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The Roles of Honeybee Solution on the Physiological Parameters of Rats Exposed to Cadmium Chloride

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Abstract: This study was conducted to determine changes in some physiological parameters of albino rats (*Rattus norvegicus*) caused by (1) two levels of dietary cadmium chloride alone and (2) honeybee solution added to cadmium chloride together. The experimental rats distributed into two experiments with a shared control group (first group). In experiment first low and high dose, (50 and 100 mg/kg body weight) of cadmium chloride were orally administrated to the rats and named second and third groups respectively. In experiment second, the same two concentrations of cadmium chloride and honeybee solution (10g/kg body weight) were added to each and named fourth and fifth groups respectively. Water and food were provided *ad libitum*. The results indicated that, in experiment first, serum albumin & calcium and blood hemoglobin were significantly decreased compared with control. Moreover, honeybee solution showed significant improvement of albumin, hemoglobin and calcium of experiment second compared with experiment first. In addition, honeybee solution appears significantly decreased serum urea of the experiment second, compared with experiment first, while; cadmium dosed alone demonstrated highly significant increase in serum urea compared to the corresponding control group. Serum iron highly significant increase, in experiment first compared with control. Moreover, urine delta aminolevulinic acid was significantly increased in experiment first compared with the control rats. On the other hand, administering honeybee solution with cadmium chloride do not normalize iron and delta aminolevulinic acid in relation to control, while improvement of (iron and delta aminolevulinic acid) compared with the experiment first. In addition, adding honeybee solution to cadmium level did not normalize serum sodium and chloride in relation to control group, while improvement was obvious after increasing cadmium alone. The enzyme activity of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), Acid phospatase (ACP), serum alkaline phaospatase (ALP) and lactate dehydrogenase (LDH) were highly significant increased by orally administration of low and high cadmium alone compared with control group, while adding honeybee solution to low and high cadmium concentrations did not normalize these enzymes comparing with the control, but showed that improvement in comparing with groups orally cadmium alone. These results demonstrate that honeybee solution could have protective effects on the functions of cells by inhibiting the translocation of bad effects of cadmium chloride, and that honeybee solution improve the studied physiological parameters in cadmium intoxificated rats.

Key words: honeybee solution- cadmium chloride - physiological parameters – rats.

INTRODUCTION

Trace elements were known to have a variety of important biological functions and in, many instances, they may have adverse effects on biological system (Tephyly *et al.,* 1978; Deure *et al.,*1981 and Abd-Reheem & Zaahkcuk, 2007). Cadmium exists in the air and water pollutants .In this respect, cadmium is a heavy metal of wide occupational and environmental contamination ,and present in trace levels in seawater and in a broad range of animal and plant species ,relatively large quantities of cadmium are found in commercial phosphate fertilizer ,thus the increases in soil and plant cadmium contents may lead to increases in dietary cadmium. Also, cadmium poses a potential environmental hazard due to increased in its industrial use (Vallee and Ulmer, 1972; McDowell, 1992; Klos, 2001 and kowalczyk *et al.,* 2003). Cadmium toxic effects on biological systems have been extensively reported (Lewis, 1997). Free radicals are evolved at the early stages of cadmium intoxication (Ochi *et al*., 1987 and Rechelmi *et al.,* 1989). Gastrointestinal absorption of cadmium is affected by the type of diet and nutritional status (Yannai and Sachs, 1993).Absorption of ingested cadmium is only

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about 5% and when absorbed it accumulates first in the liver and then in the kidney where its half-life is about 20-30 years (Khandelwal *et al.*1991 and McDowell, 1992).The high dietary levels of cadmium results in suppressed feed intake, reduction in bone mineralization and anemia (McDowell, 1992). The biochemical alteration occur prior to morphological changes in the organs, and changes in certain enzyme levels in the extracellular fluids may reflect the extent of cadmium –induced damage in target organs (Khandelwal *et al.,* 1991 and Abd EL-Reheem, 2008). Kidneys and liver are considered the most susceptible organs in the case of exposure to cadmium (Yamano *et al.*, 1999; Yiin *et al*., 1999 and Ryan *et al.,* 2000). An increase of asparatate aminotransferase (AST) and the most specific marker of liver cell damage- alanine aminotransferase (ALT) (Sauer *et al.,* 1997; Blasco and Puppo, 1999 and Kowa lcyk *et al.,* 2003) manifest the damaging effect of cadmium on the liver. Sherlock and Dooley (2002) and Lee *et al.* (2007) reported that, Lactate dehydrogenase (LDH) is another index of hepatotoxicity, although the plasma LDH level is relatively insensitive when exposed to cadmium.

It is known that chronic exposure to cadmium can induce severe nephropathy in humans (Goyer, 1995) and animals (Aughey *et al.,* 1984 and Brozoska *et al.,* 2003). This nephrotoxic causes reabsorptive and secretory dysfunction of the renal tubule .The main signs include generating free radicals (Hassoun *et al*.,1996; Reyes *et al*., 2002 and Jacquillet *et al*., 2006) and by inducing necrosis and apoptosis (Dally and Harwig, 1997).Several mechanism have been proposed to explain the toxic effect of Cd^{2+} on renal cells. Cd^{2+} may cause nephrotoxicity by generating free radicals (Hassoun and Stohs, 1996 and Reyes *et al.,* 2002) and by inducing necrosis and apoptosis (Dally and Harwing, 1997).

Wahadan (1998) reported that the honeybee contains compounds have antimicrobial and antioxidant activities. On the other hand, the tent also honey and *Nigeila sativa* are medicine are indicated by Bergman, *et al.,(*1983); Elkhadi and Khandil (1986); Ali *et al*. (1997) and Qidwia *et al*. (2003) found that honey and *Nigella sativa* have ant-inflammatory , anticancer antithrombotic and cardiovascular effects or different medical conditions have been documented. Also Abd EL-Reheem (2008) reported that honeybee solution protected against the bad effect of cadmium on some physiological parameters .Few studies were dealt with the therapeutic effect of honey bee solution against the bad effect of heavy metals, therefore in this study, we tested the effects of honeybee solution in rats by examining its protective effects against cadmium chloride induced toxicity in rats.

MATERIALS AND METHODS

Experimental animals and design:

Albino female rats (*Rattus norvegicus*) with mean body weight of 131±10 g were kept in animal house with stable temperature, humidity. These animals were acclimatized to pilot experimental conditions for two weeks before the onset of the experimental period of other (five weeks). The distributed considered rats were divided into two experiments sharing a control group and named first group. Each experiment has two groups, and each group has five female rats. Doses were done weekly through stomach tube. All groups were fed with standard foodstuffs and they had free access to drinking water, (Food and water were supplied *ad libitum* during the five weeks of the experimental periods).

Experiment first:

The experimental animals solution contains 50mg/kg body weight of cadmium chloride (low level) and named second group; however, the third group received a solution contain 100 mg/kg body weight of cadmium chloride (high level) orally administrated to the rats in each week to each rat.

Experiment second:

The rats received solution contains honeybee (10g/kg body weight) plus 50mg/kg body weight of cadmium chloride (low level) and named fourth group. Finally, fifth group-received solution contains honeybee (10g/kg body weight) and solution of (100 mg/kg body weight) cadmium chloride together and orally administrated to each rat.

