

Research Article

Effect of Hydromethanolic Leaf Extracts of *Chromolaena odorata* and *Carica papaya* on Inflammatory Markers and Digestive Enzyme Activities of Cadmium Damage in Rats

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Abstract

Background: Cadmium (Cd) is an environmental toxicant associated with inflammation and gastrointestinal injury. Cadmium-induced intestinal injury is associated with inflammatory activation and impairment of intestinal epithelial and brush-border functions. This study evaluated the effects of hydromethanolic leaf extracts of *Carica papaya* (HECP) and *Chromolaena odorata* (HECO), administered individually and in combination, on inflammatory markers and intestinal enzyme activities in cadmium-exposed Wistar rats. **Materials and Methods:** Sixty-four Wistar rats were randomly assigned to eight groups. Intestinal injury was induced with cadmium chloride (20 mg/kg) orally for 14 days. This was followed by 14 days of treatment with *C. papaya* extract (300 or 600 mg/kg), *C. odorata* extract (250 or 500 mg/kg), or combined extracts (300 or 600 mg/kg). Serum cadmium, interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF- α), lipase, trypsin and intestinal fatty acid-binding protein (I-FABP), together with intestinal alkaline phosphatase (ALP) and histopathology of mid-jejunal tissues were assessed. Data were analyzed using SPSS version 25.0. **Results:** Cadmium significantly increased IL-6, TNF- α , lipase, trypsin and I-FABP activities, while intestinal ALP activity was significantly reduced ($p < 0.001$). Histologically, cadmium caused villous atrophy, villous fusion, epithelial disruption and crypt changes. IL-6 increased from 17.10 ± 2.01 pg/mL in controls to 198.57 ± 7.88 pg/mL in cadmium-exposed rats. High-dose *C. papaya* reduced IL-6 to 25.83 ± 0.73 pg/mL. TNF- α increased from 38.13 ± 1.91 to 52.17 ± 2.54 pg/mL; the high-dose combined extract produced 29.47 ± 4.92 pg/mL. Intestinal ALP decreased from 537.67 ± 20.13 to 242.67 ± 13.80 IU/L and increased to 430.33 ± 13.58 IU/L with high-dose combined treatment. Lipase and trypsin and I-FABP returned to near-normal values after extract treatment with the high-dose combined extract showing the most favourable overall pattern. There was an improved histological recovery. **Conclusion:** These findings suggest that Hydromethanolic extracts of *C. papaya* and *C. odorata* attenuated cadmium-associated inflammatory responses and disturbances in intestinal enzyme activities while enhancing tissue-protective mechanisms in wistar rats.

Keywords

Cadmium, Intestinal Injury, *Carica Papaya*, *Chromolaena Odorata*, Tumour Necrosis Factor-alpha, Interleukin-6, Intestinal Alkaline Phosphatase, Wistar Rats

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1. Introduction

Cadmium is an environmental toxicant which is able to illicit inflammatory responses as well as cause tissue injuries or damage [1]. Cadmium contamination arises from anthropogenic and natural activities leading to its accumulation in soil, water, and biota [2]. Human exposure occurs principally through contaminated food and water, tobacco smoke and occupational sources. Cadmium can accumulate in biological systems and interfere with cellular signaling and normal organ function [3]. The gastrointestinal tract is an important target following oral exposure because intestinal epithelial cells encounter cadmium before systemic distribution. Current evidence indicates that cadmium can disturb intestinal homeostasis through oxidative and inflammatory mechanisms and may alter intestinal barrier function and the gut microbiota [3, 4]. Ingestion of contaminated food and water represents the predominant exposure pathway for cadmium toxicity [5].

Inflammatory mediators are very important indicators that shows tissue responses to toxicant exposure. Interleukin-6 (IL-6) and tumour necrosis factor- α (TNF- α) are involved in inflammatory signaling and may increase during cadmium-associated cellular injury. Experimental studies have also demonstrated cadmium-related disruption of intestinal barrier integrity and systemic inflammatory responses [6].

