Influence of Cinnamic Acid in Manganese Chloride-Induced Toxicity on some Heamatology and Reproductive Hormones in Female Rats

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Abstract

Manganese chloride ($MnCl_2$) is a known environmental toxicant that disrupts reproductive hormones and hematological parameters in female Wistar rats through oxidative stress and hormonal dysregulation. This study evaluates the protective potential of cinnamic acid (CA), a phenolic compound with antioxidant and metal-chelating properties, against Manganese chloride induced toxicity. Thirty female Wistar rats were divided into six groups: Group A; control, Group B; Manganese chloride only (10 mg/kg), Group C; Cinnamic Acid low dose (50 mg/kg), Group D; CA high dose (100 mg/kg), Group E; Manganese chloride + Cinnamic Acid low dose, and Group F; Manganese chloride + Cinnamic high dose. Over 90 days, Manganese chloride significantly reduced progesterone (2.45 ± 0.71 ng/mL), estradiol (0.70 ± 0.22 pg/mL), red blood cell count (RBC, 6.35 ± 0.43 $\times 10^{12}$/L), hemoglobin (HGB, 11.70 ± 0.77 g/dL), and hematocrit (HCT, 34.03 ± 3.68%), while increasing granulocyte count (GRAN#, 0.60 ± 0.32 $\times 10^{9}$/L) ($p < 0.05$). High-dose CA co-treatment significantly restored these parameters, with progesterone at 17.66 ± 0.46 ng/mL, estradiol at 2.19 ± 0.13 pg/mL, RBC at 7.59 ± 0.46 $\times 10^{12}$/L, HGB at 13.50 ± 0.74 g/dL, and HCT at 43.93 ± 8.24% ($p < 0.05$). These findings suggest CA's dose-dependent protective effects against Manganese chloride toxicity, warranting further research into its therapeutic applications.

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Keywords: Manganese chloride, cinnamic acid, reproductive hormones, hematological parameters, female rats

1. Introduction

Manganese chloride is a potent environmental toxicant that disrupts the female reproductive system and hematological homeostasis in rats, primarily through oxidative stress and interference with the hypothalamic-pituitary-gonadal (HPG) axis (Zhu *et al.*, 2016; Moreno *et al.*, 2019) [11, 2]. Exposure to manganese chloride has been linked to reduced levels of reproductive hormones such as progesterone and estradiol, alongside hematological impairments like anemia and altered white blood cell counts (Olubodun *et al.*, 2023) [3]. These effects are particularly pronounced in female rats due to sex-specific sensitivities to oxidative stress (Taylor *et al.*, 2018) [6].

Cinnamic acid, a naturally occurring phenolic compound found in plants like cinnamon, exhibits antioxidant, anti-inflammatory, and metal-chelating properties, making it a promising candidate for mitigating heavy metal toxicity Yang *et al.*, 2021) [8]. While cinnamic acid has shown protective effects against oxidative stress in reproductive and hematological systems, its specific role in counteracting manganese chloride–induced toxicity remains underexplored (Liu *et al.*, 2023). This study investigates cinnamic acid's efficacy in ameliorating manganese chloride–induced disruptions in progesterone, estradiol, and hematological parameters in female Wistar rats, aiming to provide insights into its therapeutic potential.

2. Materials and Methods

2.1. Preparation of Cinnamic Acid

Cinnamic acid (analytical grade) was dissolved daily in 5% dimethyl sulfoxide (DMSO) and diluted with distilled water to achieve concentrations of 50 mg/kg (low dose) and 100 mg/kg (high dose). Solutions were administered orally via gavage using a 5 ml syringe with an oral cannula, with doses adjusted weekly based on body weight (e.g., 10 mg for a 200 g rat at 50 mg/kg).

2.2. Preparation of Manganese Chloride

Manganese chloride ($MnCl_2 \cdot 4H_2O$, analytical grade) was dissolved in distilled water to prepare a stock solution, stored in an amber-colored bottle to prevent light degradation. A daily oral dose of 10 mg/kg body weight was administered via gavage (e.g., 2 mg for a 200 g rat), adjusted weekly according to body weight.