Blood sampling from the rats:

Blood samples were withdrawn from the retro-orbital sinus of the eye each rat using heparinized micro-haematocrit capillary tube at the end of each week one part of blood to determined hemoglobin at once during the time sampling of blood in each rat, and the other part was serum.. Sera were separated by centrifugation at 3000 rpm for 15 minutes after 1-hour incubation at room temperature and , sera were stored at (-70 °C)for the other physiological parameters analyses.

Urine sampling from each rat:

Urine was collected for twenty four hours from each rat, total urine was recorded and one ml of urine was placed into polypropylene tube with 0.2g of sodium bicarbonate and stored in aluminum foil-wrapped tubes at(-70˚C) for determined the delta aminolevulinic acid in urine (δ ALA).

Physiological analyses:

Albumin in serum.

Colorimetric method for the quantitative determination of albumin based on reaction with, Bromocresol green forming, a green colored complex. The colour intensity of which is proportional, to the concentration of albumin present in the sample and albumin concentration by (mol/L), was assayed using an analysis kit according to manufacturer's instructions (Quimica Clinica Aplicada S.A. Spain) and analyzed on spectrophotometer Jacso V560.

Urea in serum:

Kits using the method described by Chaney and Marbach. (1962) for estimated urea in serum, (mmol/L).The samples were analysed for urea concentration using spectrophotometer Jacso V560.

Hemoglobin in blood:

Hemoglobin in blood concentration was determined according to the method of Drabkkin & Austin (1993) and the concentration of hemoglobin in blood was (mmol/L.

Iron in serum:

Colorimetric method for the quantitative determination of iron ions react with ferrozin to form a colored complex under acidic conditions, iron is liberated from transferrin and the concentration by (µ mol/L) according to the method by Siedel *et al*., (1983) .Was assayed using an analysis kit according manufacturer's instructions (ProDia International UAE European authorized representative ID consulting service e.k. Korbach /Germany). Using spectrophotometer Jacso V560.

Delta dminolevulinic acid in urine (δ ALA):

Urinary delta aminolevulinic acid (µmol/L) was assayed in urine by the method of Davis and Andelman (1967).

Calcium serum:

Vitro calcium reagent is intended for the in vitro quantitative determination of calcium in serum; colorimetric endpoint method based on the cersolphthalein comlexone reaction and calculated by (mmol/L) was assayed using an analysis kit according to the manufacturer's instructions (Vitro Scient, Egypt). Using spectrophotometer Jacso V560.

Sodium in serum:

Colourimetric test, magnesium-uranyl acetate method for the *in vitro* determination of sodium in serum rats, after the precipitation of sodium magnesium –uranyl acetate, in the supematant form with uranyl ions in solution with thioglycolic acid a yellow-brown coloured complex. The optical density difference between the reagent blank (without precipitation of sodium) and the result of the analysis is proportional to the sodium concentration (mmol/L) was assayed using an analysis kit according manufacturer's instructions (Quimica Clinica Aplicada S.A. Spain). Using spectrophotometer Jacso V560.

Chloride in serum:

Colorimetric method for the quantitative determination of chloride ions reacts with mercurious thiocyanate to form mercury perchlorate and thiocyanate. The liberated thiocyanate forms a red complex with ferric chloride in the presence of nitric acid and chloride concentration by (mmol/L) according to the method by was assayed using an analysis kit-according manufacturer's instructions (Quimica Clinica Aplicada S.A. Spain). Using spectrophotometer Jacso V560.

Serum acid phosphatase:

Acid Phosphatase and alkaline Phosphatase in serum (activity U/L) was assayed using analysis kit according to the manufacturer's instructions (Customer service diagnostic com.)And read on spectrophotometer Jacso V560

Serum alkaline Phosphatase:

Alkaline Phosphatase in serum (activity IU/l) was assayed using analysis kit by the method according to the manufacturer's instructions (Customer service diagnostic com.). Using spectrophotometer Jacso V560

Serum alaninine aminotransferse (ALT) and aspartate aminotransferase (AST):

ALT and AST in serum (activity U/l) were assayed using analysis kit for each respective enzyme according to the manufacturer's instructions (Sclavo diagnostics kite Italia S.P.A.).The concentration was determined Using spectrophotometer Jacso V560.

Lactate dehydrogenase (LDH):

In vitro LDH reagent is intended for the in Vitro quantitative determination of lactate dehydrogenase activity in serum rats by using the following formula: U/L=8095× ΔA × 1.22 at (340 nm/min and assay temperature 25 °C) where (ΔA) is the change in absorbance per minute from the linear portion of the reaction curve and (1.22 is the temperature correction) was assayed using an analysis kit according to the manufacturer's instructions (Vitro Scient, Egypt**)**. Using spectrophotometer Jacso V560.

Statistical method:

ANOVA and Student t-test were used to analyze differences in quantitative variables between data of control and experimental data of animal groups. In addition, comparisons between the two groups of the effect experiment first with the effect of two groups of the experiment second. Significant differences were considered only at ($P < 0.05$). The obtained data were expressed as means ± Standard deviation. Statistical analyses were performed using a statistical software package (SPSS) according to the method of Sokal and Rahif (1981). The data were figured as the general mean of twenty-five reading of each result.

RESULTS AND DISCUSSION

Variation in total serum albumin:

Data in (Table 1) and (Fig. 1A) and the statistical analyses in (Table 3). showed that, cadmium chloride caused highly significant decreases in serum total albumin of rats orally administrated low and high cadmium chloride in relation to the control group. On the other hand, addition honeybee solution to cadmium chloride did not normalize the serum total albumin concentration comparing with control group, while honeybee solution significantly increased total albumin in relation to the rats orally cadmium alone (albumin decreased in cadmium alone).

Effect of treatment on serum urea of the rats:

Data in (Table 1) and (Fig. 1B) and the statistical analyses in (Table 3) revealed that, highly significant increased in serum urea concentration through the experimental period of rats under low and high dose of cadmium chloride compared with the control group. While adding honeybee solution to the low or high cadmium groups resulted in decreased significant of serum, urea compared with treated rats with cadmium alone but not normalized when compared with control rats.

Effect of treatment on the blood hemoglobin in the rats:

As shown in (Tables 1&3) and (Fig. 1C): exposure rats to cadmium chloride resulted in highly significant decreased in blood hemoglobin at low and high levels of cadmium chloride compared with the results of control group. On the other hand, adding honeybee solution to the same levels of cadmium chloride did not normalized the hemoglobin of the rats in comparing with the control group. While comparing the honeybee solution plus cadmium groups found that increased of blood hemoglobin compared with the cadmium groups alone (hemoglobin was decreased after administering cadmium chloride alone).

Changes in serum levels iron in the rats:

As shown in (Table 1) & (Fig. 1D) and the statistical analyses in (Table 3); the obtained results indicated that rats exposed to low and high levels of cadmium chloride resulted in a significant increased in serum iron concentration in comparing with the control group. On the other hand, adding honeybee solution to the low or high cadmium chloride to the rats resulted in highly significant decrease in serum iron concentration in the rats compared with the rats orally cadmium alone ,while adding honeybee to the cadmium did not normalized the serum iron compared with the control group.

