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Hepato- and nephro-toxicity of coumatetralyl rodenticide in some wild rat species

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Abstract. Coumatetralyl (COM) is an anticoagulant rodenticide absorbed quickly after oral dosing. It causes rodent's death due to internal or external bleeding after complete depletion of plasma vitamin K-dependent coagulation factors. The present study aimed was to shed light on metabolic alterations as the potential hepato- and nephrotoxicity caused by ¼ LD_{50} COM in *Rattus rattus, Arvicanthis niloticus, and Geribellus geribellus* wild rat species. Elevation in plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total free amino acids, and erythrocyte lysate glucose-6-phosphate dehydrogenase levels were observed in COM fed rats. Furthermore, plasma creatinine and urea and free hemoglobin levels increased following COM exposure in the challenged rats compared with that in the control ones. It was concluded that ¼ LD_{50} COM induced hepato- and nephron-toxicity in the fighting rodents.

Keywords: *Coumatetralyl, metabolic alterations, hepatotoxicity, nephrotoxicity, rodents.*

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1. Introduction

Rodents are the most destructive vertebrate animals on the earth. They gnaw through almost any object in their path to obtain food and shelter. The damage from rodents causes loss everywhere. Because rodents give rise to a severe practical problem to crop fields, rodent control is urgent. Nevertheless, an emerging genetic resistance against rodenticide represents one of the biggest challenges to removal programs (Desvars-Larrive et al., 2017).

Egypt suffered from rodent problems in agricultural areas at the beginning of the 1980s (Eissa and Yassin, 2014). *Rattus rattus* is the most abundant, has a wide distribution, high adaptation worldwide. It is most common in coastal areas and on large ships. *Arvicanthis niloticus* is a genus of rodents from Africa (Musser and Carleton, 2005). It is a common pest of agriculture in grassland areas, causes severe damage to rice, cereals, sugar cane, and root crops in the field. Moreover, *Gerbillus gerbillus* is distributed mainly in Morocco, Northern Nigeria to Jordan, and Kenya. This species of rodent is much smaller than other gerbils.

In Egypt, (El-Abd and Abd El–Hady, 2017) evaluated the field efficiency of zinc phosphide 1.5%, COM 0.0375%, and brodifacoum 0.005% as a rodenticide. COM is an anticoagulant of the 4-hydroxy coumarin vitamin K antagonist type (Reigart and Roberts, 2013). The liver is an organ involved in excretory, synthetic, and metabolic functions (Yap and Aw, 2010). It is responsible for carbohydrate, protein, and fats metabolism. Some of the enzymes and the end product of the metabolic pathway may be considered a biochemical marker of liver dysfunction (Gowda et al., 2009). It is well known that ALT and AST liver enzymes are sensitive indicators of hepatocellular injury.

Furthermore, albumin is synthesized in the liver and decreased by inflammatory conditions, trauma, and malnutrition (Yap and Aw, 2010). Moreover, bilirubin had been released in unconjugated form, enters into the liver. It is the catabolic product of haemoglobin produced within the reticuloendothelial system (Mauro et al., 2006). In the same context, amino acids are necessary

proteins and kinds of nitrogenous components that play vital and diverse roles in metabolism (Zhang et al., 2018). Also, ceruloplasmin is a copper-containing glycoprotein synthesized mainly in the liver (Hellman and Gitlin, 2002). An enzyme carries more than 95% of the total copper in healthy human plasma (O'Brien and Bruce, 2009). It is known that the kidney plays an essential role in the excretion of wastes and toxins such as creatinine, urea, and uric acid (Okoro and Farate, 2019). A previous study showed that hemolysis led to vascular and kidney injury mediated by cell-free plasma hemoglobin (Gladwin et al., 2012). The current study aimed to shed light on the hepato- and nephrotoxicity of COM rodenticide in *R. rattus, A. niloticus, and G. geribellus* wild rats.

