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Subacute influence of Mancozeb (80 % WP) on Hematological and Biomarkers in Male Rats.

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Abstract

Aim: To test the influence of mancozeb (MCZ) on metabolic alterations in male albino rats.
Methods: forty adult male rats weighing 120 ± 10 g were used, divided into four groups of ten animals for each and administered mancozeb (Anadol, 80 % WP) at doses (150, 300 and 600 mg / kg B. w / day) for 4 weeks. Hematological parameters and markers for liver, kidney and lipid profiles were determined.
Results: Results showed mancozeb exposure induced abnormal and highly significant changes in hematological and biochemical activities during the exposure period. Also, the current investigation observed an obvious increase in the organs weight ratios of intoxicated rats.
Conclusions: Mancozeb induced alterations in hematological indices may be a defensive mechanism against mancozeb toxicity through stimulation of leucopoiesis. In addition, hepatorenal toxicity and changes in lipid profile leading to physiological impairment.

Keywords: Fungicides, Mancozeb, Hematology, Clinco - Biochemical Parameters.

Introduction

Mancozeb, an inorganic - Zinc dithiocarbamate, is a typical fungicide with a carbamate (an organocarbamate) structure where sulphurs replace both oxygens in the amide functional group (**Fiorella *et. al.*, 2002; Suresh *et. al.*, 2005**). It is belonging to ethylenebisdithiocarbamate (EBDC) group that among the most widely used fungicides in pre - harvest agricultural applications to protect crops from a range of fungal diseases (**Paro, *et al.*, 2012**). The EBDTC are regarded as polymeric DTC because their metal ions can bind several molecules to form polymeric complexes (i. e. zineb, maneb, and mancozeb). The toxicological effects of dithiocarbamates (DTC) can occur from their absorption through skin exposure, the digestive tract (ingestion), respiratory tract (inhalation) and mucous membranes, and have as their final main metabolite ethylenethiourea (ETU; **Jordan and Neal 1979)**. The lipophilic nature of DTC makes them suitable for their passage across the cell membrane. Tissue or organ specific toxic effects of these

chemicals may be due to the differential competency of their intracellular passage and binding to crucial structural and functional entities of the cells eventually leading to the metabolic disruptions, pathological changes, and cell death (**Narayan *et al.*, 2011).** Peripheral neuropathy induced by DTC is a major toxic effect which has been reported in humans and animals **(Frisoni and Di Monda, 1989).**

Blood parameters have been widely employed as pathophysiological indicators to diagnose the structural and functional status of animals exposed to a variety of toxicants (**Adhikari, *et al.*, 2004)**. Hematological study is important in toxicological research because a hematological alteration is a good method for rapid evaluation of the chronic toxicities of a compound. The knowledge of hematological characteristics of the human is important in determining its health status, toxicological and parasitological investigations (**Jaya and Ajay, 2014)**.

Hematological parameters are probably the more rapid and detectable variations under stress and are fuel in assessing different health conditions (**Hymavathi and Rao, 2000**). Assessment of hematological parameters can therefore be used to determine the extent of deleterious effect of foreign substances on the blood constituents of an animal (**Friday *et al.*, 2012**).

Materials and Methods

Fungicide Used:

Mancozeb (Anadol 80 % WP) was gained from Mammalian Toxicology Dept., Central Agricultural Pesticides Lab. (CAPL), Agriculture Research Center (ARC), Dokki, Giza, Egypt.

Experimental Design:

Forty adult male rats (*Rattus norvegicus*) weighing 120 ± 10 g were used. Animals were supplied by the breeding unit of the Egyptian Organization for the Biology and Vaccine Production, Egypt. Animals were kept under standard laboratory conditions for at least two weeks before and throughout the experimental work. They were maintained on a standard diet and water was available *ad libitum*. The rats were randomly divided into four groups of ten animals each either control (C) or treatments (MCZ) and administered orally by gavage in early morning at the used doses for 4 weeks as follows:

Group I (C): was held as a control group and were given distilled water. **Group II (MCZ1), Group III (MCZ2) and Group VI (MCZ3):** were given 150, 300 and 600 mg mancozeb / kg b. w / day respectively.