Effect of administration cadmium chloride and honeybee on concentration of Delta Aminolevulinic acid in urine (δ ALA):

The results of groups (in which the rats were given orally low and high cadmium chlorides only) and groups (in which rats orally honeybee solution and cadmium chloride) are shown in (Tables 1) and (Fig. 1E) and the statistical analyses in (Table 3).Significant increases of delta Aminolevulinic acid in urine (δ ALA) groups orally low and cadmium chloride solution alone comparing with the control group .However adding honeybee solution to the low and high levels of cadmium chloride and orally administrated to rats (experiment second)did not normalized the delta aminolevulinic acid in urine comparing with the control group. While honeybee with cadmium chloride solution decreased delta aminolevulinic acid in urine of rats orally administrated honeybee plus cadmium chloride compared with rats orally cadmium alone in experiment first.

Change in calcium concentration of the serum experimental groups:

Results in (Tables1) & (Fig. 1F) and the statistical analyses in (Table 3), showed that, administering low and high cadmium chloride solution levels to rats resulted in a statistically significant decrease of calcium concentration of serum rats (experiment first) in comparing with the control group. On the other hand, rats orally administrated solution of honeybee and cadmium chloride (experiment second) did not normalize the calcium concentration in blood of rats in relation to the control group. While, comparing experiment second in which addling a solution of honeybee and cadmium chloride with experiment second first, resulted in increased of serum calcium in (experiment second) compared with rats in experiment first in which rats orally administrated cadmium chloride alone.

Changes in the serum sodium and chloride:

Effects of cadmium chloride at low and high levels administrated (experiment first) to the rats on serum sodium was showed in (Table 2) and (Fig.1G) and serum chloride in (Table 2) and (Fig. 2A) and the statistical analyses in (Table 3). Orally administrated of cadmium chloride to rats' results in a statistically highly significant increased of sodium and chloride concentration in serum rats in relation to the control group. On contrast, adding honeybee and cadmium chloride do not normalized the sodium and chloride concentration in serum of rats compared with the control group. While comparing experiment second (in which, adding a solution of honeybee and cadmium chloride) with experiment first (in which orally administrated a solution of cadmium chloride only to the rats) results in statistically highly significant decreased of sodium and chloride concentration in (experiment second) in relation to (experiment first).

Change in serum enzymes activity of the experimental rats:
Alanine and Aspartate aminotransferase activity (ALT & AST):

Results in (Table 2) and (Fig. 2B & C) and the statistical analyses in (Table 3) showed that, administering low and high cadmium chloride levels (experiment first) to rats resulted in a statistically significant increased of alanine and aspartate aminotransferase activity of blood rats in comparing with the control group. On the other hand, rats orally administrated a solution of honeybee and low or high cadmium do not normalized the alanine aminotransferase and aspartate aminotransferase activity in relation to the control group. However, adding honeybee solution to the cadmium chloride resulted in highly significant decreased of each alanine and aspartate aminotransferase activity of serum rats (experiment second) in comparing with the rats (experiment first orally cadmium alone) ALT &AST increased after administering cadmium chloride alone).

Serum acid and alkaline phosphatases activity:

Results in (Tables 2) and (Fig. 2D & E) and the statistical analyses in (Table3) showed that, administering low and high cadmium chloride levels to rats (experiment first) resulted in a statistically significant increased of each acid and alkaline phosphatases activity of blood rats in comparing with the control group. On the other hand, rats orally administrated a solution of honeybee and low or high cadmium chloride (experiment second) do not normalized the acid phosphatas or alkaline phosphatase activity in blood of rats in relation to the control group. However, when comparing experiment second and experiment first resulted in highly significant decreased of each acid and alkaline phosphatases activity of serum of rats in(experiment second) comparing with the rats orally cadmium alone (experiment first) (the above two enzymes increased with cadmium alone in experiment first).

Lactate dehydrogenase activity LDH:

Results in (Table 2) and (Fig. F.) and the statistical analyses in (Table 3) showed that, administering low and high cadmium chloride levels to rats resulted in a statistically significant increased lactate dehydrogenase activity (LDH) in serum of rats in comparing with the control group. On the other hand, rats in (experiment second) did not normalize the Lactate dehydrogenase activity (LDH) in relation to the control group. However, comparing experiment second with experiment first resulted in highly significant decreased of Lactate dehydrogenase activity LDH in serum rats in (experiment second) comparing with the rats in (experiment first in which LDH increased after administering cadmium chloride alone.

Table 1: Effect of honeybee solution (10g/Kg body weight) on the means concentrations of each of serum albumin, Urea, hemoglobin, Iron, calcium and urine delta amino levulinic acid of the rats orally received cadmium chloride solution at low level (50mg/kg. body weight) and high dose (100mg/Kg. body weight) in five weeks.

