes a significant difference between group I and group II, IV and V; **** (P<0.0001) denotes a significant difference between group II and III; *** (P<0.001) denotes a significant difference between group III and IV; ** (P<0.01) denotes no significant difference between group II and V; while * (P<0.05) denotes a significant difference between group III and V.

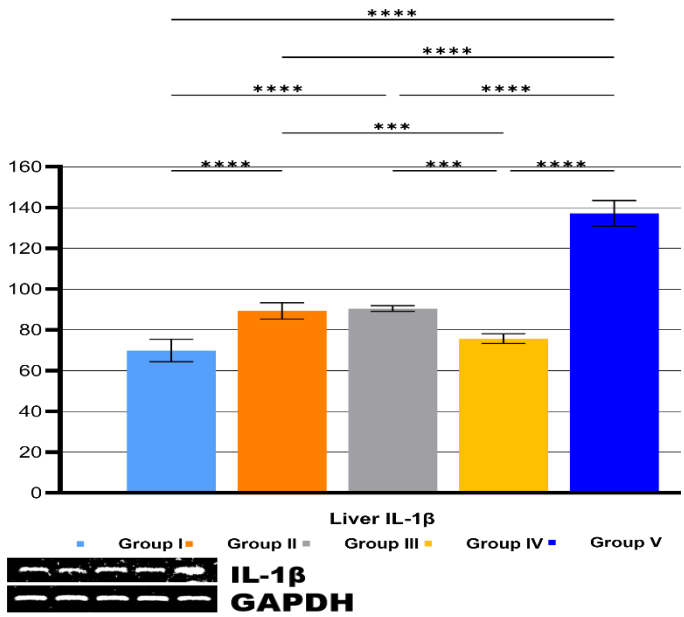

Figure 4. Relative mRNA expression of IL-1β in the liver across all the groups
Statistical analysis was performed by one-way ANOVA followed by Tukey's post hoc test (P<0.05). **** (P<0.0001) denotes a significant difference between group I and group II, III & V; *** (P<0.001) and **** (P<0.0001) denotes a significant difference between group II and IV & V.

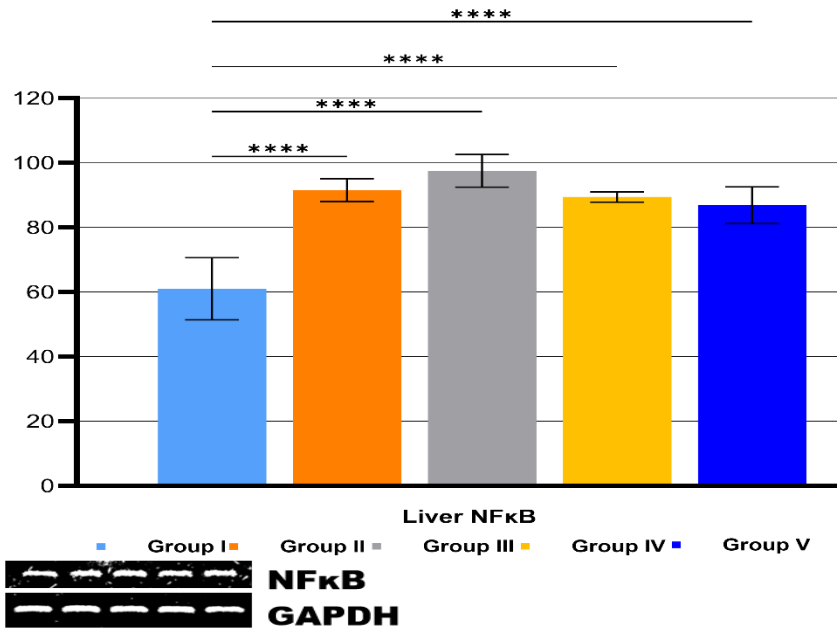

Figure 5. Relative mRNA expression of NFκB in the liver across all the groups

Statistical analysis was performed by one-way ANOVA followed by Tukey's post hoc test (P<0.05). **** (P<0.0001) denotes a significant difference between group I and group II, III, IV & V.