Intestinal enzymes provide additional information about tissue function. Intestinal alkaline phosphatase (ALP) is associated with the intestinal brush border and contributes to intestinal homeostasis and barrier-related functions [7, 8]. Altered ALP activity may therefore accompany epithelial dysfunction. Lipase and trypsin are digestive enzymes whose circulating concentrations can be affected by disturbances involving the gastrointestinal and digestive systems, although they are not specific markers of enterocyte injury. Damage to intestinal epithelial cells can result in increased circulating intestinal fatty acid-binding protein (I-FABP), while alterations in digestive enzyme homeostasis and brush-border enzymes may accompany structural injury [9, 10].

Medicinal plants with antioxidant and anti-inflammatory properties are being investigated as possible modulators of toxicant-associated injury. *Carica papaya* leaves contain diverse phytochemicals and have documented antioxidant and anti-inflammatory activities [11, 12]. *Chromolaena odorata* has also demonstrated anti-inflammatory activity in experimental studies [13, 14]. However, evidence concerning their effects on inflammatory markers and intestinal enzyme activities in cadmium-induced intestinal injury remains limited. This study therefore investigated the effects of hydro methanolic leaf extracts of *C. papaya* and *C. odorata*, individually and in combination, on IL-6, TNF- α , intestinal ALP, lipase and trypsin in cadmium-exposed Wistar rats.

2. Materials and Methods

2.1. Experimental Animals

Sixty-four albino Wistar rats weighing 150–200 g were used for the study. Animals were acclimatized and maintained under standard laboratory conditions at approximately 25–31°C with a 12-h light/dark cycle and free access to standard rat feed and drinking water *ad libitum*, and all animal handling was conducted in accordance with NIH Ethical Guidelines for Care and Use of Laboratory Animals [15].

2.2. Extract Preparation

Leaves of *C. papaya* and *C. odorata* were collected in Rumuosi and Choba, Port Harcourt, Rivers State, Nigeria, and authenticated with voucher numbers UPH/P/450 and UPH/P/451, respectively. Extraction was carried out according to the maceration method described by Sofowora [16], using 70% methanol (25 g leaf powder in 100 mL methanol) with mechanical agitation at room temperature. The suspension was filtered through a mesh and Whatman No. 1 paper, concentrated in an evaporating dish in a water bath (~55°C), and air-dried in a fume hood until constant weight. Crude extracts were stored at 4°C. Combined extract was prepared at a 1:1 (w/w) ratio.

2.3. Chemicals

20 mg/kg oral Cadmium chloride administered for 13 days was used for induction of intestinal injury which was confirmed by biochemical and histopathological evidence of intestinal injury. Phosphate-buffered saline (PBS; pH 7.4) and 10% neutral buffered formalin were used for preparation and tissue fixation following the cold spring harbour protocol [17]. Analytical-grade reagents were used throughout.

2.4. Dose Selection and Experimental Groups

Treatment doses were 300 and 600 mg/kg for *C. papaya*, 250 and 500 mg/kg for *C. odorata*, and 300 and 600 mg/kg for the combined extract as adopted from the study of Igattah et al [18].

Rats were allocated to eight groups: Group 1, normal control; Group 2, cadmium toxicity; Groups 3 and 4, cadmium + low- and high-dose *C. papaya*; Groups 5 and 6, cadmium + low- and high-dose *C. odorata*; and Groups 7 and 8, cadmium + low- and high-dose combined extracts. Cadmium was given for 14 days, followed by extract treatment for 14 days.

Sixty-four rats were randomly assigned to eight groups ($n = 8$), based on the following treatment schedule:

- 1) *Group 1 (Negative Control)*: feed and water only.
- 2) *Group 2 (Positive Control)*: cadmium chloride 20 mg/kg orally for 14 days; then feed and water for another 14 days.

- 3) *Group 3*: cadmium 20 mg/kg for 14 days; then HECF 300 mg/kg for 14 days.
- 4) *Group 4*: cadmium 20 mg/kg for 14 days; then HECF 600 mg/kg for 14 days.
- 5) *Group 5*: cadmium 20 mg/kg for 14 days; then HECO 250 mg/kg for 14 days.
- 6) *Group 6*: cadmium 20 mg/kg for 14 days; then HECO 500 mg/kg for 14 days.
- 7) *Group 7*: cadmium 20 mg/kg for 14 days; then combined extract 300 mg/kg for 14 days.
- 8) *Group 8*: cadmium 20 mg/kg for 14 days; then combined extract 600 mg/kg for 14 days.

Treatments were administered orally by gavage. All animals had free access to standard pellets and water.