Parameters	weeks	control	Experiment I		Experiment II	
			Low dose cadmium	High dose cadmium	Honeybee and low dose cadmium	Honeybee and high dose cadmium
Albumin mol/L serum	1	588.4±7.7	443.6±12.9	440.4±12.9	574.2±12.9	568.2±19.2
	2	588.4±12.5	446.2±16.1	452.0±6.7	571.2±13.0	574.0±16.40
	3	587.6±25.5	440.6±7.7	437.0±6.7	576.8±12.2	559.4±16.6
	4	608.6±20.3	434.8±10.3	408.2±18.7	577.0±15.7	577.0±15.7
	5	600.0±8.2	434.8±10.3	437.2±12.2	579.8±17.6	570.8±24.3
	Means	594.6±17.	440.±11.7	434.±18.	575.8±13.5	568.5±119.
Urea mmol/L serum	1	3.4±0.40	6.4±0.9	8.8±0.12	3.7± 0.7	4.4±0.6
	2	3.9 ±0.4	7.4 ±0.8	10.3 ±1.1	4.1 ±0.5	5.1 ±0.5
	3	4.1 ±0.5	7.7 ±0.9	10.7 ±1.2	4.2 ±0.2	5.2 ±0.5
	4	4.3 ±0.3	7.7 ±0.2	11.2 ±0.6	4.5 ±0.3	5.6 ±0.3
	5	4.3 ± 0.2	8.2 ± 0.4	11.7 ± 0.6	4.8 ± 0.2	5.6 ± 0.4
	Means	4.0± 0.5	7.5± 0.9	10.6± 1.4	4.3± 0.6	5.2 ± 0.5
Hemoglobin mmol/L blood	1	2.02±0.2	1.6±0.2	1.4 ± 0.2	1.4 ±0.01	1.4±0.12
	2	1.9 ±0.11	1.5 ±0.02	1.3 ±0.2	1.7 ±0.01	1.6 ±0.01
	3	1.9 ±0.01	1.5 ±0.01	1.3 ±0.01	1.7 ±0.01	1.6 ±0.01
	4	2.0 ±0.01	1.4 ±0.02	1.2 ±0.02	1.8 ±0.02	1.7 ±0.02
	5	2.0 ± 0.01	1.4 ± 0.1	1.3 ± 0.1	1.8 ± 0.1	1.7 ± 0.01
	Means	2.0± 0.02	1.50± 0.25	1.30± 0.18	1.70± 0.25	1.60± 0.13
Iron µmol/L serum	1	20.3 ±3.2	78.4 ±9.5	96.6 ±5.5	38.0 ±6.2	61.0 ±6.3
	2	23.1 ± 3.3	83.9 ± 4.2	111.0 ± 9.5	36.3 ± 5.6	58.7 ± 5.0
	3	25.2 ±2.4	90.2 ±2.6	116.4 ±6.8	32.5 ±1.7	55.4 ±5.3
	4	25.5 ±1.0	107.6 ±3.2	120.9 ±9.8	30.3 ±1.0	51.7 ±4.8
	5	25.7 ±1.1	114.4 ±5.6	142.6 ±12.6	27.4 ±1.7	42.8 ±2.7
	Means	24.0 ±1.1	94.9 ±4.19	117.5 ±9.1	32.9 ±4.9	53.9 ±4.9
Delta Aminolevulinic acid µmol/L urine	1	19.3 ± 5.4	48.8 ± 2.5	49.9 ± 12.0	29.7 ± 0.4	31.9 ± 2.1
	2	24.3 ± 3.7	57.1 ± 1.2	67.1 ± 5.4	29.5 ± 0.4	31.1 ± 1.2
	3	25.9 ± 2.9	65.2 ± 3.2	79.4 ± 14.3	28.1 ± 0.6	30.6 ± 1.3
	4	28.0 ± 1.9	73.2 ± 2.6	86.8 ± 14.6	27.5 ± 1.1	31.9 ± 0.7
	Means	25.2 ± 4.6	64.1 ±10.6	75.3 ±10.3	28.4 ±1.6	31.2 ±1.6
Calcium mmol/L serum	1	2.34±0.012	1.4±0.13	1.3±0.13	2.14±0.11	2.04±0.11
	2	2.2 ±0.01	1.3 ±0.01	1.2 ±0.12	2.2 ±0.13	2.06 ±0.01
	3	2.3 ±0.01	1.3 ±0.01	1.23 ±0.11	2.2 ±0.01	2.12 ±0.04
	4	2.3 ±0.01	1.2 ±0.01	1.2 ±0.01	2.0 ±0.01	2.12 ±0.02
	5	2.31 ± 0.01	1.2 ± 0.01	1.12 ± 0.01	2.16 ± 0.01	2.12 ± 0.03
	Means	2.3± 0.12	1.3± 0.12	1.2± 0.11	2.15± 0.02	2.1± 0.03
Sodium mmol/L	1	150.2±2.2	204.5±11.6	263.1±4.2	150.3± 1.1	150.7±2.1
	2	143.4±2.4	210.4±8.4	252.6±3.4	145.4±1.4	150.3±1.7
	3	143.0 ±2.2	214.0 ±7.2	261.6 ±2.3	145.0 ±2.5	145.5 ±1.8
	4	142.8±1.92	222.8±10.4	264.8±3.7	144.7±2.01	148.1±5.18
	5	143.41 ± 2.07	224.0 ± 11.57	266.0 ± 4.7	145.4 ± 2.07	151.3 ± 1.7
	Means	144.6± 3.5	215.3± 11.9	261.6± 5.9	146.2± 2.7	149.2± 3.4

All values are given as the means ± standard deviation (mean ± SD); each value represents five rats in each week

Table 2: Effect of honeybee solution (10g/Kg body weight) on the means concentrations of each of serum sodium, chloride, ALT, AST, ACP, ALK and LDH of the rats orally received cadmium chloride solution at low level (50mg /kg. body weight) and high dose (100mg /Kg. body weight) in five weeks.

Parameters	weeks	Control	Experiment I		Experiment II	
			Low dose cadmium	High dose cadmium	Honeybee and low dose cadmium	Honeybee and high dose Cadmium
Chloride mmol/-^{1} serum	1	101.6±0.8	137.4±7.8	176.34±2.8	109.16±17.3	100.1±0.7
	2	99.1±1.2	145.5±1.2	174.4±4.2	101.7±1.7	101.7±1.2
	3	100.8±1.2	150.8±5.0	183.6±2.8	103.2±1.0	102.3±1.7
	4	100.8±2.3	158.3±12.3	186.1±7.3	102.2±3.0	103.3±1.3
	5	103.0±1.2	161.2±8.2	190.3±3.4	105.4±1.6	104.0±0.9
	Means	101.1±1.8	150.6±11.7	182.1±7.1	104.1±7.8	102.3±1.7
Serum Alanine amino transferaseU/l	1	42.2±2.6	78.5±6.9	113.7±2.4	39.4±3.7	75.7±3.6
	2	40.5±3.2	83.7±3.3	116.8±2.7	32.9±2.2	54.7±2.9
	3	41.0±3.4	85.5.±5.3	120.5±2.4	33.0±1.6	52.9±1.8
	4	42.0±1.3	91.4±1.4	123.3±2.6	31.2±1.3	52.0±1.6
	5	39.0±2.0	92.6±1.4	127.2±3.2	29.1±1.0	50.9±0.9
	Means	40.9±2.6	86.3±6.6	120.3±5.4	33.1±4.0	57.3±9.8
Serum Aspartate amino transferase U/l	1	64.2±2.6	116.9 ±11.5	189.6±7.2	90.8±2.1	95.6±4.1
	2	63.3±2.5	145.5±4.4	191.2±4.9	84.2±3.1	92.8±3.1
	3	63.6±1.6	147.8±5.3	194.8±4.6	79.7±2.5	88.6±3.1
	4	64.6±2.2	152.2±1.6	200.2±2.7	75.9±2.8	81.8±2.1
	5	62.7±2.4	154.6±2.4	200.8±2.4	67.3±2.6	68.7±2.9
	Means	63.7±2.2	143.4±6.6	196.2±7.2	79.6±8.4	85.5±10.2
Serum Acid phosphatase U/l	1	13.8± 0.9	13.0± 1.1	19.8± 1.2	13.4± 3.3	15.2±1.7
	2	13.1±0.6	14.6±0.9	21.2±0.9	13.7±0.7	15.2±1.3
	3	12.7±0.6	16.5±1.4	22.2±1.0	14.2±5	14.7±1.2
	4	12.3±0.3	17.9±1.6	23.4±1.0	13.4±.5	14.5±0.6
	5	12.2±0.2	21.0±2.2	25.6±1.3	13.1±.7	13.5±0.6
	Means	12.9±1.1	16.6±3.1	22.4±2.3	13.6±1.4	14.6±1.3
Serum Alkaline phosphatase IU/L	1	72.2± 4.6	167.4± 22.3	181.0± 27.8	81.6± 14.6	82.6± 18.2
	2	75.2±9.5	175.5±13.1	196.8±12.2	79.2±12.3	80.9±10.2
	3	73.8±8.1	186.0±16.3	201.8±6.8	79.8±8.1	85.4±9.4
	4	72.0±6.7	187.0±13.1	211.2±6.7	76.0±1.7	87.6±9.4
	5	70.4±8.4	198.0±14.4	218.8±6.3	75.8±0.8	78.0±11.6
	Means	72.7±2.2	182.8±14.6	201.9±12.2	78.5±2.0	82.9±11.0
Serum Lactate dehydrogenase U/L	1	162.9± 20.9	289.5± 7.2	346.7± 57.5	170.6± 19.7	228.5± 27.2
	2	165.±21.3	293.3±7.0	352.4±50.0	173.5±21.4	216.3±18.0
	3	166.5±21.7	302.6±4.1	357.6±46.2	171.3±20.3	212.3±18.1
	4	167.2±16.0	306.2±6.3	363.6±47.3	174.7±17.8	209.3±16.8
	5	168.6±9.4	312.8±4.2	373.8±4.2	175.6±9.7	206.8±16.8
	Means	165.8±16.9	301.4±10.6	358.7±46.5	174.4±16.7	214.6±19.8

All values are given as the means ± standard deviation (mean± SD); and each values represented five rats in each weeks.