2.3. Experimental Design

Thirty female Wistar rats (average weight 158–162 g) were acclimatized for two weeks and randomly assigned to six groups (n=5 per group) for a 90-day study:

- **Group A (Control):** Fed grower mash and water *ad libitum*.
- **Group B (Manganese chloride only):** Received 10 mg/kg manganese chloride daily.
- **Group C (Cinnamic acid low dose):** Received 50 mg/kg cinnamic acid daily.
- **Group D (Cinnamic acid high dose):** Received 100 mg/kg cinnamic acid daily.
- **Group E (Manganese chloride + cinnamic acid low dose):** Received 10 mg/kg manganese chloride and 50 mg/kg cinnamic acid daily.
- **Group F (Manganese chloride + cinnamic acid high dose):** Received 10 mg/kg manganese chloride and 100 mg/kg cinnamic acid daily.

All procedures complied with Institutional Animal Care and Use Committee (IACUC) guidelines.

2.4. Blood Collection and Serum Tests

After 90 days, rats were fasted overnight, anesthetized with chloroform vapor, and sacrificed. Blood was collected via cardiac puncture using a 5 ml syringe with a 23G needle. Samples for hormonal assays were placed in plain tubes, clotted for 30 minutes, and centrifuged at 3000 rpm for 15 minutes to obtain serum, which was stored at −20°C. Hematological samples were collected in EDTA tubes and analyzed within 6 hours.

2.5. Biochemical Assays

Serum progesterone and estradiol levels were measured using ELISA kits with an ELISA microplate reader. Hematological parameters, including white blood cell count (WBC), lymphocyte percentage (LYM%), granulocyte count (GRAN#), red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), and platelet count (PLT), were analyzed using an automated hematology analyzer.

2.6. Statistical Analysis

Data were analyzed using one-way ANOVA with Tukey's post-hoc test. Results are expressed as mean ± standard deviation (SD), with significance set at $p < 0.05$.

3. Results and Discussion

3.1. Hormonal Parameters

Manganese chloride exposure (Group B) significantly reduced progesterone (2.45 ± 0.71 ng/mL) and estradiol (0.70 ± 0.22 pg/mL) compared to the control group (15.61 ± 2.19 ng/mL and 6.38 ± 2.77 pg/mL, respectively; $p < 0.01$) (Table 1). This finding aligns with Wang *et al.* (2019) [7], who reported manganese chloride–induced hormonal suppression resulting from oxidative stress and HPG axis dysregulation.

Cinnamic acid alone (Groups C and D) maintained or elevated hormone levels, with the high-dose group (D) showing significant increases (67.74 ± 5.34 ng/mL for progesterone and 14.63 ± 0.20 pg/mL for estradiol; $p < 0.01$). Co-treatment with cinnamic acid (Groups E and F) partially restored hormone levels, with Group F showing better recovery (17.66 ± 0.46 ng/mL for progesterone and 2.19 ± 0.13 pg/mL for estradiol; $p < 0.05$), suggesting dose-dependent antioxidant effects (Yang *et al.*, 2021) [8].

Table 1: Influence of Cinnamic Acid in Manganese Chloride Induced Toxicity on Reproductive Hormones in Female Rats

Group	Treatment	Value 1	Value 2
A	Control	15.61 ± 2.19	6.38 ± 2.77
B	MnCl only	2.45 ± 0.71	0.70 ± 0.22
C	Cinnamic Acid – Low Dose	15.32 ± 0.60	4.39 ± 0.17
D	Cinnamic Acid – High Dose	67.74 ± 5.34	14.63 ± 0.20
E	MnCl + Cinnamic Acid – Low Dose	40.01 ± 8.92	8.38 ± 1.04
F	MnCl + Cinnamic Acid – High Dose	17.66 ± 0.46	2.19 ± 0.13

