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Hemato - Biochemical Responses under Stress of Mancozeb Fungicide (75 % WP) in Male Albino Rat.

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Abstract

The aim of this study is to evaluate the effects of mancozeb (MZ) - an organocarbamate fungicide - on some hematological parameters and biochemical indices related to kidney and liver functions, Mancozeb was administered orally by gavage at doses of 250 (MZ1) and 500 (MZ2) mg / kg body weight / day to male albino rats for 30 days. Treating male albino rats with mancozeb induced various hematological and clinical biochemistry changes. These changes include a significant decrease in total erythrocyte count (TEC), total leukocyte count (TLC), and significant elevation in mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH). Our findings showed that mancozeb had some effect on the clinical - biochemical parameters of male albino rat by elevation in plasma aspartate aminotransferase (AST), alkaline phosphatase (AKP) and acetylcholinesterase (AChE) activity, and albumin (Alb), total lipid (TL), total cholesterol (TC), high density lipoprotein **(**HDL**)** and low density lipoprotein (LDL**)** content; while, blood urea nitrogen (BUN), creatinine and triglyceride (TG) concentrations were decreased. Also, the current investigation observed an obvious increase in the weight of liver, kidney, brain, and testes but, weight of and heart of intoxicated rats were decreased.

Keywords: Mancozeb Fungicide (MZ), Hematological Parameters, Kidney and Liver Functions, Lipid Profile, Rat.

1- Introduction

In agriculture, fungicides are used to maximize the modern agriculture, to improve food production and to protect fruits and vegetables during storage or are applied directly to ornamental plants, trees, field crops, cereals (**Gupta, and Aggarwal, 2007)** but causing systemic poisoning in humans (**(Mortazavi and Jafari - Javid, 2009)**.

The most important class of fungicides for controlling the fungi of agricultural crops was known to be ethylenebisdithiocarbamate (EBDC) forms. This class includes Ferbam, Nabam, Maneb, Mancozeb, Meteriam and Zeineb (**Seiler, 1974, Graham *et al.*, 1973 and SaKr *et al.*, 2007).** Mancozeb is a polymeric complex of 20 % Manganese by 2 - 5 % Zinc salt of EBDC group. It is a contact fungicide in a subclass of carbamate pesticides called dithiocarbamates (DTCs). It is commonly used as a protective fungicide either alone or in combination with copper or sulfur for foliar application and seed - treatment in agriculture against a wide range of fungal diseases of field crops, seeds, fruits ornamentals and

vegetables, etc. (**Kurttio *et al*. 1990; Worthing, 1991; Axelstad *et al*., 2011; Paro, *et al*., 2012; Ananthan and Kumaran, 2013**). Besides its fungicidal property, it is used in the industry as a slimicide in water - cooling systems, in sugar, pulp, and paper manufacturing as a vulcanization accelerator, an antioxidant in the rubber industry, and as a metal scavenger in wastewater treatment because of its chelating properties (**IPCS, 1988; Worthing, 1991 and Swarupa, *et al*., 2013)**.

Despite its low acute toxicity, mancozeb has been shown to produce several adverse effects on human and animal health, when repeated exposure can alter various functions (**Negga, *et al*., 2012)**. Reports are available on the toxicity of mancozeb on the skin, liver, kidney, central nervous system, male and female reproductive system, and chromosomes of bone marrow cells in mice, rats and human (**Edwards *et al*., 1991; Georgian, *et al*., 1983; Baligar and Kaliwal, 2001; Bindali and Kaliwal, 2002; Nordby, *et al*., 2005; Domico, *et al*., 2006; Tsang and Trombetta, 2007**).

Mancozeb reduces its biological effects via its primary metabolites like ethylene thiourea (ETU) and carbon disulphide (CS_2) (**Thorn and Ludwing, 1962**; **Ivanova - Chemishanska, 1962**). ETU stable (persistence of 5 - 10 weeks), has high water solubility, and is of particular importance because of its specific toxicity. For this reason, toxicological information on this compound should be investigated.