Discussion

Cadmium is a toxic heavy metal that accumulates progressively in the body due to persistent environmental and occupational exposure (7, 9). Phytochemicals naturally present in foods and medicinal plants play a crucial role in mitigating oxidative stress-related chronic diseases through their antioxidant properties (14, 33). In this study, histopathological analysis of $CdCl_2$-exposed untreated rats (Group II) revealed severe hepatic lesions, including hepatocytic vacuolation, ballooning degeneration, sinusoidal dilation, vascular congestion, and Kupffer cell activation. Corresponding renal pathology included severe interstitial dilation with mononuclear infiltration, periglomerular inflammation, and tubular distortion with reduced luminal spaces. These findings are consistent with those of Afework et al. (36) and Alharbi et al. (37), who documented hepatocellular disintegration, cytoplasmic vacuolation, nuclear pyknosis, and renal tubular necrosis following cadmium exposure.

mRNA expression analysis further demonstrated significant upregulation of NFκB and IL-1β in the liver and kidneys of $CdCl_2$-exposed untreated (Group II) rats, corroborating the observations of Das and Al-Naemi (38), who reported similar elevations of pro-inflammatory markers in cadmium toxicity. In contrast, treatment with A. melegueta and R. vomitoria (Group III – V) at 200 mg/kg body weight markedly ameliorated hepatic and renal lesions, highlighting their protective and restorative effects against $CdCl_2$-induced hepatorenal toxicity. Previous reports documented that methanolic extracts of R. vomitoria mitigated toxicity associated with potassium dichromate and sodium arsenite in mice by reducing oxidative stress and fortifying the antioxidant system (39). Our previous study also demonstrated that these plant extracts mitigate oxidative stress as evidenced by significant reductions in tumour necrosis factor alpha (TNF-α) and interleukin 6 (IL-6), alongside marked increases in superoxide dismutase (SOD) and glutathione peroxidase (GPx) activities, while reversing histoarchitectural alterations (40).

The ameliorative features observed in A. melegueta-treated rats (Group IV) are indicative of ongoing repair of cadmium-induced renal and hepatic impairment. Oyinloye et al. (41) documented comparable dose-dependent amelioration with A. melegueta at 200 and 400 mg/kg body weight, attributing its effects to the radical-scavenging activity of its bioactive constituents.

Nwozo and Oyinloye (42) further confirmed its hepatoprotective effects in ethanol-induced toxicity. Key bioactive constituents of A. melegueta, including theophylline, sparteine, 6-gingerol, 6-paradol, and shogaol derivatives, contribute to its free radical scavenging and cytoprotection (14, 43, 44). The ameliorative role observed in this study has been linked to its modulation of oxidative stress biomarkers and inflammatory mediators such as NFκB and IL-1β. Histopathological assessment of the liver from A. melegueta-treated rats showed normal hepatic architecture, devoid of congestion and inflammatory infiltration, in contrast to the $CdCl_2$-exposed untreated group. This qualitative improvement supports the plant's antioxidant and anti-inflammatory actions, indicating effective mitigation of $CdCl_2$-induced hepatic injury and partial restoration of tissue integrity.

The mRNA expression data showed relative suppression of renal NFκB in Group IV compared with Group II and other treatment groups. Earlier studies corroborate this finding, reporting upregulation of IL-10 and Nrf2 alongside histological improvement in cadmium-exposed rats treated with A. melegueta (34). Its immunomodulatory influence on renal tissue and cardiopulmonary protective effects have also been independently documented (16, 45). The leaf extract significantly reversed $CdCl_2$-induced alterations in antioxidant enzyme activities, inflammatory markers, and histoarchitectural integrity; specifically, treatment with A. melegueta markedly enhanced the activities of SOD and GPx, while significantly reducing IL-6 and TNF-α levels.

The hepatic and renal recovery observed in R. vomitoria-treated rats (Group III) further supports its pharmaco-restorative capacity, consistent with prior reports on the preservation of hepatic and renal architecture (46). Significant downregulation of myeloperoxidase in R. vomitoria- and A. melegueta-treated animals was also previously reported (16). The relative suppression of NFκB in A. melegueta–treated rats aligns with its known anti-inflammatory activity (43, 47). Supporting the antioxidative effects observed here, El-Halawany et al. (48) demonstrated that A. melegueta markedly reduces elevated alanine aminotransferase (ALT), thiobarbituric acid reactive substances (TBARS), TNF-α, IL-1β, and caspase-3 and -9, while restoring hepatic glutathione (GSH) in CCl_4-induced liver injury. Reversal of $CdCl_2$-induced depletion of SOD and GPx, and reductions in IL-6 and TNF-α in cardiopulmonary tissues have also been documented following A. melegueta administration (41-42, 45). These effects are plausibly mediated by the flavonoids, alkaloids, terpenoids, and saponins identified in A. melegueta leaf extracts (49).