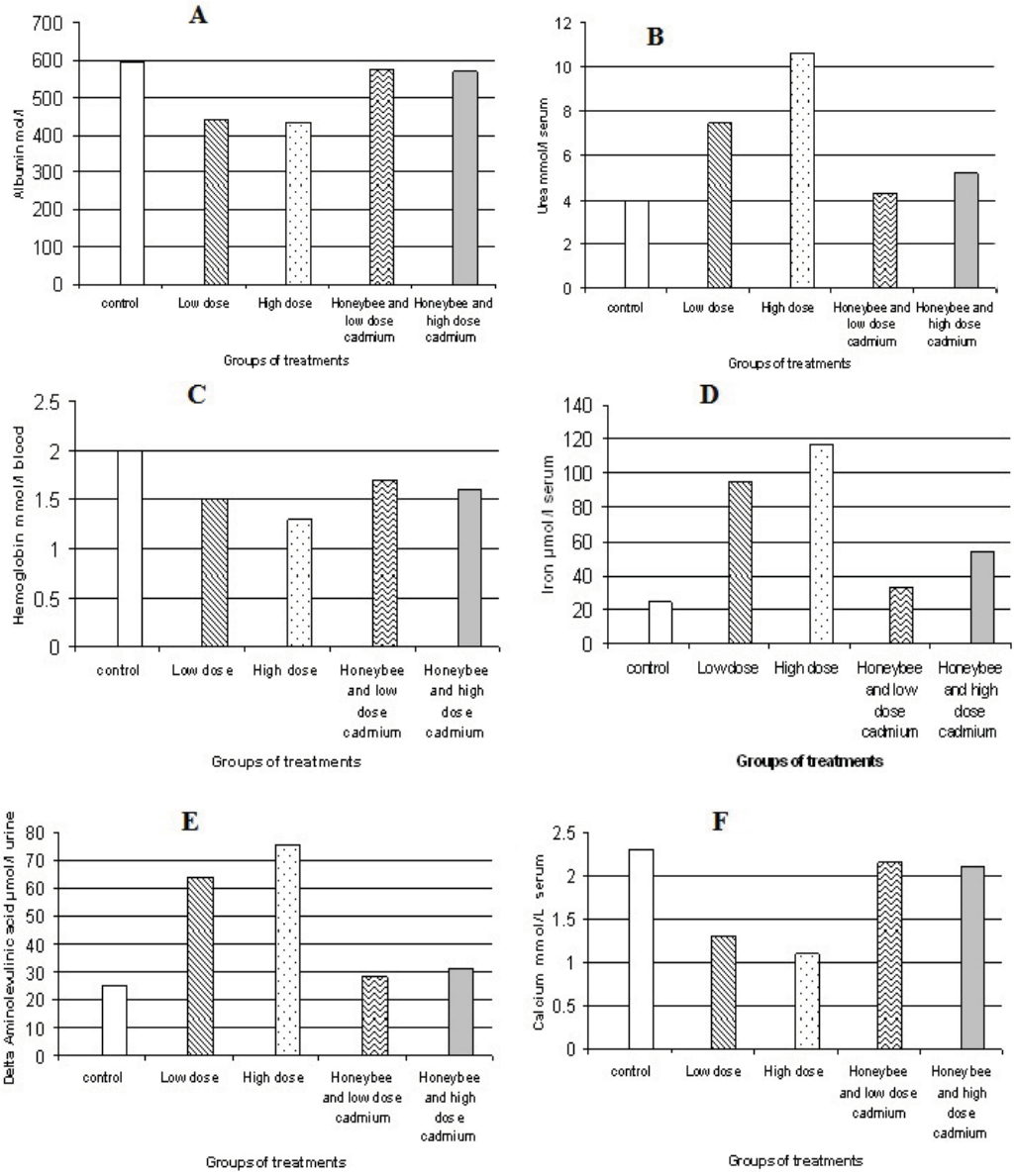
Table 3: The statistical analysis (The Student t- Values) on different physiological Parameters in female rats exposed two levels of cadmium chloride and/or honeybee supplementation.

Parameters	Statistical analysis	Control with the groups				Cadmium only with honeybee solution	
		Control and Low dose cadmium only	Control and honey bee plus low cadmium	Control and high dose cadmium only	Control and honey bee plus high cadmium	honey bee plus low cadmium and low cadmium only	honey bee plus high cadmium and high cadmium only
Albumin mol/l serum	F. values)	38.18**	4.67 **	26.56 **	5.156 **	-32.6**	-29.171 **
Urea mmol/l serum	F. values	-38.714**	-6.835 **	-36.99 **	33.873 **	-33.175**	35.407 **
Hemoglobin mmol/l blood	F. values	15.89**	6.67 **	17.74 **	10.3636 **	-4.63**	-6. 517 **
Iron µmol/l serum	F. values	-25.586**	-5. 87 **	-30.485 **	16.956 **	-16.953**	13.666 **
Delta Aminolevulinic acid µmol/l urine	F. values	-26.01**	-2.897 **	15.813 **	-6.888 **	-15.448**	11.449 **
Calcium mmol/L serum	F. values	-38.205**	-5. 862**	-39.64**	9. 951**	-32.819**	-34. 321**
Sodium mmol/L	F. values	-26.492**	-4. 574**	-91.74 **	-.5.746 **	26.63**	86. 282 **
Chloride mmol/l serum	F. values	-18.205**	-3. 862 **	-19.64 **	-7. 951 **	17.819**	14. 321 **

Table 3: Continue

Serum Alanine amino transferase U/L	F. values	-31.591**	9 .754 **	-60.04 **	-8. 669 **	26.26**	22 . 65 **
Serum Aspartate amino transferase U/L	F. values	-3.188**	-9.364 **	-95.834 **	-10.96 **	2.73**	34. 494 **
Serum Acid phospatase U/L	F. values	-5.049**	-2.173 **	-18.011 **	-7. 98 **	4. 233**	13.397 **
Serum Alkaline phospatase IU/L	F. values	-27.12**	-7. 67 **	-34.724 **	-4.985 **	4.599**	32.917 **
serum Lactate dehydrogenase /L	F. values	-31.585**	51 -10.**	-27.032 **	-18.393 **	30.151**	16.698 **