For monitoring stress responses, predicting systematic relationships and the physiological adaptations of animals, hematological parameters have been widely used for the description of the general health of animals (**Akhtarunnessa and Masudul, 2012**). So, assessment of hematological parameters can therefore be used to determine the extent of the deleterious effect of foreign substances on the blood constituents of an animal (**Friday *et al*., 2012**). Minimum hematological indices must include packed cell volume (PCV, or hematocrit, Hct), hemoglobin (Hb) concentration, total erythrocyte counts (TEC), mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC); these parameters have been frequently included in toxicological studies (**Gad and Chengelis, 1988; Shah, and Altindag, 2004**).

Analysis of serum biochemical parameters, especially useful to identify target organs of toxicity as well as the general health status of animals, and is advocated to provide early signs of critical modifications in stressed organisms (**Jacobson - Kram, and Keller, 2001**). This investigation is aimed at studying the changes in hematological as well as biochemical status related to liver, and kidney functions and organ weight changes of mancozeb exposed male albino rat using different doses: 1 / 20, and 1 / 10 LD_{50}.

2- Materials and Methods

2 - 1 - Animals and Experimental Conditions:

Thirty healthy adult male albino rats, *Rattus norvegicus*, approximately (3 – 4) months age and each weighs 130 ± 10 g, were used. Animals were supplied by the breeding unit of the Egyptian Organization for the Biology and Vaccine Production, Egypt. The animals were housed and regrouped in large polypropylene cages (5 rats per cage), allowed to adjust to the new environment for two weeks before starting the experiment and kept in an air - conditioned animal house at a temperature 25 ± 5 ºC with a steady hygrometry (50 %) on a 12 / 12 h light / dark cycle. They were provided with a standard diet and water was available *ad libitum*. The rats were randomly divided into three groups of ten animals each either control or treatments.

2 - 2 - Chemicals and Exposure:

Common Name: Mancozeb:

Chemical Abstract Name: [[1, 2- ethanediylbis] carbamodithioate]] (2-)] manganese mixture with [[1, 2 - ethanediylbis] [carbamodithioate]] (2-) zinc.

Trade Name: Blanko (75 % WP) was purchased from Cam Company for Agrochemicals, New City Nubaria, Beheira, Egypt.

Mancozeb was administered orally by gavage in the early morning with a stomach tube for 30 days at the doses used:

Group I (C): was held as a control group and were given orally distilled water.

Group II (MZ1): Animals were given mancozeb orally in a dose of 250 mg / kg b. w / day as 1 / 20 of LD_{50}.

Group III (MZ2): Animals were given mancozeb orally in a dose of 500 mg / kg b. w / day as 1 / 10 of LD_{50}.

2 - 3 - Hematological Determination:

Approximately 2 ml of blood was collected from the retro - orbital plexus using separate heparinized disposable syringes containing 0.5 mg ethylene diamine tetra acetic acid (EDTA) an anticoagulant; it was properly mixed and used for hematological analysis. Hematological parameters such as total erythrocyte counts (TEC) or total red blood corpuscles (RBCs) and total leukocyte counts (TLC) or white blood corpuscles (WBCs), hemoglobin content (Hb), packed cell volume (PCV) or hematocrit value (Hct), and erythrocyte indices such as mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) concentration were determined by the method described by **Dacie and Lewis (1991)**.

2 - 4 - Biochemical Assay:

At the end of the treatment, the blood samples were collected through the retro - orbital plexus vein 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) until biochemical analysis.

Markers for liver and kidney damage were determined using the commercial diagnostic kit of Stanbio Co., Spain. Plasma transaminases (AST and ALT) activities were determined according to **Reitman and Frankel, (1957**). Acetylcholinesterase (AChE) activity was determined by the method of **Ellman *et al.*, (1961**). Plasma albumin was carried out according to **Doumas *et al.*, (1971**). Total protein was measured by the method of **Bradford (1976**). The plasma urea level was determined by the method of **Fawcett and Scott (1960**), while, the plasma creatinine level was determined by the kinetic method of **Siest *et al.*, (1985**).

Plasma lipids, total cholesterol (TC), triglyceride (TG) and low and high density lipoprotein (LDL and HDL) cholesterol levels in plasma were measured spectrophotometrically by the method described elsewhere (**Allian *et al.*, 1974; Buccolo and David 1973; Friedwald *et al.*, 1972**).