Histopathological evaluation of co-treated rats (Group V) revealed apparently normal renal and hepatic architecture, with normal glomeruli, tubules, and portal structures, and an absence of mononuclear cell infiltration. Mild residual interstitial congestion in the kidneys may reflect the duration of the study rather than treatment inefficacy. The absence of inflammation and glomerular distortion corroborates the anti-inflammatory potential of both plant extracts. Similarly, hepatic histology showed preserved architecture, consistent with previous reports (34, 40, 41).

Notwithstanding these histological improvements, a paradoxical and significant elevation of hepatic IL-1β was observed in Group V relative to all other groups, alongside elevated renal NFκB compared with Group IV. These divergent molecular findings suggest that the combined extract may exert antagonistic interactions at the transcriptional level. It is well established that constituent phytochemicals such as polyphenols, flavonoids, alkaloids,

and terpenoids can engage in antagonistic interactions when combined, despite their individual beneficial activities (50). Furthermore, the hepatotoxicity reported for R. vomitoria at 300 mg/kg in chronic administration (51) and the significant IL-1β upregulation observed here at 200 mg/kg in combination suggest that caution is warranted in the co-administrative use of both plants, notwithstanding reports of safety in acute exposures (52). Adefegha et al. (53) and Kadiri and Apiamu (54) have additionally documented the antioxidative potential of A. melegueta in hypercholesterolaemic and cyanide-induced hepatotoxicity models, respectively, further establishing its broad hepatoprotective utility.

Collectively, these findings indicate that A. melegueta and R. vomitoria possess significant pharmaco-restorative, antioxidant, and anti-inflammatory potentials capable of mitigating cadmium-induced oxidative and inflammatory damage in hepatic and renal tissues.

Conclusion

This study confirms the hepatotoxic and nephrotoxic effects of cadmium exposure, as evidenced by severe histopathological alterations alongside marked upregulation of NFκB and IL-1β mRNA expression. Treatment with R. vomitoria conferred marked hepatoprotection and mild nephroprotection, while A. melegueta exhibited robust restorative and anti-inflammatory effects in both organs. Co-administration of both extracts yielded near-normal histological profiles, suggesting partial synergistic protection; however, paradoxical IL-1β upregulation in co-treated animals warrants caution. Both plants demonstrate significant antioxidant and pharmaco-restorative properties capable of attenuating cadmium-induced oxidative and inflammatory injury, with modulation of NFκB and IL-1β mRNA expression underscoring their potential as natural protective agents against heavy-metal-induced organ toxicity. Future studies should elucidate the molecular basis of their combined effects, particularly potential antagonistic phytochemical interactions, to further optimise their therapeutic application.

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Original Article

Phytomodulation of NF-κB and IL-1β and Histopathological Alterations in Cadmium Chloride–Induced Hepatorenal Injury in Rats Treated with Aframomum Melegueta and Rauvolfia Vomitoria

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Abstract:

Introduction: *Cadmium, classified as a Group I human carcinogen by the International Agency for Research on Cancer (IARC), induces toxicity primarily through oxidative stress driven by the excessive reactive oxygen species (ROS) generation, triggering inflammatory responses and causes multi-organ damage, particularly in the liver and kidneys. This study evaluated the histopathological and molecular changes associated with cadmium chloride ($CdCl_2$)-induced hepatorenal toxicity and the protective effects of methanolic extracts of Aframomum melegueta and Rauvolfia vomitoria in adult male Wistar rats.*

Methods: *Twenty-five rats weighing 200 g each were randomly assigned to five groups (n=5). Group I was administered only distilled water without CdCl2 exposure, while Groups II–V received $CdCl_2$ (12 mg/kg body weight) by oral gavage once weekly. Group II remained untreated, Groups III and IV received R. vomitoria or A. melegueta, respectively, at a dose of 200 mg/kg body weight, while Group V received a combined treatment of both extracts. After 28 days, liver and kidney tissues were collected for histopathological examination and mRNA expression analysis of nuclear factor kappa B (NFκB) and interleukin-1 beta (IL-1β).*

Results: *$CdCl_2$ exposure significantly increased NFκB and IL-1β expression ($P<0.05$), indicating enhanced inflammatory signalling response and tissue injury. Treatment with either A. melegueta or R. vomitoria significantly downregulated these pro-inflammatory markers and ameliorated $CdCl_2$-induced histopathological damage. However, co-administration of both extracts did not produce additional protective effects.*

Conclusion: *A. melegueta and R. vomitoria individually attenuate $CdCl_2$-induced hepatorenal toxicity by modulating NFκB and IL-1β pathways, while their combined use offers no added benefit.*

Keywords: Cadmium-chloride, Ecotoxicology, Hepatorenal protection, Immunomodulation, Oxidative stress, Phytotherapy.

Conflict of Interest: No

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