**Highly significant value at P<0.001), Degree of freedom, 24.



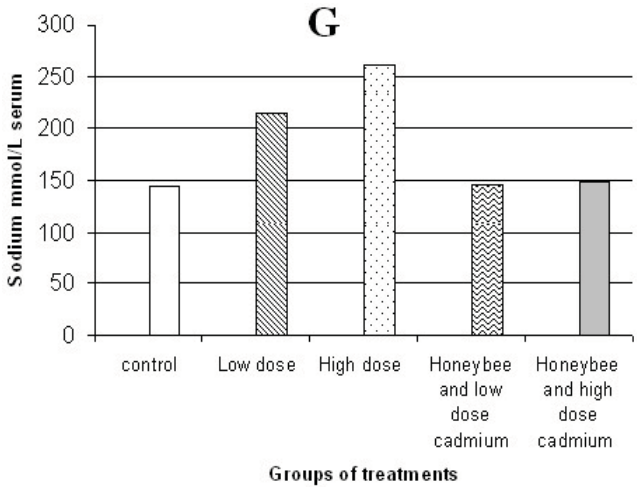
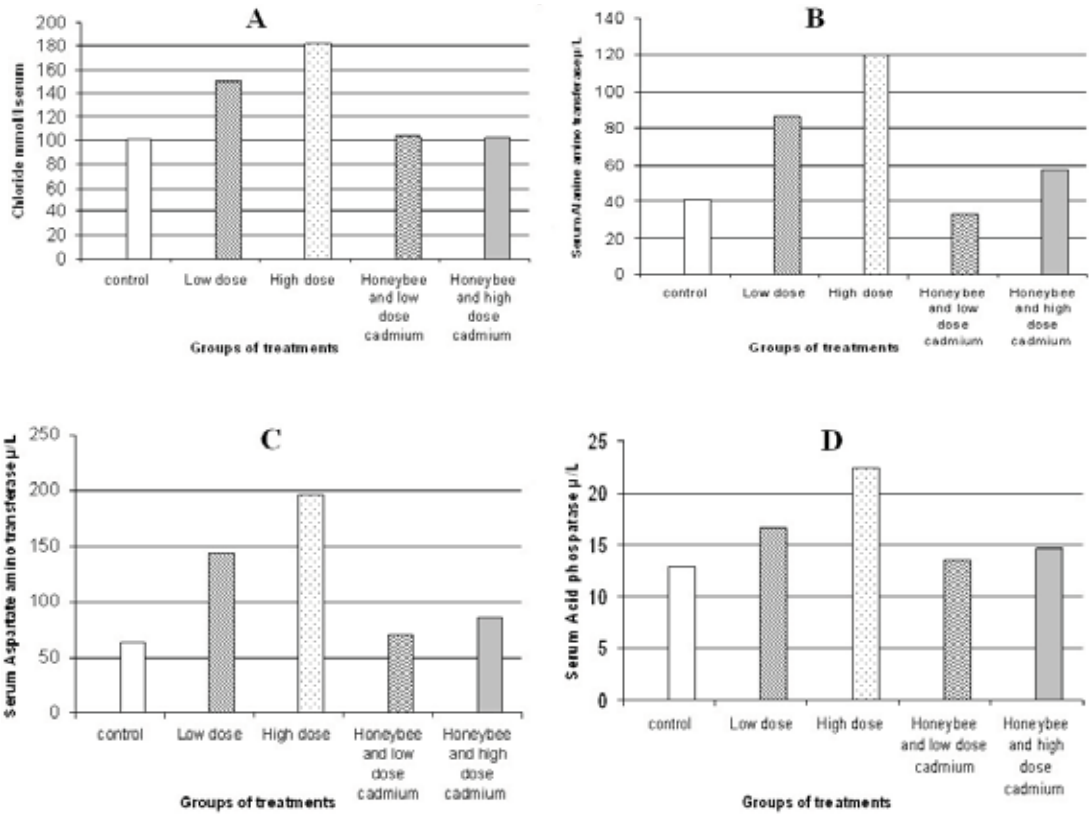


Fig. 1: Effect of honeybee solution (10g/Kg body weight) on the means concentrations of twenty five reading of each of serum albumin (A), Urea (B), hemoglobin (C), Iron (D), calcium (F), sodium (G) and urine delta amino levulinic acid (E) of the rats orally received cadmium chloride solution at low level (50mg/kg body weight) and high dose (100mg/Kg. body weight).



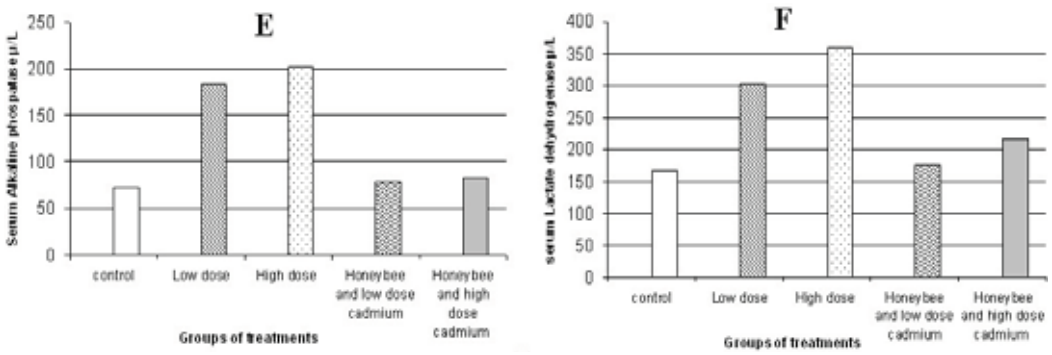


Fig. 2: Effect of honeybee solution (10g/Kg body weight) on the means concentrations of twenty five reading of each of serum chloride (A), ALT(B), AST(C), ACP(D), ALK(E) and LDH (F) of the rats orally received cadmium chloride solution at low level (50mg/kg. body weight) and high dose (100mg/Kg. body weight).

Discussion:

Cadmium is a dangerous occupational and environmental toxin. It accumulates in the human organism mainly in liver and kidneys. Cadmium half- life is about 10 years, so the symptoms of cadmium intoxication may occur several years after the exposure. Until now in treating intoxication with this metal chelating compounds have been used, burdened with numerous undesirable symptoms. In this study, honeybee solution was used to reduce the harmful results caused by cadmium. The mechanism of the harmful activity of cadmium is not fully explained. It seems that the toxicity of this metal on the one hand lies in a direct action of free cadmium ions not bound with metallothionein, while on the other hand, in forming reactive radicals being able to change functions and structure of many system and organs (Stohs *et al.,* 2001 and Kowalczyk *et al*., 2003).

Albumin is the most abundant protein in human plasma, representing 55-65% of total protein. It synthesized in the liver at a rate that is dependent on protein intake subject to feedback regulation by the plasma albumin level .The molecule contains no carbohydrates and is not stored to any extent in parenchymal cells. Littler albumin is filtered through the kidney glomerali, and most of that is reabsorbed by proximal tubule cells and degraded by their lysosomal enzymes into fragment that are returned to the circulation. Plasma albumin is catabolized in various tissues where cells remove it by pinocytosis its constituent amino acids are released by intracellular proteolysis and returned to the body pool. Albumin useful indicator of the integrity of glomerular and other membranes. It chief biological functions are to transport and store a wide variety of ligands, to maintain the plasma oncotic pressure, and to serve as a source of endogenous amino acids (Peters, 1975).From this point in this study concentrated on the, serum albumin of rats and the results were significantly lower serum albumin in which rats exposed to low or high dose of cadmium chloride as compared to the control rats indicating poor liver functions or impaired synthesis, either primary as in liver cells damage or secondary to diminished protein intake and reduced absorption of amino acids caused by malabsorption syndromes or malnutrition. Other interpretation may cadmium cause loss protein in urine, due to nephritic syndrome, chronic glomerulonephritis .On the other hand, the results indicated that in the present study, honeybee affected on the negative effect of cadmium chloride that significantly decreased serum total albumin in rats feed on cadmium chloride only comparing with the control rats where, rats feed on honeybee solution and cadmium chloride do not normalize the albumin in blood comparing with the control rats, while it significantly increased albumin in relation to rats orally cadmium only (low and high dose of cadmium chloride). Honeybee solution may be is one of the nutrients that can reduce the toxicity of orally consumed cadmium chloride and shows its affect by competing with cadmium; honeybee solution has a protective effect on liver cellular damage by maintaining membrane integrity due to its direct action on free radicals of cadmium or honeybee solution as antioxidative activity. These results agree with Radwan *et al.*, (1984) and Abd El Reheem (2008) reported that, honeybee solution has specific agent, which may play an important role in scavenging the toxins substances. In addition treatment with honeybee solution which scavenging the activity of the digestive system to digest and absorb food to body cells that is restore less of albumin of animals fed on honey bee solution and cadmium chloride together.