2 - 5 - Relative Organ Weight Assay:

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 carefully dissected out, washed with saline solution, dried and then weighed individually in grams (absolute organ weight). The relative organ weight of each animal (organ body weight ratio) was then calculated according to (**Stanley *et al.*, 2005**).

2 - 6 - Statistical Analysis:

The results are presented as means ± SEM (standard error of the mean) of ten replicates was calculated for each parameter. Differences between parameters were analyzed using SPSSWIN software version 17 by analysis of variance one - way (ANOVA). Least Significant Differences (LSD) test for comparison between groups and an overall significance level of $p \leq 0.05$, 0.01, and 0.001 followed by Dunnett's Test.

3- Results

Most human health risk assessments are based on animal studies. The human data together with animal data can contribute to a weight - of - evidence analysis in the characterization of human health risks. Similarly, animal data at high doses or routes of exposure not typical for humans also pose challenges to dose-response evaluations needed for risk assessments (**Li *et al.*, 2012**). Many studies conclude significant adverse health effects in the absence of adequate or even rudimentary exposure quantification. Moreover, it appears that epidemiological studies in humans and toxicological studies in experimental animals may both suffer from inadequate exposure assessment (**Ritter and Arbuckle, 2007**).

3 - 1 - Hematological Indices:

Hematopoitic and leukocytes systems are the two dynamic systems which react quickly to environmental changes and maintain the homeostasis. Hematological parameters show conspicuous and significant changes in response to any kind of toxic stress. (**Haratym - Maj, 2002)**.

The hematological study revealed a highly significant decrease of ($p \leq 0.01$) in total erythrocyte counts (TEC) at the mancozeb - treated group III (500 mg / kg b w., MZ2) and very highly significant decrease of ($p \leq 0.001$) in total leukocyte counts (TLC) at a dose of 250 mg / kg b w. (Group II, MZ1) as compared to the control group (Table 1). Meanwhile, the MCV and MCH were increased significantly ($p \leq 0.001$) with higher doses. Furthermore, no significant changes in hemoglobin (Hb), packed cell volume (PCV) and mean corpuscular hemoglobin concentration (MCHC) values were recorded in all treatment groups (Table 1).

Table (1): Effect of Mancozeb (Blanko - 75 % WP) on hematological parameters of male albino rats after exposure for 30 days.

Parameters \ Treatments	C	MZ1	MZ2
TEC (X 10^6 / µl)	6.518 ± 0.2216	6.322 ± 0.4734	4.856 ± 0.2663 **
TLC (X 10^3 / µl)	12.65 ± 0.2842	8.238 ± 0.4214 ***	12.16 ± 0.4383
Hb (g / dl)	10.667 ± 0.4479	9.671 ± 0.7369	10.965 ± 0.4341
PCV (%)	47.2 ± 0.8602	44.6 ± 2.9933	48.6 ± 2.2271
MCV (Fl)	72. 663 ± 1.8236	71.818 ± 5.8607	102.83 ± 10.053 **
MCH (Pg)	16.46 ± 0.8714	17.128 ± 1.6071	23.9 ± 2.3415 **
MCHC (%)	22.6 ± 0.8452	23.54 ± 1.5610	22.633 ± 0.4412

TEC = Total Erythrocyte Count. TLC = Total Leukocyte Count. Hb = Hemoglobin. PCV = Packed Cell Volume. MCV = Mean Corpuscular Volume. MCH = Mean Corpuscular Hemoglobin. MCHC = Mean Corpuscular Hemoglobin Concentration.
Data expressed as means ± SEM (ten rats).
C = group I as Control group. MZ1 = group II treated with 250 mg / Kg b. w / day. MZ2= group III treated with 500 mg / Kg b. w / day. *= $p \leq 0.05$ vs. control. **= $p \leq 0.01$ vs. control. ***= $p \leq 0.001$ vs. control.

3 - 2 - Clinco - Biochemical Parameters:

Liver and kidney are important vital organs in the animal body as they are the sites of detoxification and elimination of toxic materials. A foreign body in the form of a chemical stress is sufficient enough to cause severe hepatic and renal dysfunction (**Waggas, 2013).**

Some of the biochemical findings in mancozeb treated male albino rats published in the accessible literature have been shown in Tables 2. Our data showed an increase ($p \leq 0.05$) in enzymatic activity of aspartate aminotransferase (AST) and in albumin concentration at the highest dose (MZ2, 500 mg / kg / b w.) and the lowest dose (MZ2, 500 mg / kg / b w.). Meanwhile alkaline phosphatase (AKP) and acetylcholine esterase (AChE) activity was inhibited significantly at the lowest dose and the both doses, respectively (Table 2).