2. Materials and methods

2.1. Animals

Sixty wild rats were trapped from Assiut Governorate and kept in typical 12 h light/12 h dark at a temperature of 23±2 ºC using an air conditioner. Twenty rats of each of *R. rattus, A. niloticus, and G. geribellus* were divided equally. Ten rats served as a control group that fed a regular diet, and ten rats served as a treated group that provided wheat-containing 0.0375% g of coumatetralyl (COM). *G. geribellus, A. niloticus, and R. rattus* were exposed to daily doses of ¼ LD_{50} COM equal to 8.82, 10.71, and 9.83 mg/kg BW, respectively.

2.2. Sample collection

After four days (the end of the experiment), rats were anesthetized, and blood samples were collected in disodium citrate (3.8 %) by retro-orbital sinus. Plasma samples were prepared by centrifugation of collected blood at 3000 rpm for 15 minutes. Rats had been sacrificed, and liver and kidney tissues were removed, immediately washed with saline solution, and weighted.

2.3. Determination of hepatosomatic and renosomatic indexes

Hepatosomatic index (HSI) =100 x (liver weight/ rat body weight).

Renosomatic index (RSI) =100 x (two kidneys weight/ rat body weight).

2.4. Estimation of ALT and AST activities

Plasma ALT and AST activities were determined according to Reitman and Frankel (1957) method using commercial colorimetric ALT and AST kits provided by Bio-diagnostic Company, Egypt.

2.5. Determination of erythrocyte lysate glucose-6-phosphate dehydrogenase (G6PDHs)

It was estimated by the G6PDHs kit, according to Sood et al. (1981).

2.6. Analysis of copper (Cu) ions and plasma ceruloplasmin

Estimating free ions of Cu^{++} in plasma samples was carried out after dilution with distilled water using the atomic absorption spectrophotometer model (ICP-OES) (I Cap 6200) at Chemistry Department, Faculty of Science, Assiut University. Whereas plasma ceruloplasmin was determined, according to Houchin (1958).

2.7. Determination of plasma creatinine and urea

Colorimetric creatinine and urea kits (Spectrum Diagnostics Company, Egypt) were used, according to Tietz et al. (1999) method.

2.8. Determination of plasma total bilirubin, glucose, albumin, free hemoglobin (Hb), and total free amino acids (TFAA)

Plasma total bilirubin was determined by colorimetric assay kits (Diamond Diagnostics Company, Egypt) (Tietz et al., 1999). Blood glucose level was estimated by the GOD-PAP enzymatic colorimetric method using (Spectrum Diagnostics Company, Egypt) kits (Trinder, 1969). Moreover, plasma albumin was estimated using kits of Spectrum Diagnostics Company, Egypt (Doumas and Biggs, 1972). Besides, the colorimetric method using plasma free Hb was determined using (Spectrum Diagnostics Company, Egypt) kit (Tietz et al., 1999). Plasma TFAA was determined by the ninhydrin method (Rosen, 1957).

2.9. Determination of tissue glycogen

Carbohydrate content of liver and kidney tissue homogenates was assessed by anthrone reagent after hydrolysis in HCL (4 N) for 2 hours in a boiling water bath (Van- Handel, 1965).

2.10. Statistical analysis

Data were expressed as mean ± standard error of (SEM) mean. The results were analyzed statistically using column statistics, and one-way analysis of variance (ANOVA) followed by Newman-Keuls multiple comparison test as a post-test. These analyses were carried out using a computer statistics program in GraphPad Prism 3.0 (Graph pad software, Inc., San D.). A probability (p) value of <0.05 was considered significant statistically.

3. Results and discussion

3.1. Effect of coumatetralyl on liver function parameters

3.1.1. Hepatosomatic index

As shown in **table (1)**, there was a significant (p<0.001) increase in HSI in *G. gerbillus* supplemented with COM compared with the control. It was found that liver enlargement was accompanied by elevated hepatic enzyme activities (Slooff et al., 1983). In a previous study, increased HSI due to hepatocellular hypertrophy was noted in mice exposed to acetone toxicity in drinking water (Dietz, 1991).