At the end of the treatment, the blood samples were collected through the retro - orbital plexus vein. The blood samples were divided into two parts the first part was taken on EDTA and used for hematological analysis. The second part was put in heparinized dry tubes, then centrifuged at 3600 rpm for 15 minutes at 4 °C to obtain plasma and kept in the freezer (- 40 °C) for further biochemical analysis.

At the end of the experimental period, all animals were euthanized by exsanguinations under diethyl ether anesthesia. Some vital organs (liver, kidneys, brain, spleen, heart, lungs, and testes) were quickly removed and weight individually to assay relative organ weight.

Hematological Determination:

Red blood corpuscles (RBCs) count was determined with a Neubauer crystalline counting chamber as described by **Davidson and Henry (1969).** White blood corpuscles (WBCs) count was done as per the procedure described by **Hunter and Bonford (1963).** Hemoglobin (Hb) content in the blood was estimated by cyanmethaemoglobin method as described by **Dacie and Lewis (1975).** Packed cell volume (PCV) or haematocrit (Hct) value was determined by method of **Schalm *et al.*, (1975).** Erythrocyte indices were determined by the method of **Dacie and Lewis (1991)**.

Biochemical Assay:

All assayed biomarkers were determined using the commercial diagnostic kit of Stanbio Co., Spain. Plasma lipids, total cholesterol (TC, **Allian *et. al.*, 1974**) and triglyceride (TG, **Buccolo and David 1973**) also, low and high density lipoprotein (LDL and HDL) cholesterol levels (**Friedwald *et. al.*, 1972)** were measured.

Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activity were assayed by colorimetric method of **Reitman and Frankel, (1957).** Alkaline phosphatase (ALP) activity was assayed by method of **Roy, (1970).** Acetylcholinesterase (AChE) activity was determined

by the method of **Ellman *et. al.*, (1961).** Plasma total protein (T. P, **Bradford, 1976),** albumin (Alb) (**Doumas *et. al.*, 1971),** plasma urea (**Fawcett and Scott 1960),** and creatinine level (**Siest *et. al.*, 1985)** were determined.

Relative organ weight assay:

The relative organ weight of each animal (organ body weight ratio) was then calculated according to (**Stanley *et. al.*, 2005**)

Statistical Analysis:

Differences between parameters were analyzed using SPSSWIN software version 25 by analysis of variance one - way (ANOVA). Least Significant Differences (LSD) test for comparison between groups and an overall significance level of $p \leq 0.05$, followed by Dunnett's Test (a: significant differences versus cont., b: significant differences versus MCZ1 and c: significant differences versus MCZ2).

Results and Discussion

Particularly, literature reports have proved that the alterations in the haematological parameters, from normal state, may be used as valuable indicators of disease, or stress in different animal species (**Uboh *et al.*, 2005; Yakubu *et al.*, 2007**).

Data in Table (1) represented haematological aspects tested in the studied animals treated with mancozeb (80 % WP) showed that there were significantly difference decrease in WBCs at all treated groups and in RBC values between MCZ3 exposed animals and the control group. Whereas Hb, MCH and MCHC values were significantly higher in the all exposed animals as compared with controls, also, Hct (in MCZ2) and MCV (in MCZ2 and MCZ3) values were significantly higher comparing with control group.

Table (1): Influence of Mancozeb (Anadol 80 % WP) on hematological parameters of male albino rats after treatment for 28 days.