Urea in serum showed was highly significant increased of rats administrated orally two levels of cadmium chloride comparing with the control group that may impair kidney tubular functions. Wide variety of renal diseases can cause an increase in plasma urea concentration, unfortunately, the usefulness of urea as an independent indicator of renal function is limited by the variability of its blood levels because of nonrenal factors. Mild dehydration, high- protein diet, increased protein catabolism, muscle wasting as in starvation, reabsorption of food proteins after hemorrhage, with drugs or decreased perfusion of the kidneys may cause asotemia (increased blood urea).This agree with several other occupational studies that reported increased serum concentrations of urea indicating reduced glomerular filtration rate (GFR) in cadmium-exposed workers (Roels *et al*., 1989 and Thun *et al*., 1989).Cadmium dose remained the important predictor of serum urea even after controlling for age, blood pressure, body size, and other extraneous factors (Roels *et al.,* 1989). It has been suggested that cadmium-induced tubular damage leads to a certain degree of interstitial nephritis, which in turn results in a decreased GFR (Flinder *et al.,* 1985). It has also been proposed that cadmium exerts a direct toxic effect on the glomerulus (Roels *et al*., 1989). Also, the present study agree with Shibutani *et al*. (2001) who reported that cadmium can affect on renal tubules damage and then glomerular filtration impairment .In the present investigations, simultaneous administration of honeybee solution with cadmium chloride significantly decreases the concentration of urea in blood rats. The mechanism of the beneficial effect of honeybee solution on kidneys is undoubtedly heterogeneous. Honeybee solution decreases the inflammatory process. The application of honeybee solution resulted in a high improvement of albumin and urea concentration in serum rats.

The measurement of hemoglobin; iron and delta –aminoleuvinic acid concentration are one of the most frequently performed clinical laboratory tests. Blood hemoglobin concentration may be diminished may be hemorrhage or hemolysis or because of impaired blood formation in bone marrow when rats administrated low and high cadmium chloride compared with hemoglobin in blood of rat control group. Moreover, the cadmium has been found to have direct effect on blood hemoglobin by decreasing its formation as results from two basic red cell defects, shortened life span and impaired haem synthesis. The mechanisms by which synthesis of the red cell pigment heam is inhibited by cadmium involves at least two enzymes, a cytoplasm one (delta –aminoleuvinic acid) at the beginning of heam synthesis and a mitochondrial one, ferrochelatase, at the end of synthesis (Moore *et al.,* 1985) .The inhibition of leading to anaemia have been suggested, Cadmium may compete with iron, leading to the occurrence of anaeamia due to iron deficiency to reach the bone marrow in which synthesis the hemoglobin, whereas on the other hand renal failure, developing under the influence of cadmium, results in increased urinary concentrations of (delta –aminoleuvinic acid (60µmol/L) or more under low or high dose of cadmium than those in control group (25.2 µmol/L) .On the other, hand orally cadmium chloride leads to increased in iron concentration under low or high cadmium chloride and decreased of heamoglobin in blood than the control group is another sensitive indicator of liver cell damage and disturbances in bone marrow functions .Cadmium inhibits the bone marrow to make hemoglobin by interfering with several enzymatic steps in the heme pathway. In this study investigations is in agreement with (Moore *et al.,* 1985 and McDowell, 1992) who reported that iron is transported from one organ to another as Fe (III) bound to a plasma protein called apotransferrin, the apotransferrin- Fe (III) complex is called transferring. Transferring occurs within the cytosol of many cells and may serve as an intracellular iron transport protein. Ferritin is the major iron-storage compound; it occurs in nearly all body cells but particularly in hepatocytes. The apoferritin shell surrounds an interior ferric oxyhydroxide crystalline core that contains more Fe (III) atoms. Nonenzymatic reduction of Fe (III) to Fe (II) occurs as iron is released from ferritin. Thus, ferritin is both a very efficient iron trap and a readily an available source of iron for metabolic requirements and for formation of hemoglobin and other heme proteins. The minute concentration of ferritin in serum is an indicator of total body storage iron. Liver injury results in release of relatively enormous amounts of ferritin into plasma, resigning the serum ferritin concentration several thousands times and serum iron concentration. Hemosiderin; the other form of storage iron, consists of aggregated, practically deproteinized ferritin. In contrast to ferritin, hemosiderin is insoluble in aqueous solution, and iron is only slowly released from hemosiderin. Like ferritin, hemosiderin normally occurs predominally in cells of the liver, spleen and none marrow. Also Moore *et al*. (1985) and Tokebayashi *et al., (*1993) reported that hypoactivity of aminlevulinate dehydrase can be accompanied by increased urinary excretion of and porphyrins (ALA). In addition, Campagna *et al.* (1999) reported that elevation of delta –aminolevulinic acid (ALA) level, due to inhibition of (ALAD) enzyme, is major neurotoxic mechanism for lead poisoning. On the other hand, rats orally administrated solution of honeybee and cadmium chloride resulted in the increased blood hemoglobin ,while decreased serum iron compared with the results in rats orally cadmium alone. In addition, delta –aminolevulinic acid decreased in urine of rats in experiment second compared with experiment first. This result improved after administrated honeybee solution may be honey affect on the bad effect of cadmium on the blood hemoglobin formation in

bone marrow .For instance, honeybee solution, like so many other antioxidant, complexes with and inactivate heavy metals in the intestine, so they are excreted harmlessly from the body, in addition honeybee solution detoxifies other materials in a similar manner and leads to inhibiting the translocation of bad effects of cadmium chloride and that honeybee solution improve the function of the organs in the body.

Cadmium affects bone development and mineralization (Khandelwal *et al.,* 1991), and has an antagonistic activity in calcium metabolism (McDowell, 1992). In the present study, administering cadmium chloride to rats resulted in a statistically significant decrease of calcium concentration in serum of rats in relation to the control group, which is in a agreement with the results obtained for a proposed mechanism for the decreased calcium absorption and negative calcium balance seen in rats exposed to cadmium is that this metal inhibits activation of vitamin D in the renal cortex (Fedman and cousin, 1974). Cadmium inhibits vitamin D- stimulated intestinal calcium transport in rats (Ando *et al*., 1981 and Pleasants *et al.*, 1993) renal conversion of 25-hydroxycholealceferol to 1, 25-dihydroxycholecalceferol in rats is inhibited by low and a high dietary concentration of cadmium (Lorentzon & Larsson, 1977). Also the present results agree with a series of studies in Japan, described in detail in WHO (1992), on the effect of dietary cadmium in monkeys, a dose of (30 mg/kg bw) was found to worsen osteomalacic changes in the bones of animals fed diets with low concentration protein, calcium, and vitamin D. Several studies on the effects of oral administration of cadmium on bone and calcium metabolism showed decreased calcium content in bone and increased urinary excretion of cadmium that resulted in decalcification and cortical atrophy in the skeleton, associated with renal cortical concentrations (Kawai *et al.*., 1976; Kelman *et al*., 1978 and jacquillet *et al*., 2006).