2.5. Sample Collection and Analysis

At the end of cadmium induction (day 14), three rats per group were sacrificed for assessment of the respective analytes. After the 14-day treatment phase, the remaining animals were euthanized under anesthesia, and blood was collected by cardiac puncture. Serum was separated for biochemical assays. Mid-jejunal segments were excised, homogenized for ALP analysis. The Mid-jejunal tissues were fixed in 10% formalin, processed through graded alcohol and xylene, embedded in paraffin, sectioned and stained with haematoxylin and eosin. Sections were examined microscopically and photomicrographs obtained at $\times 100$ magnification.

At the end of treatment, blood was collected and serum separated by centrifugation at 3,000 rpm for 5 min. IL-6 was measured by fluorescence immunoassay. TNF- α , lipase and

trypsin were determined using ELISA methods. Intestinal tissue was collected and ALP activity was determined by kinetic colorimetry using a Mindray BS-120 analyzer. I-FABP was quantified by sandwich ELISA with HRP-conjugated detection and colorimetric measurement at 450 nm.

2.6. Statistical Analysis

Results were expressed as mean $\pm$ SD. One-way analysis of variance followed by Tukey post-hoc testing was used to compare groups. Statistical significance was set at $p < 0.05$ using SPSS version 25.0.

3. Results

Table 1 showed that cadmium exposure produced a marked inflammatory response and significant changes in intestinal enzyme-related parameters. IL-6 was 17.10 ± 2.01 pg/mL in the normal control and increased to 198.57 ± 7.88 pg/mL in the cadmium control. Treatment reduced IL-6 in all extract-treated groups, with high-dose C. papaya producing 25.83 ± 0.73 pg/mL.

TNF- α increased from 38.13 ± 1.91 pg/mL in the normal control to 52.17 ± 2.54 pg/mL in the cadmium control. Extract treatment reduced TNF- α , with the high-dose combined extract producing the lowest observed concentration (29.47 ± 4.92 pg/mL).

Intestinal ALP activity decreased markedly after cadmium exposure, from 537.67 ± 20.13 IU/L in the normal control to 242.67 ± 13.80 IU/L. Treatment increased ALP activity, with high-dose combined extract producing 430.33 ± 13.58 IU/L.

Table 1. Mean $\pm$ SD of Inflammatory markers and intestinal alkaline phosphatase Levels Across the Experimental Groups in Albino Rats.

Group	IL-6 (pg/mL)	TNF- α (pg/mL)	Intestinal ALP (IU/L)
1 Normal control	17.10 ± 2.01^a	38.13 ± 1.91^a	537.67 ± 20.13^a
2 Cadmium control	198.57 ± 7.88^b	52.17 ± 2.54^b	242.67 ± 13.80^b
3 C. papaya 300 mg/kg	28.73 ± 1.85^c	38.10 ± 3.32^a	283.67 ± 19.63^c
4 C. papaya 600 mg/kg	25.83 ± 0.73^c	37.33 ± 3.27^a	327.00 ± 10.82^d
5 C. odorata 250 mg/kg	56.57 ± 1.24^d	34.37 ± 3.16^a	379.00 ± 6.56^e
6 C. odorata 500 mg/kg	64.47 ± 4.51^e	36.50 ± 1.48^a	421.67 ± 13.50^f
7 Combined 300 mg/kg	30.93 ± 0.35^c	32.47 ± 1.27^a	401.67 ± 10.02^e
8 Combined 600 mg/kg	33.97 ± 3.25^c	29.47 ± 4.92^c	430.33 ± 13.58^f
F-value	823.598	15.549	129.030
p-value	<0.001	<0.001	<0.001
Remark	SS	SS	SS

KEY: Values in the same column with different superscripts differ significantly at $p < 0.05$. IL6 = Interleukin-6, TNF = Tumour Necrosis Factor, ALP = Alkaline Phosphatase, SS = Statistically Significant, NS = Not Significant ($p > 0.05$).