Parameters \ Treatments	Cont.	MCZ1	MCZ2	MCZ3
WBCs (X 10^3 / µl)	12.650 ± 0.2842	10.360 ± 0.4551 [a]	9.182 ± 0.4085 [a]	10.860 ± 0.5026 [ac]
RBCs(X 10^6 / µl)	6.5176 ± 0.2216	6.3900 ± 0.3671	5.7960 ± 0.1782	5.6160 ± 0.1700 [ab]
Hb (g / dl)	10.942 ± 0.2950	14.058 ± 0.3620 [a]	13.961 ± 0.5132 [a]	12.434 ± 0.4188 [abc]
Hct (%)	47.2 ± 0.8602	48.0 ± 1.7607 [c]	52.0 ± 0.6325 [ab]	46.4 ± 0.9274 [c]
MCV (Ft)	72.662 ± 1.8236	71.542 ± 1.3161 [c]	84.028 ± 3.6411 [ab]	85.406 ± 2.2266 [ab]
MCH (Pg)	17.094 ± 0.3954	22.388 ± 0.5079 [ac]	24.800 ± 0.3828 [ab]	23.292 ± 0.4526 [ac]
MCHC (%)	23.244 ± 0.3036	29.892 ± 0.2961 [ac]	27.988 ± 0.6340 [ab]	26.902 ± 0.4666 [ab]

WBCs = White blood corpuscles. RBCs = Red blood corpuscles. Hb = Hemoglobin. Hct = Haematocrit. MCV = Mean Corpuscular Volume. MCH = Mean Corpuscular Hemoglobin. MCHC = Mean Corpuscular Hemoglobin Concentration. Data expressed as means ± SEM (5 rats). Cont. = group I as Control group. MCZ1 = group II treated with 150 mg / Kg b. w / day. MCZ2= group III treated with 300 mg / Kg b. w / day. MCZ3= group VI treated with 600 mg / Kg b. w / day. [a] significant differences versus cont., [b] significant differences versus MCZ1, [c] significant differences versus MCZ2 at $p \leq 0.05$.

Decline in the erythrocyte count can be correlated with the alteration in the values of MCH, MCV and MCHC (**Joshi, *et al.*, 2005)**. The changes may be due to physiological dysfunctioning of the haemopoitic system (**Srinivasan, and Radhakrishnamurthy, 1983;** and **Siddiqui, *et al.*, 1987)**.Erythrocytes reflect the state of the organism over a prolonged period of time. High concentration of pesticides or long term exposure of animal to sublethal concentration usually decreases erythrocyte indices (**Adedeji *et. al.*, 2009**). When animals were in stressful condition the erythrocyte count was found to be decreased. The lower count may be due to the destruction of red blood cells or either by the inhibition of erythropoiesis (**Dhanya and Sushama, 2018)**.

The lipid results showed a significant decrease in total lipids of rats treated with mancozeb compared with the healthy control ones as showing in Table (2). Similar findings showed that exposure to anticholinesterase such as carbamates can increase the degradation of lipids (**Mansour and Mossa, 2011**).

Table (2): Influence of Mancozeb (Anadol 80 % WP) on plasma lipid profile of male albino rats after treatment for 28 days.

Treatments / Parameters	Cont.	MCZ1	MCZ2	MCZ3
T. Lipids (g / dl)	59.893 ± 0.2041	72.418 ± 0.4297 ^{ac}	57.788 ± 0.4510 ^{ab}	38.421 ± 0.3710 ^{abc}
T. Cholesterol (mg / dl)	59.813 ± 0.3324	50.942 ± 0.3874 ^{ac}	57.762 ± 0.2869 ^{ab}	70.475 ± 0.3484 ^{abc}
Triglyceride (mg / dl)	82.386 ± 0.7030	57.531 ± 0.4461 ^{ac}	70.278 ± 0.6018 ^{ab}	79.416 ± 0.2821 ^{abc}
HDL (mg / dl)	18.714 ± 0.1829	18.483 ± 0.1196 ^{c}	21.605 ± 0.1086 ^{ab}	26.687 ± 0.1800 ^{abc}
LDL (mg / dl)	24.622 ± 0.2455	20.953 ± 0.3338 ^{ac}	22.101 ± 0.2933 ^{ab}	27.905 ± 0.3296 ^{abc}

HDL = High Density Lipoprotein. LDL = Low Density Lipoprotein. Data expressed as means ± SEM (5 rats).
Cont. = group I as Control group. MCZ1 = group II treated with 150 mg / Kg b. w / day. MCZ2= group III treated with 300 mg / Kg b. w / day. MCZ3= group VI treated with 600 mg / Kg b. w / day. ^{a} significant differences versus cont., ^{b} significant differences versus MCZ1, ^{c} significant differences versus MCZ2 at $p \leq 0.05$.