3.1.2. Alanine transaminase and aspartate aminotransferase and erythrocyte lysate glucose-6-phosphate dehydrogenase

Table (1) showed a significant elevation in AST and ALT activities in *G. gerbillus* (p<0.001), *A. niloticus* (p<0.01 and p<0.001, respectively), and *R. rattus* (p<0.001 and p<0.05, respectively) when compared with the control group. AST and ALT levels are elevated in a variety of hepatic disorders. They are the most consistent enzyme markers of hepatocellular injury (Giboney, 2005). Navarro et al. (1993) suggested that liver function enzymes increased in plasma due to the leakage of these enzymes from the liver cytosol into the bloodstream. In the same line with our findings, dogs administered COM; there was an increase in serum AST, lactate dehydrogenase, and creatinine kinase, referring to tissue damage (Park et al., 2011).

Table 1. Effect of $^1/_4$ LD_{50} of coumatetralyl on liver function indicators in each wild rat species.

Parameter	*Gerbillus gerbillus*		*Arvicanthis niloticus*		*Rattus rattus*	
	Control	Treated	Control	Treated	Control	Treated
HSI (g/kg BW)	19.37±0.53	24.76±0.62***	40.28±0.78	41.65± 0.42	21.24± 0.60	22.91 ± 0.63
AST (U/L)	14.00±1.27	37.32±1.35***	16.87±1.53	23.75±2.05**	26.42±0.88	36.63 ±1.71***
ALT (U/L)	20.08±0.85	35.82±1.07***	12.88± 1.02	21.71±1.43***	18.27±0.71	22.19 ±0.55*
eG-6-PD (U/g/dl Hb)	5.47±0.68	13.83±2.09***	30.81±3.50	22.79±1.36***	7.01±0.297	14.07 ±0.72**
Plasma total bilirubin (mg/dL	0.443±0.01	0.440±0.03	0.37±0.02	0.45±0.03*	0.34± 0.02	0.37 ±0.01
Plasma glucose (mg/L)	53.61±2.82	43.99±0.68**	40.80±2.07	44.96±2.55	30.58±1.11	29.82 ±1.51
Plasma albumin (mg/L)	51.93± 0.66	61.92± 0.79	57.20± 5.65	90.70± 4.61***	26.02± 2.67	67.99 ±2.58***
Plasma TFAA (mg/mL)	2.91± 0.06	3.07± 0.02	9.76± 0.58	7.54± 0.19***	7.29± 0.46	6.46 ± 0.07*
Cu^{2+} (µg/dL)	170.20±3.49	208.20±8.72*	252.5±6.37	348.5±11.73***	329.0±16.08	183.1±4.45***
Plasma ceruloplasmin (mg/dl)	52.56±1.50	57.60± 2.30	71.07±1.47	80.52± 3.58	247.9±4.95	231.8 ± 6.69*
Liver glycogen (mg/mL)	2.51± 0.15	1.59 ± 0.15***	1.17± 0.09	1.36± 0.08	2.26± 0.07	2.45 ± 0.11

Note. HSI: hepatosomatic index; AST: aspartate aminotransferase; ALT: alanine transaminase; eG-6-PD: erythrocyte glucose-6-phosphate dehydrogenase; TFAA: total free amino acids; Cu^{2+}; copper ions. Data are present as means ± SEM. Number of rats (n) =10. *=significant difference from control at p<0.05, **=highly significant difference from control at p<0.01, and ***= very highly significant difference from control at p<0.001.

Erythrocyte lysate glucose-6-phosphate dehydrogenase was significantly increased in *G. gerbillus* and *R. rattus* (p<0.001 and p<0.01, respectively) and decreased in *A. niloticus* (p<0.001) fed COM compared with the control group. This result showed a species-specific response. G6PDH is the primary source of NADPH (a cofactor required to convert oxidized glutathione to the reduced form) and is essential for protecting cells against oxidative stress (Leopold et al., 2003; Matsui et al., 2006). The increased G6PD activity may be attributed to NADPH's increased production required for the regeneration of some antioxidants to counteract the detoxification process and overproduction of free radicals. This probably reflects an adaptation to oxidative conditions to which animals have been exposed (Lenartova et al., 1997). In the early stage of liver damage, cytoplasmic enzymes in hepatocytes may leak from cells into the blood due to increased membrane permeability (Sallie et al., 1991).