Table (2): Effect of Mancozeb (Blanko - 75 % WP) on liver and kidney functions in plasma of male albino rats after exposure for 30 days.

Parameters \ Treatments	C	MZ1	MZ2
Liver Functions			
ALT (U / l)	30.336 ± 1.8622	30.054 ± 0.7023	26.557 ± 2.6483
AST (U / l)	103.71 ± 5.9394	105.86 ± 4.1868	127.30 ± 9.3376 *
AKP (U / l)	273.23 ± 16.5804	216.49 ± 21.3413 *	237.78 ± 9.0017
AChE (U / l)	769.00 ± 44.18	705.25 ± 26.23 ***	701.35 ± 51.085 ***
T. Protein (gm / dl)	7.5102 ± 0.14933	6.5332 ± 0.4792	6.698 ± 0.4844
Albumin (gm / dl)	3.7174 ± 0.2498	5.2396 ± 0.5048 *	4.6752 ± 0.3200
Glucose (mg / dl)	96.5322 ± 1.3838	87.533 ± 6.9814	85.9334 ± 4.5987
Kidney functions			
BUN (mg / dl)	28.0646 ± 1.0496	22.1034 ± 1.3553 **	19. 4168 ± 1.1652 ***
Creatinine (mg / dl)	0.952 ± 0.03725	0.6528 ± 0.04080 ***	0.884 ± 0.03725

ALT = Alanine Aminotransferase. AST = Aspartate Aminotransferase. AKP = Alkaline Phosphatase. AChE = Acetyl Choline Esterase. BUN = Blood Urea Nitrogen.
Data expressed as means ± SEM (ten rats).
C = group I as Control group. MZ1 = group II treated with 250 mg / Kg b. w / day. MZ2= group III treated with 500 mg / Kg b. w / day. *= $p \leq 0.05$ vs. control . **= $p \leq 0.01$ vs. control. ***= $p \leq 0.001$ vs. control.

The results of the biochemical analysis revealed no significant changes in alanine aminotransferase (ALT) activity; total protein and glucose concentration in all treatment groups (Table 2). On the other hand, blood urea nitrogen (BUN) and creatinine were decreased with the all treatments of mancozeb and MZ1 (Table 2).

The biochemical analysis of lipid profiles in the mancozeb - treated groups as compared to the control group of albino rats for 30 days (Table 3), the total plasma lipid level showed highly significant ($p \leq 0.01$) increase (at a dose of 250 mg / kg b w., MZ1), total cholesterol (TC) level showed very highly ($p \leq 0.001$) and highly significant ($p \leq 0.01$) increase at both doses respectively. Also, high and low density lipoprotein (HDL and LDL) showed very highly significant ($p \leq 0.001$) increase in low and both doses respectively. While, triglyceride (TG) showed a significant decrease ($p \leq 0.05$) at the lowest dose as compared to the control group (Table 3).

Table (3): Effect of Mancozeb (Blanko - 75 % WP) on lipid profile in plasma of male albino rats after exposure for 30 days.

Parameters \ Treatments	C	MZ1	MZ2
T. Lipids (g / dl)	**55.4612 ± 2.8588**	**74.1694 ± 5.3981** **	**60.526 ± 4.1836**
T. Cholesterol (mg / dl)	**67.9614 ± 2.1811**	**86.6076 ± 2.9806** ***	**93.998 ± 1.7611** ***
Triglyceride (mg / dl)	**64.734 ± 4.8928**	**44.711 ± 4.1501** *	**65.946 ± 6.3739**
HDL (mg / dl)	**23.106 ± 1.1017**	**22.2324 ± 1.2308**	**34.9982 ± 1.4031** ***
LDL (mg / dl)	**29.1915 ± 1.8491**	**55.4330 ± 2.9798** ***	**45.8106 ± 2.6792** ***

HDL = High Density Lipoprotein. LDL = Low Density Lipoprotein.
Data expressed as means ± SEM (ten rats).
C = group I as Control group. MZ1 = group II treated with 250 mg / Kg b. w / day. MZ2= group III treated with 500 mg / Kg b. w / day. *= $p \leq 0.05$ vs. control . **= $p \leq 0.01$ vs. control. ***= $p \leq 0.001$ vs. control.