Pesticide - induced changes in the liver can be regarded as an index for the identification of pollution stress. The liver can store more toxicants than any of the tissues in the body. This increases in the occurrence of adverse effects in the liver and it provides toxicologists a significant site for investigation (**Patel, *et al.*, 2001**).

Table (3) presents levels of biochemical parameters determined for the exposed animals and the control group. Significantly lower activities of certain plasma enzymes, such as AST, ALT, ALP, as well as total proteins and albumin levels, were observed in intubated animals as compared with control group. There was also a significant inhibition of AChE activity in treated rats with 600 mg mancozeb / kg b. w (MCZ3). Meanwhile exposed to mancozeb (80 % W. P) caused significant increase in glucose level at all treated groups.

The results of the biochemical analysis revealed significant alters in total protein concentration in all treatment groups which might be due to the inactivation of various transcription factors (**Eraslan, *et al.*, 2009**). Hepatic proteins and ALP activity decreased due to lysis of structural proteins and leakage of enzymes into the blood stream (**Bhushan, *et al.*, 2013).** Mancozeb is a fungicide, subclass of carbamate pesticides called dithiocarbamates. They have a similar action to carbamate insecticides they affect the nervous system through their main metabolite, carbon disulfide and ethylenethiourea (**Adjrah**, ***et al.*, 2013**).

Table (3): Influence of Mancozeb (Anadol 80 % WP) on liver function and cholinesterase activity in plasma of male albino rats after treatment for 28 days.

Treatments / Parameters	Cont.	MCZ1	MCZ2	MCZ3
ALT (U / l)	33.085 ± 1.0117	38.627 ± 0.7737 [ac]	31..966 ± 0.6389 [b]	28.695 ± 0.6695 [abc]
AST (U / l)	108.74 ± 4.0250	96.308 ± 1.2293 [a]	86.788 ± 3.2316 [a]	110.49 ± 4.5920 [bc]
ALP (U / l)	212.10 ± 4.3082	152.45 ± 3.0831 [ac]	124.85 ± 1.2596 [ab]	129.02 ± 3.4055 [ab]
T. Protein (g / dl)	7.6830 ± 0.0798	6.7602 ± 0.1125 [a]	6.5504 ± 0.0865 [a]	6.1838 ± 0.1026 [abc]
Albumin (g / dl)	4.6500 ± 0.0514	3.7048 ± 0.0578 [ac]	4.2620 ± 0.0717 [ab]	4.5416 ± 0.0797 [bc]
Glucose (mg / dl)	97.793 ± 0.8444	119.02 ± 2.8498 [ac]	136.68 ± 2.0176 [ab]	135.57 ± 2.4419 [ab]
AChE Activity (U / l)				
AChE (U / l)	818.82 ± 23.868	866.16 ± 32.796[ac]	828.95 ± 26.745[ab]	761.20 ± 27.56[ac]
% Activity	100	105.78	101.24	92.96
Alteration (%)	0	- 5.78	- 1.24	7.04

ALT = Alanine Aminotransferase. AST = Aspartate Aminotransferase. ALP = Alkaline Phosphatase. AChE = Acetyl Choline Esterase. Data expressed as means ± SEM (5 rats). Cont. = group I as Control group. MCZ1 = group II treated with 150 mg / Kg b. w / day. MCZ2= group III treated with 300 mg / Kg b. w / day. MCZ3= group VI treated with 600 mg / Kg b. w / day. [a] significant differences versus cont., [b] significant differences versus MCZ1, [c] significant differences versus MCZ2 at $p \leq 0.05$.

On the other hand, creatinine and urea levels were increased between treated male rats with the high dose group (MCZ3) and the control group as observed in Table (4). The results have shown an increase in the urea and creatinine concentrations: these parameters indicate a renal damage and their plasma levels can be attributed to the decrease of the kidney's filtration. Administration of Mancozeb causes nephrotoxicity as indicated by elevation in serum levels of urea (BUN), and creatinine. The high levels of creatinine and urea are indicators of severe damage to the structural integrity of nephrons (**Hany *et al.*, 2019)**.