3.1.3. Plasma total bilirubin and albumin

Except in *R. rattus*, total bilirubin level significantly ($p<0.05$) increased in COM-fed rats compared with the control ones. There was a significant ($p<0.001$) increase of the albumin level in both *A. niloticus* and *R. rattus* challenged with COM versus the untreated ones (Table 1). Bilirubinemia was found in shepherd dogs intoxicated with anticoagulant rodenticide bromadiolone (Binev et al., 2005). Hyperalbuminemia occurs with serum albumin >4.8 g/dL due to dehydration, liver diseases, or impaired renal function (LeFever et al., 2010; Leeuwen et al., 2011). Furthermore, hyperalbuminemia reported in a human patient was suffered from hepatocellular carcinoma (Cooper et al., 2009).

3.1.4. Plasma total free amino acids

The level of TFAA significantly decreased in *A. niloticus* ($p<0.001$) and *R. rattus* ($p<0.05$) fed COM compared with the control ones (Table 1). Supporting our findings, chronic kidney disease patients were characterized with low plasma free amino acid concentrations accompanied by inflammation and inversely correlated with inflammatory markers (Suliman et al., 2005; Kumar et al., 2012).

3.1.5. Plasma free copper ions and ceruloplasmin

A significant elevation was found in free Cu^{2+} in *G. gerbillus* ($p<0.05$) and *A. niloticus* ($p<0.001$), and a significant reduction was found in *R. rattus* ($p<0.001$) when supplemented with COM in comparison with the control group. Following the supplementation of *R. rattus* with COM, the ceruloplasmin level was significantly decreased ($p<0.05$) compared with the control group. The current data showed that the only pronounced decrease in plasma ceruloplasmin was observed in *R. rattus* in concomitant with a significant decline in the level of Cu^{2+} in the same rat species in response to COM. This drop-in plasma ceruloplasmin may be associated with the extent of the damaging effect of rodenticide on its liver more than in the other studied species and the diminished level of plasma Cu^{2+} in *R. rattus* induced by COM supplementation. This result could also be due to the more significant role of ceruloplasmin in *R. rattus* in preventing hydroxyl radicals' formation on iron ions through the Fenton reaction, as reported by Halliwell and Gutteridge (1999). Ceruloplasmin levels were previously shown to be decreased in patients with severe hepatitis (Yang et al., 2005).

3.1.6. Plasma glucose and hepatic glycogen

Table (1) also indicated that the levels of plasma glucose and hepatic glycogen in *G. gerbillus* had been fed with COM significantly (respectively, $p<0.01$ and $p<0.001$) decreased versus the control. The present study showed significant hypoglycemia accompanied by a considerable increase in HSI in *G. gerbillus,* suggesting a shortage of tissue glucose and disruption of the cellular energy transfer. Toxic substances such as pesticides decreased glycogen content in animal tissues (Ferrando and Andreu-Moliner, 1991). Some pesticides, like deltamethrin, impaired glucose metabolism in mice (Desai et al., 2015). A previous study concluded that reducing hepatic glycogen indicates energy consumption because of stress caused by deltamethrin in fish (Datta and Kaviraj, 2003). Results obtained herein showed that ¼ LD_{50} of COM led to a pronounced decrease in liver glycogen only *G. gerbillus,* and this outcome may affect the liver function in this species.

3.2. Effect of coumatetralyl on kidney function parameters

3.2.1. Renosomatic index

Table (2) showed a significant increase ($p<0.001$) in RSI of COM fed *G. gerbillus* in comparison with the control. Our study showed a substantial increase in HSI and RSI in *G. gerbillus*, while the result revealed a non-significant change in these indices in other rat species. Inconsistent with our results, bromadiolone administration to *Mus Musculus* for 48 hours led to increased kidney and liver (Revathi and Yogananda, 2006).