3 - 3 - Relative Organ Weight Changes:

The analysis of relative organ weight in toxicological studies is an important criterion for identification of potentially harmful effects of chemicals (**Bailey *et al.*, 2004**).

In the present study, repeated exposure to mancozeb has caused a significant increase in the relative weight of the liver ($p \leq 0.001$), kidneys ($p \leq 0.05$) and brain ($p \leq 0.05$) at the highest dose as compared to the control group (Table 4). As well as, the organ body weight ratio of the testes was increased ($p \leq 0.01$) at both doses but, spleen ($p \leq 0.01$) and heart ($p \leq 0.05$) was decreased in MZ1 group (Table 4).

Table (4): Effect of Mancozeb (Blanko - 75 % WP) on organ weight ratio (mg / 100 g b. w) of male albino rats after exposure for 30 days.

Organs \ Treatments	C	MZ1	MZ2
Liver	**10.700 ± 0.1383**	**10.995 ± 0.1189**	**12.166 ± 0.2543** ***
Kidney	**4.8377 ± 0.06754**	**4.6658 ± 0.10556**	**5.1151 ± 0.07321** *
Brain	**5.1352 ± 0.07091**	**5.1722 ± 0.12914**	**5.5115 ± 0.06075** *
Spleen	**3.7243 ± 0.08294**	**3.7140 ± 0.02305** *	**3.5354 ± 0.06837**
Heart	**3.4771 ± 0.05386**	**3.3034 ± 0.04774** *	**3.5692 ± 0.03291**
Lung	**4.3398 ± 0.10890**	**4.3984 ± 0.07290**	**4.5069 ± 0.07995**
Testes	**5.2405 ± 0.29699**	**6.1430 ± 0.06975** **	**6.2693 ± 0.07580** **

Data expressed as means ± SEM (ten rats).
C = group I as Control group. MZ1 = group II treated with 250 mg / Kg b. w / day. MZ2= group III treated with 500 mg / Kg b. w / day. *= $p \leq 0.05$ vs. control . **= $p \leq 0.01$ vs. control. ***= $p \leq 0.001$ vs. control.

4- Discussion

Blood or hematological parameters are probably the more rapid and detectable variations under stress and are fuel in assessing different health conditions (**Hymavathi and Rao, 2000; Friday *et al.*, 2012).**

In the present investigation a significant decrease in total erythrocyte and leukocyte counts were observed, however, the increase in MCV and MCH was noticed. These results were agreeing with **Wael, 2012** who reported treating mice with metalaxyl for 2 and 4 weeks induced a significant decrease in the RBC count**.**

Lowering of RBC count might be due to the damaging action of pesticides on peripheral red cell due to which viability of the cell was affected (**Jerald, and Saradhamani, 2015). Witeska (2004)** suggested that the decrease in WBC count could be the result of autolysis caused due to hemolytic enzymes leaked out by the cells under toxicant stress.

The increase in MCV and MCH values after exposure to deltamethrin indicates that a reduced RBC count may be due to the destruction of erythrocytes or their decreased synthesis in bone marrow (**Rauf and Arian, 2013**).

The present study showed that mancozeb induced many biochemical changes in the plasma of male rats. The liver function, enzyme AST was elevated; AKP and AChE were depressed in the plasma of mancozeb - treated rats. This is in agreement with the result of **Sakr *et al.* (2005)** who found that these enzymes increased in sera of mice administered with mancozeb. **Kackar *et al.* (1999)** also reported that oral administration of mancozeb at doses 500, 1000 and 1500 mg / kg / day for 98, 180 and 360 days in male rats induced changes in the activities of ALT, AST, alkaline phosphatase, and acetylcholinesterase throughout the period of the study in a dose - dependent manner. Treating albino rats with mancozeb induced various histological changes in the liver. Mancozeb also caused a significant elevation in serum AST activities (**Sakr, 2007**). Also, **Sunder and Rao (1998)** have reported administration of mancozeb along with metalaxyl to male rats for 90 days caused a significant increase in the serum aspartate amino transferase (ASAT).