Table (4): Influence of Mancozeb (Anadol 80 % WP) on kidney function in plasma of male albino rats after treatment for 28 days.

Treatments / Parameters	Cont.	MCZ 1	MCZ 2	MCZ 3
BUN (mg / dl)	27.2342 ± 0.3594	27.128 ± 0.2707 [c]	28.754 ± 0.3828 [ab]	31.163 ± 0.3909 [abc]
Creatinine (mg / dl)	0.9432 ± 0.00595	0.9594 ± 0.01530 [c]	0.9266 ± 0.00566 [b]	0.9994 ± 0.00874 [abc]

BUN = Blood Urea Nitrogen. Data expressed as means ± SEM (5 rats). Cont. = group I as Control group. MCZ1 = group II treated with 150 mg / Kg b. w / day. MCZ2= group III treated with 300 mg / Kg b. w / day. MCZ3= group VI treated with 600 mg / Kg b. w / day. [a] significant differences versus cont., [b] significant differences versus MCZ1, [c] significant differences versus MCZ2 at $p \leq 0.05$.

Organ weights are widely accepted in the evaluation of test article - associated toxicities (**Wooley, 2003**), and the different biomarkers might be used to detect early biochemical effects of pesticides before adverse clinical health effects occur (**Hernandez *et al*., 2006**).

In the present investigation a significant increase in relative weight values of organs was observed, however no significant changes in relative weight of kidney was noticed (Table 5). Changes in body weight gain and internal organ weights reflect toxicity after exposure to toxic substances (**Teo, *et al*., 2002).** The detected increase in the weight of different organs under the effect of mancozeb might be because of necrosis and apoptosis, which were accompanied by the accumulation of lipids in the tested organs (**Hwang and Wang, 2001).**

Table (5): Influence of Mancozeb (Anadol 80 % WP) on organ weight ratio of male albino rats after treatment for 28 days.

Treatments / Parameters	Cont.	MCZ1	MCZ2	MCZ3
Brain	5.0841 ± 0.0333	5.3895 ± 0.0441 [ac]	5.5260 ± 0.0155 [ab]	5.2444 ± 0.0432 [abc]
Heart	3.4391 ± 0.0271	3.7169 ± 0.0317 [ac]	3.4306 ± 0.0182 [b]	3.6285 ± 0.0205 [abc]
Lung	4.2893 ± 0.0343	4.8291 ± 0.0186 [ac]	4.5871 ± 0.0313 [ab]	4.4576 ± 0.0140 [abc]
Liver	10.600 ± 0.0623	11.316 ± 0.0555 [ac]	10.027 ± 0.0843 [ab]	10.400 ± 0.0627 [bc]
Kidney	4.8377 ± 0.0676	4.8487 ± 0.0351	4.8713 ± 0.0281	4.9561 ± 0.0341
Spleen	3.6460 ± 0.0141	3.6838 ± 0.0125 [c]	3.8029 ± 0.0190 [ab]	3.7856 ± 0.0142 [ab]
Testes	5.1170 ± 0.0302	6.6932 ± 0.0268 [ac]	6.4231 ± 0.0429 [ab]	5.9469 ± 0.0177 [abc]

Data expressed as means ± SEM (5 rats). Cont. = group I as Control group. MCZ1 = group II treated with 150 mg / Kg b. w / day. MCZ2= group III treated with 300 mg / Kg b. w / day. MCZ3= group VI treated with 600 mg / Kg b. w/ day. [a] significant differences versus cont., [b] significant differences versus MCZ1, [c] significant differences versus MCZ2 at $p \leq 0.05$.

Conclusion

Different doses of Mancozeb induced alterations in hematological indices may be a defensive mechanism against mancozeb toxicity through stimulation of leucopoiesis. In addition, hepatorenal toxicity and changes in lipid profile leading to physiological impairment.

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