3.2.2. Plasma creatinine and urea

The current data obtained from the table (2) showed that COM induced a significant elevation in creatinine level in *A. niloticus* and *R. rattus* ($p<0.001$) compared to the control group. There was a considerable rise in the urea level of COM fed *G. gerbillus* ($p<0.05$), *A. niloticus* and *R. rattus* ($p<0.01$) in comparison with the control. Creatinine and urea are significant indicators of renal function (Yakubu and Musa, 2012). Renal damage detected in rats exposed to mercuric chloride was apparent by elevation in the

plasma urea and creatinine levels (Hazelhoff et al., 2012). Since an increase in kidney function parameters (creatinine and urea) reflects impairment in its normal functions, it may reflect kidney damage. However, in *G. gerbillus*, the situation was different where the plasma creatinine was not changed, which may be due to the variation in species resistance to COM rodenticide.

Table 2. Effect of 1/4 LD50 of coumatetralyl on kidney function indicators in each wild rat species.

Parameter	*Gerbillus gerbillus*		*Arvicanthis niloticus*		*Rattus rattus*	
	Control	Treated	Control	Treated	Control	Treated
RSI (g/Kg BW)	5.51±0.39	8.99± 0.27***	6.297± 0.36	6.386±0.24	4.93±0.37	5.01±0.13
Plasma creatinine (mg/L)	1.77± 0.10	1.65± 0.11	1.94± 0.17	3.13± 0.19***	1.85±0.11	2.87±0.21***
Plasma urea (mg/L)	10.53±0.45	16.09±0.73*	13.96± 1.33	20.38± 1.59**	8.33±0.58	14.22±1.06**
Plasma free Hb (mg/L)	5.88± 0.83	58.06±1.28***	9.83±1.13	26.72± 1.14***	5.624±0.696	29.39±1.44***
Renal glycogen (mg/mL)	1.22± 0.17	1.87± 0.16**	1.16± 0.095	1.13± 0.12	1.53± 0.08	1.69± 0.11

Note. RSI: Renosomatic index; Hb: hemoglobin. Data are present as means ± SEM. Number of rats (n) =10. *=significant difference from control at p<0.05, **=highly significant difference from control at p<0.01, and ***= very highly significant difference from control at p<0.001

3.2.3. Plasma free hemoglobin

Table (2) represented a significant increase (p<0.001) of plasma level of free Hb in COM fed *G. gerbillus, A. niloticus* and *R. rattus* compared with the control. This finding suggests that the rise in free Hb in all studied rat species may exacerbate COM's damaging effect on the kidney and vascular endothelium. The increased kidney's oxidative stress in warfarin-related nephropathy accompanied free Hb release by RBCs in the tubular lumen by generating reactive oxygen species and increasing lipid peroxidation (Patel et al., 1996). The current result is in harmony with a previous study that concluded that brodifacoum induced hemolysis and caused an increase in free Hb in the serum (Ware et al., 2015).

3.2.4. Renal glycogen

The data obtained from table (2) indicated that COM significantly (p<0.001) raised glycogen level in the kidney of *G. gerbillus* in comparison with the control group. The kidney plays an essential role in the release of total glucose (renal gluconeogenesis) in normal and pathophysiologic states (e.g., hepatic insufficiency and counter-regulation of hypoglycemia) (Marsenic, 2009). For this reason, the increase in the renal glycogen content of *G. gerbillus* suggested being a compensatory mechanism for hypoglycemia.

4. Conclusion

In conclusion, the current study revealed that COM's toxic properties were related to the disruption of liver and kidney functions' metabolic activities. The hepato- and nephron-toxicity can be considered as a part of the mechanism of action of this rodenticide in rodent control.

Conflicts of interest. There are no conflicts of interest.

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