Previous studies have shown that mancozeb alone is toxic to the liver by increasing plasmatic concentration of hepatic enzymes such as alanine aminotransferase, aspartate amino transferase (**Hernández *et al.*, 2006**).

A metabolite of mancozeb into glycine, affect several enzymatic pathways. Mancozeb has ability to modify the effect of several enzymes. These enzymes are blood soluble enzyme and best indicator of stress conditions (**Palanivelu, *et al.*, 2005).** The presence of manganese and zinc in the additional formula could also cause the production of free radicals (**Negga, *et al.*, 2012)**. The increased activity of hepatic aminotransferases reflects a genetic abnormality in their production in order to overcome toxicants - induced oxidative stress (**Arshad *et al.*, 2007; Afshar *et al.*, 2008**).

Membrane damage might have caused leakage of AKP from hepatocytes into the blood stream, so the lower hepatic AKP was seen in the present study as reported by **Bhushan, *et al.*, (2013); Arshad, *et al.*, (2007); Singh, and Saxena, (2001); Singh, *et al.*, (2005) and Pereira, *et al.*, (2006).**

Similar to this **Nagoha *et al.*, (1989)** reported decreased AKP in liver and kidney of rats treated with chloroquine. In addition, decreased ALP activity has been found in serum and liver in the rats administered with HCH and methyl parathion, (**Dikshith *et al.*, 1991**).

Cholinesterase was markedly depressed to a different degree in plasma of mancozeb - treated rats at both doses. These findings also was conformed by **Wielgomas and Krechniak, 2007** who noticed that cholinesterase was markedly depressed to a different degree in plasma and brain of animals receiving chlorpyrifos alone or in combination daily in rapeseed oil for 14 and 28 days. Also, **Jacobsen *et al.*, (2004)** reported that in a repeated dose 28 - day oral study, significant inhibition in plasma ChE in male rats exposed to chlorpyrifos at doses of 0.15 and 0.3 mg / kg bw / day, was found.

Mancozeb metabolites, Carbon disulphide and Ethylene thiourea are involved in the dysfunction of the nervous system. The ability of DTC to inhibit acetylcholine esterase was considered to cause neuropathy (**Edwards *et al.*, 1991**). Increased production of reactive oxygen species by the actions of mancozeb and zineb is also implicated in their neuronal toxicities (**Domico *et al.*, 2007**).

Renal function indices such as serum electrolytes, urea and creatinine are commonly used to evaluate the functional capacity of the nephrons of animals, (**Yakubu, *et al.*, 2003).** The present study showed that mancozeb induced decrease in level of urea and creatinine at MZ1 and MZ2 groups compared with the control group. The study reveals that mancozeb might have affected cell metabolism and active transport of ions across cell membranes, cellular defense mechanism and detoxification system in the liver and kidney (**Ksheerasagar, *et al.*, 2011).** Studies have shown that the serum creatine concentration is a better indicator of glomerular filtration rate (**Khalil, *et al.*, 2002)**.

The lipids are the sources of energy. Cholesterol is essential for membrane synthesis and the precursor for steroid hormones also for vitamin D, which is essential for regulation of calcium and phosphorus metabolism and bone growth **(Razia, 2015; Ksheerasagar, *et al.*, 2011)**.

The obtained results are summarized as follows: administration of mancozeb at both doses does induce an increase in total lipid, cholesterol, HDL and LDL levels and triglyceride level was decreased in treated groups. Our result are similar to those obtained by **Djeffal *et al.*, (2012)** who founded an increase in cholesterol levels of the rats after exposing to methomyl; **Haneia, *et al.*, (2013)** who showed that other observations revealed an increase in rats` total lipids after 28 days of oral administration of methomyl and **Devendra, *et al.*, (2009)** who reported treatment with individual doses of carbofuran (50 % LD_{50}) and cartap (50 % LD_{50}) caused significant alterations in the levels of serum lipid parameters. The pesticide treatment resulted in marked significantly elevated at the level of other lipids.