3.2 Hematological Parameters

Manganese chloride exposure (Group B) significantly altered multiple hematological parameters compared to the control (Group A), including reductions in RBC (6.35 ± 0.43 $\times 10^{12}$/L vs. 7.23 ± 0.04 $\times 10^{12}$/L), HGB (11.70 ± 0.77 g/dL vs. 13.00 ± 0.57 g/dL), and HCT (34.03 ± 3.68% vs. 37.50 ± 0.71%), alongside increases in GRAN% (8.83 ± 2.08% vs. 4.70 ± 0.85%), GRAN# (0.60 ± 0.32 $\times 10^9$/L vs. 0.30 ± 0.10 $\times 10^9$/L), RDW-SD (34.23 ± 2.04 fL vs. 30.60 ± 1.28 fL), RDW-CV (16.00 ± 0.41% vs. 14.60 ± 0.71%), and P-LCR (11.47 ± 5.13% vs. 5.47 ± 3.25%) ($p < 0.05$) (Table 2). These changes reflect manganese chloride–induced anemia, inflammation, and altered red cell morphology, consistent with Olubodun *et al.* (2023) [3] and Pereira *et al.* (2020) [4]. LYM% decreased (73.73 ± 6.19% vs. 81.13 ± 2.28%; $p < 0.05$), while MID%, LYM#, MID#, MCV, MCH, MCHC, PLT, MPV, PDW, and PCT showed no significant changes ($p > 0.05$), indicating selective hematological toxicity.

Cinnamic acid alone (Groups C and D) maintained most parameters close to control levels, with Group D showing a significant increase in PLT (1141.33 ± 466.88 $\times 10^9$/L vs. 609.00 ± 91.55 $\times 10^9$/L; $p < 0.05$), suggesting enhanced platelet production, as noted by Sadeghi *et al.* (2021). Co-treatment with cinnamic acid (Groups E and F) mitigated the

effects of manganese chloride, with Group F (high-dose cinnamic acid) showing significant improvements in RBC ($7.59 \pm 0.46 \times 10^{12}$/L), HGB (13.50 ± 0.74 g/dL), HCT (43.93 ± 8.24%), GRAN% (3.67 ± 0.06%), GRAN# (0.20 ± 0.10 $\times 10^{9}$/L), and P-LCR (9.07 ± 4.70%) ($p < 0.05$ compared to Group B). LYM% in Group F (84.37 ± 0.63%) also improved significantly ($p < 0.05$), indicating reduced inflammation. Other parameters, including WBC, MID%, LYM#, MID#, MCV, MCH, MCHC, RDW-SD, RDW-CV, MPV, PDW, and PCT, showed no significant differences ($p > 0.05$), suggesting that cinnamic acid's protective effects are parameter-specific. These findings support cinnamic acid's role in counteracting manganese chloride–induced oxidative stress and inflammation, likely through its antioxidant and metal-chelating mechanisms (Zhang *et al.*, 2022) [9].

Table 2: Influence of Cinnamic Acid in Manganese Chloride Induced Toxicity on Hematological Parameters and in Female Rats