Comparison of lipase, trypsin, and IFABP levels across the experimental groups in the serum of albino rats is shown in Table 2. Lipase increased from 72.33 ± 0.58 in controls to 103.00 ± 2.65 in the cadmium group. Treatment generally reduced lipase toward control values; high-dose *C. papaya*, both low and high dose of *C. odorata* doses and high-dose combined treatment were not significantly different from the normal control. Trypsin increased from 46.00 ± 3.61 in controls to 56.33 ± 5.69 in cadmium-exposed rats. Treatment generally reduced trypsin, with high-dose combined extract producing a low level of Trypsin (32.67 ± 2.08 , $P=0.001$). IFABP levels in the cadmium-treated positive control group (Group 2: 137.67 ± 6.11 pg/mL) were significantly higher than those of the normal control group (Group 1: 80.67 ± 8.02 pg/mL). However,

in Group 3, the level was (90.67 ± 6.03 pg/mL; cadmium + low-dose *Carica papaya*), Group 5 (82.33 ± 2.08 pg/mL; cadmium + low-dose *Chromolaena odorata*), Group 6 (80.33 ± 4.04 pg/mL; cadmium + high-dose *Chromolaena odorata*), Group 7 (92.00 ± 6.08 pg/mL; cadmium + low-dose combined extract), and Group 8 (78.33 ± 0.58 pg/mL; cadmium + high-dose combined extract) were not significantly different from the normal control group but were significantly lower than the positive control group. Group 4 (96.00 ± 3.61 pg/mL; cadmium + high-dose *Carica papaya*) showed significantly higher IFABP levels than in the normal control group ($p < 0.001$).

Table 2. Mean $\pm$ SD of Some Intestinal Enzymes and IFABP Levels Across the Experimental Groups in Albino Rats.

Group	Lipase (pg/mL)	Trypsin (pg/mL)	IFABP (pg/mL)
1 Normal control	72.33 ± 0.58^a	46.00 ± 3.61^a	80.67 ± 8.02^a
2 Cadmium control	103.00 ± 2.65^b	56.33 ± 5.69^b	137.67 ± 6.11^b
3 <i>C. papaya</i> 300 mg/kg	90.67 ± 1.16^c	43.00 ± 5.20^a	90.67 ± 6.03^a
4 <i>C. papaya</i> 600 mg/kg	72.67 ± 2.08^a	43.33 ± 4.73^a	96.00 ± 3.61^c
5 <i>C. odorata</i> 250 mg/kg	73.67 ± 2.52^a	46.00 ± 2.65^a	82.33 ± 2.08^a
6 <i>C. odorata</i> 500 mg/kg	72.00 ± 3.46^a	43.67 ± 5.51^a	80.33 ± 4.04^a
7 Combined 300 mg/kg	86.33 ± 3.06^c	44.67 ± 3.79^a	92.00 ± 6.08^a
8 Combined 600 mg/kg	73.00 ± 1.00^a	32.67 ± 2.08^c	78.33 ± 0.58^a
F-value	69.024	6.574	43.431
p-value	<0.001	0.001	<0.001
Remark	SS	SS	SS

4. Discussion

Cadmium exposure produced a clear inflammatory response, demonstrated by substantial increases in IL-6 and TNF- α . IL-6 increased more than tenfold relative to the normal control, while TNF- α also increased significantly. These findings are consistent with current evidence that cadmium toxicity involves oxidative stress and inflammatory signaling, with the gastrointestinal tract representing an important target following oral exposure [3, 4].

Treatment with the plant extracts attenuated the inflammatory response. High-dose *C. papaya* produced the strongest numerical reduction in IL-6 among the treatment groups, bringing the value close to the normal-control concentration. This response is compatible with reports describing antioxidant and anti-inflammatory

activities of *C. papaya* leaf phytochemicals [12]. On the other hand, *C. odorata* also reduced inflammatory markers, consistent with experimental evidence of anti-inflammatory activity of its extracts [14].

The high-dose combined extract produced the lowest TNF- α concentration among the treatment groups. Ursolic acid has been associated with reductions in inflammatory mediators in experimental studies [18, 19] while several constituents identified in *C. odorata*, including phenolic and flavonoid compounds, have documented anti-inflammatory activities [19, 20]. This finding suggests a substantial response for this particular inflammatory endpoint as seen in the low TNF- α level observed with the combined extract indicating a favourable effect of the extracts to attenuate the inflammatory response associated with cadmium exposure. However, the different responses observed across IL-6 and TNF- α also indicate that the extracts may not act uniformly across inflammatory pathways.