Also our results were in the conformity with that reported by **Kumar - Verma, and Singh, (2014)** who showed significant increase in total lipid and total cholesterol after acute and subacute ziram treatment on rat; and **El - Tawil, (2014)**, who suggested that there were significant increases in total lipid content for both treated sexes compared to those of control rats on adult male and female albino rats fed on poisoned diet containing chlorpyrifos (at 200 ppm), or Chlorpyrifos - methyl (at 2000 ppm) for 12 weeks followed by 3 weeks of recovery period.

The increased cholesterol level could be attributed partially to disorder of metabolic pathways (**Shivanandappa, and Krishnakumari, 1981 & Shakoori *et al.*, 1988)** and / or to the effect of pesticides on the permeability of the liver cell membrane (**Yousef, *et al.*, 2003 and 2006).** The increase in cholesterol level indicates inhibitory action of the pesticide (Diethyl Dithiocarbamate) on hepatic Cyt - p - 450 enzymes in rats (**Siddiqui *et al.*, 1987; Stott *et al.*, 1997**), or might be due to the high affinity binding (**Zarh *et al.*, 2002**).

We observed a significant increase in total plasma cholesterol accompanied with increase LDL - cholesterol while triglyceride was not significantly altered. It is possible to suggest that reverse cholesterol transport is not affected; rather cholesterol synthesis and transport to the peripheral tissue might be affected. It is possible that in addition to increase activities of 3 - hydroxyl -3 - methylglutaryl coenzyme A reductase (HMGCoA) the rate limiting enzyme is reduction of LDL receptors for cholesterol in cholesterol biosynthesis resulting in increase synthesis of cholesterol in the monosodium glutamate (MSG) treated rats (**Okediran *et al.*, 2014)**.

Relative organ weight can be the most sensitive indicator of the effect of an experimental compound, as significant differences in organ weight between treated and untreated animals may occur in the absence of any morphological changes (**Michael *et al.*, 2007; Bailey *et al.*, 2004**). Moreover, differences in the way that vital organs react to toxins can also have a significant impact on overall toxicity (**Trimbell, 1991**).

In the present study, repeated exposure to mancozeb has caused a significant increase in the relative weight of the liver, kidneys, brain, spleen, and testes and significant drecrease of the heart and lungs. Our results are similar to those obtained by **El - Sayed, *et al.* (2012)** found that exposure to low dose equivalent to (1 / 20 LD_{50}) and high dose equivalent to (1 / 10 LD_{50}) of dimethoate, carbofuran and carbendazim administered for 30 days increased the relative weight of liver, and kidney. Also, **Kingsley and Iniobong, (2014)** noticed that a significant increase in the absolute and relative weight of liver and kidney of rats in the group treated with 400 mg / kg BW of Solignum® and **Saeed, (2016)** reported The effect of lead on the weight of different organs was markedly elevated during the experimental period of all treated groups of both sexes.

In addition **El - Tawil, (2014)** suggested that, the relative weights of lungs, liver, kidneys and brain of both sexes rats fed on poisoned diet containing chlorpyrifos (at 200 ppm), or Chlorpyrifos – methyl

(at 2000 ppm) for 12 weeks followed by 3 weeks of recovery period compared to those of controls.

Furthermore, changes in kidney weight may reflect renal toxicity, tubular hypertrophy or chronic progressive nephropathy and in brain weights were rarely associated with neurotoxicity (**Greaves, 2000**). As well as, **Creasy and Foster, (2002**) suggested that changes in testes weights may reflect changes in seminiferous tubules or interstitial edema and therefore usually contribute little further understanding of toxicity.

5- Conclusion

Results reported in the present study showed mancozeb exposure leads to detrimental effects and significant changes in hematological and biochemical activities during the exposure period on male albino rats. It is concluded that the rat hematological parameters showing anemia conditions. Mancozeb has strong potential to disturb normal blood biochemistry inducing hepatocellular, renal damage, hyperlipaemia, hypochalesterolemia, and increase in the weight of different organs.

Finally, importance of this compound and the number of people potentially exposed such as workers engaged in the production and use of the fungicide, people living in agricultural areas where the compound is sprayed and people consuming polluted products. Therefore, the results suggest that the present study is too immensely because mancozeb has been one of the most commonly used fungicides in commercial use.

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