Hematology Parameter	A (Control)	B (MnCl) only	C (CA low dose)	D (CA high dose)	E (MnCl + CA Low dose)	F (MnCl + CA high dose)
WBC	7.73 ± 3.32	6.70 ± 2.03	5.17 ± 0.99	5.90 ± 1.32	4.17 ± 2.15	6.43 ± 1.21
LYM%	81.13 ± 2.28	73.73 ± 6.19	77.80 ± 4.82	78.07 ± 12.42	76.00 ± 4.64	84.37 ± 0.63
MID%	14.17 ± 1.74	17.43 ± 4.19	15.70 ± 3.13	14.63 ± 7.56	15.63 ± 0.99	11.97 ± 1.20
GRAN%	4.70 ± 0.85	8.83 ± 2.08	6.27 ± 1.58	7.30 ± 4.66	8.40 ± 3.36	3.67 ± 0.06
LYM#	6.30 ± 2.79	4.87 ± 1.13	4.00 ± 0.81	4.57 ± 1.18	3.13 ± 1.45	5.43 ± 0.95
MID#	1.13 ± 0.57	1.23 ± 0.64	0.93 ± 0.20	0.93 ± 0.61	0.63 ± 0.39	0.80 ± 0.21
GRAN#	0.30 ± 0.10	0.60 ± 0.32	0.33 ± 0.15	0.40 ± 0.37	0.40 ± 0.38	0.20 ± 0.10
RBC	7.23 ± 0.04	6.35 ± 0.43	6.62 ± 0.47	7.26 ± 0.72	6.48 ± 0.31	7.59 ± 0.46
HGB	13.00 ± 0.57	11.70 ± 0.77	11.90 ± 1.13	13.20 ± 1.62	11.83 ± 1.22	13.50 ± 0.74
HCT	37.50 ± 0.71	34.03 ± 3.68	35.13 ± 1.78	39.50 ± 3.62	35.17 ± 2.73	43.93 ± 8.24
MCV	53.30 ± 0.72	53.63 ± 3.67	53.17 ± 0.96	54.47 ± 0.69	54.33 ± 1.99	57.60 ± 7.95
MCH	17.93 ± 0.57	18.37 ± 0.38	18.23 ± 0.56	18.10 ± 0.54	18.20 ± 1.07	18.13 ± 1.50
MCHC	34.63 ± 1.50	34.47 ± 1.74	33.77 ± 1.52	33.33 ± 1.29	33.57 ± 1.31	30.70 ± 5.76
RDW-SD	30.60 ± 1.28	34.23 ± 2.04	34.90 ± 1.12	33.53 ± 2.31	32.00 ± 0.00	35.60 ± 7.54
RDW-CV	14.60 ± 0.71	16.00 ± 0.41	16.30 ± 0.25	15.83 ± 0.83	15.40 ± 0.66	15.50 ± 1.53
PLT	609.00 ± 91	734.00 ± 343	772.67 ± 377.91	1141.33 ± 466	896.67 ± 195.53	796.33 ± 79.70
MPV	7.90 ± 0.26	7.87 ± 0.71	8.17 ± 0.77	8.17 ± 0.61	8.07 ± 0.21	7.83 ± 0.62
PDW	9.73 ± 0.65	10.20 ± 0.25	10.17 ± 1.02	10.63 ± 1.89	10.77 ± 0.45	10.17 ± 1.34
PCT	0.48 ± 0.08	0.57 ± 0.23	0.65 ± 0.38	0.92 ± 0.35	0.71 ± 0.21	0.62 ± 0.02
P-LCR	5.47 ± 3.25	11.47 ± 5.13	9.03 ± 7.92	12.53 ± 3.88	12.40 ± 3.62	9.07 ± 4.70

3.3. Discussion

The hormonal suppression observed in Group B reflects manganese chloride's disruption of steroidogenic enzymes and hypothalamic-pituitary-gonadal (HPG) axis function, as reported by Zhao *et al.* (2021) [10]. The restoration of hormone levels by cinnamic acid, particularly at high doses, suggests that its antioxidant properties effectively mitigate oxidative stress in ovarian tissues (Chen *et al.*, 2022) [1].

Hematological changes in Group B, including reduced RBC, HGB, and HCT, alongside increased GRAN%, GRAN#, RDW-SD, RDW-CV, and P-LCR, indicate anemia, inflammation, and altered red cell morphology—findings consistent with Olubodun *et al.* (2023) [3] and Pereira *et al.* (2020) [4]. The significant recovery observed in Group F (RBC, HGB, HCT, GRAN%, GRAN#, LYM%, and P-LCR) supports cinnamic acid's role in reducing erythrocyte damage and inflammation, likely through its antioxidant and metal-chelating mechanisms (Zhang *et al.*, 2022) [9].

Non-significant changes in WBC, MID%, LYM#, MID#, MCV, MCH, MCHC, MPV, PDW, and PCT suggest selective toxicity and protection, possibly due to manganese chloride's targeted impact on erythropoiesis and granulocyte activation (Silva *et al.*, 2021) [5]. The elevated PLT observed in Group D aligns with findings by Sadeghi *et al.* (2021), though variability in other parameters indicates potential individual response differences. The 90-day study duration and single manganese chloride dose may limit insight into chronic toxicity, while missing data for some parameters (e.g., PDW, PCT in Group D) suggest areas requiring further investigation (Rocha *et al.*, 2021).

4. Conclusion

This study demonstrates that manganese chloride induces significant reproductive and hematological toxicity in female Wistar rats, characterized by reductions in progesterone, estradiol, RBC, HGB, and HCT, alongside increases in GRAN%, GRAN#, RDW-SD, RDW-CV, and P-LCR. Cinnamic acid, particularly at 100 mg/kg, effectively mitigates these effects, restoring hormonal balance and improving hematological parameters through its antioxidant and metal-chelating properties.

These findings highlight cinnamic acid's therapeutic potential against manganese chloride–induced toxicity. However, further research is needed to optimize dosing, elucidate underlying mechanisms, and assess long-term safety and efficacy in chronic exposure models.

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