The marked reduction in intestinal ALP following cadmium exposure indicates disturbance of intestinal brush-border-associated enzyme activity. Intestinal ALP has recognized roles in intestinal homeostasis and barrier-related functions [8]. Recovery of ALP activity following treatment, particularly with high-dose *C. odorata* and high-dose combined extract, is therefore consistent with improvement in intestinal tissue function as a result of the phytochemicals in the extract [19, 20]. Nevertheless, ALP activity alone cannot establish epithelial regeneration or complete restoration of barrier integrity though the relatively favourable responses observed with the combined extract were also consistent with their effects on several other markers of intestinal injury.

Lipase and trypsin were also significantly altered by cadmium exposure and generally were attenuated toward control values following treatment. The normalization of lipase in several treatment groups and the reduction in trypsin, particularly with high-dose combined extract, suggest improvement in digestive enzyme homeostasis [20, 21]. The alterations in serum lipase and trypsin may also reflect disruption of digestive enzyme homeostasis associated with tissue injury. However, because these enzymes are not specific markers of enterocyte damage, they should be interpreted alongside I-FABP. [21-23] Because circulating lipase and trypsin are not specific biomarkers of intestinal epithelial injury, these findings are best interpreted together with inflammatory and tissue-specific markers rather than as independent proof of intestinal repair [23-25]. The response of I-FABP is particularly relevant because it is predominantly expressed in intestinal epithelial cells and is released into the circulation following epithelial injury, making it a useful marker of intestinal mucosal damage [25, 26]. The marked elevation observed in the cadmium-exposed group therefore supports the presence of intestinal epithelial injury. Treatment with the extracts substantially reduced I-FABP, with the high-dose combined treatment producing values of 78.33 ± 0.58 ng/mL, compared with 80.67 ± 8.02 ng/mL in the normal control.

Taken together, the findings demonstrate concordant improvement in inflammatory markers and intestinal enzyme activities following treatment with *C. papaya*, *C. odorata* and their combination. The pattern was endpoint-dependent: *C. papaya* at 600 mg/kg was particularly associated with reduction of IL-6, *C. odorata* at 500 mg/kg and the high dose combined extract showed a strong response for intestinal ALP, and the high-dose combination showed favourable responses for TNF- α , lipase and trypsin. Thus, not making any of the treatment groups uniformly superior over the other.

The study has limitations. Specific molecular inflammatory pathways were not directly measured, and intestinal permeability and tight-junction proteins were not assessed. In addition, lipase and trypsin lack specificity for intestinal epithelial injury, while ALP activity alone is insufficient to establish restoration of the complete brush-border system. Future work should incorporate quantitative histology, tight-junction proteins, intestinal permeability measurements.

5. Conclusion

The present study demonstrated that oral cadmium chloride exposure produced biochemical and intestinal injury. Hydromethanolic leaf extracts of *Carica papaya* and *Chromolaena odorata* attenuated cadmium-associated inflammatory responses and disturbances in intestinal enzyme activities in Wistar rats. Cadmium exposure markedly increased IL-6, TNF- α , lipase and trypsin while reducing intestinal ALP activity. Extract treatment generally shifted these parameters toward normal values. High-dose *C. papaya* showed a particularly marked effect on IL-6, high-dose *C. odorata* produced substantial recovery of intestinal ALP, and high-dose combined extract produced favourable responses for TNF- α , lipase and trypsin. the combined extract—especially at high dose—produced the most favourable overall pattern of anti-inflammatory. These findings support the potential therapeutic value of these widely available medicinal plants for mitigating heavy metal-associated intestinal toxicity.

Abbreviations

ALP	Alkaline Phosphatase
BMI	Body Mass Index
Cd	Cadmium
HECP	Hydromethanolic Leaf Extracts of <i>Carica Papaya</i>
HECO	Hydromethanolic Leaf Extracts of <i>Chromolaena Odorata</i>
TNF- α	Tumour Necrosis Factor-alpha
IL-6	Interleukin-6
I-FABP	Intestinal Fatty Acid-Binding Protein
ELISA	Enzyme Immunosorbant Assay
SPSS	Statistical Package for Social Sciences
SD	Standard Deviation

Author Contributions

Waribo Helen Anthony: Conceptualization, Methodology, Writing – original draft, Writing – review & editing

Igattah Prudence Akachukwu: Data curation, Formal Analysis, Writing – review & editing

Ibitoroko Maureen George-Opuda: Methodology, Software, Writing – review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

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