In the present study, honeybee solution, improvement the negative effect of cadmium on calcium metabolism and demonstrate protective action against the changes of calcium metabolism by cadmium, for improvement of and significantly increased calcium concentration of the rats orally administered honeybee solution compared with cadmium alone.The mechanism of the beneficial effect of honeybee may be on the vitamin D formation and on the functions of this vitamin on the metabolism of the calcium , in which vitamin D formed and stumulate calcium absorption from the small intestine and restore serum calcium concentration in the groups orally administrated solution of honeybee solution & cadmium chloride.

In the investigation and evaluation of dehydration, overhydration, hypernatraemia and hyponatraemia, the following estimations may be useful. Electrolytes, (the plasma sodium levels do not give any information about the total body sodium content. This estimation is only useful insofar that it classifies a subject as hyponatraemic, hypernatraemic, or normonatraemic.The plasma chloride values are useful guide to acid- base status and the major anion present in the extracellular fluid, is closely related to that of sodium (Schrier, 1990). Administering cadmium chloride to the rats resulted in a statistically significant increase sodium and chloride in serum of rats in relation to the control group. While adding the honeybee solution to cadmium chloride did not normalize the sodium and chloride concentration, but improvement and decreased of sodium, chloride in serum of rats orally honeybee solution and cadmium chloride together comparing with rats orally cadmium only (in which sodium and chloride increased). The toxicity of this metal on the one hand lies in a direct action of free cadmium ions not bound with metallothionein, while on the other hand, in forming reactive radicals being able to change functions and structure of many systems and organs (Stohs *et al*., 2001; Kowalczyk *et al*., 2003). Plasma concentrations of sodium and chloride showed different changes over the all the weeks of the experiment may be intoxication, of cadmium acts on ion transports leads to glomerular filtrations rate was decreased and fractional excretions of ions were decreased in the urine and increased in plasma. These results are in accordance with the data of Aoyagi *et al*. (2003). Another phenomenon could be responsible for tubular dysfunction and renal tissue damage, thus the proximal tubulopathy might be due to a defect in tight junction organization.the tight function constitutes the main barrier in epithelia to passive movement of electrolytes and macromolecules thrrough the paracellular pathway (Cereijido *et al.*, 1993 and Lau and Bourdeau, 1995). Another goal of the present study was to explore away of protecting renal and liver functions against cadmium intoxication by using honeybee solution to decrease cellular damage induced by cadmium. Administration of honeybee solution may be prevented changes in renal and liver functions produced by the toxic cadmium .Among the possible mechanisms, it might occur that honeybee solution reduced the renal uptake of cadmium by competition for a common transport. A better explanation for this protection is that honeybee solution plays a role in preverting apoptosis and nevrosis.

Administering cadmium chloride to rats resulted in a statistically highly significant increase the enzymes AST,ALT and LDH in the serum of the rats orally of cadmium chloride only compared with the control group .Also Administering cadmium chloride to rats resulted in a statistically highly significant increased enzymes acid and alkaline phosphatase compared with the control group. The two plasma transaminase enzymes found in the liver have been widely used for diagnostic purposes. AST is present in both the mitochondria and cytosol of liver cells, whilst (ALT) was found in the cytosol only. Liver cells damage releases these enzymes

into the extracellular fluid, and results in increased plasma levels of transaminase activity. An increase of asparatate aminotransferase (AST) and the most specific marker of liver cell damage- alanine aminotrasferase (ALT) (Sauer *et al.,* 1997; Blasco and Puppo, 1999 and Kowa lcyk *et al.,* 2003) manifest, the damaging effect of cadmium on the liver. Lactate dehydrogenase (LDH) is another index of hepatotoxicity, although the plasma LDH level is relatively insensitive when exposed to cadmium (Sherlock and Dooley, 2002 and Lee *et al.,* 2007). The results are in agreement with Shibayna, (1992); Xia and Yu (1992) and Pispirigos *et al*. (1993) who reported that hepatic damage by drugs and chemical substances in rats is characterized by the decreases in serum because of hepatic enzyme leakage led to increase in serum ALT. Also the data of the present work is in agreement with Tauda *et al*. (1999) and Kowalczyk *et al.* (2003) they recorded that the toxicity of this metal on the one hand lies in a direct action of free cadmium ions not bound with metallothionein, while on the other hand, informing reactive radicals being able to change functions and structure of many systems and organs.

On the other hand, when adding honeybee solution and cadmium together to the rats results in not normalized enzymes compared with control , while decreased and improvement significantly compared with the rats orally cadmium chloride alone (these enzymes increased in blood of rats orally cadmium only), this results are in agreement with Abd-El-Reheem (2008) who attributed to the honeybee solution components the protective action against the damages of hepatocytes by cadmium, and that improvement of the enzymes activities of liver enzymes.

In the present study, blood acid phosphatase and alkaline phosphatase showed significant elevation in both low and high cadmium doses that are attributed to the irritation of all particularly liver cells by toxin cadmium or due to increased loss of intracellular enzyme by diffusion through cell membrane, which appear to acts as a stimulus to the synthesis of more enzymes. The Alkaline phosphates (ALP) are a group of glycoprotein enzymes that bound to alkaline PH. ALP activity is found in virturally all tissues, particularly bone, liver, kidney, intestine , adrenal,and placenta. The functions and natural substances of ALP remain unknown .However Van hoof and Broe (1994) and Martins *et al.*, (2001) reported that in bone a lack of ALP is a ssociated with a lack of mineralization present evidence indicates that probably four gene loci are involved in encoding the ALP group of enzymes, producing the following primary structures 1.Tissues non–specific protein 2.Intestinal protein. 3- Placental protein. In addition, Johnson (1989) hypothesize that, in liver alkaline phosphatase (ALP) is found at two distinct sites on the sinusoidal surface of the hepatocyte, and in the microvilli of the bile canaliculi and ducts. ALP is also found in a number of other body tissues; thus, the plasma ALP activity is not specific for the liver. During obstruction of the bile passages (cholestasis) the plasma ALP level rises. This is due mainly to an increased synthesis of ALP ,but the obstruction itself also plays a part by causing regurgitation of the enzyme back into the blood stream. In obstructive jaundice, the plasma ALP is usually increased to levels greater than three times the upper reference limit. In hepatocellular disease, the level may be normal or slightly increased, but any increase is usually less than three times the upper reference limit.

Other interpretation for the improvement of the parameters of the present investigation may be to the decrease of cadmium accumulation in liver and kidneys in the rats receiving honeybee solution in addition to cadmium. Among the possible mechanisms, it might occur that honeybee solution reduced the renal uptake of cadmium by competition for a common transporter and demonstrates protective actions against the damages of hepatocytes and renal function during cadmium intoxication in the rats. These results explain the therapeutic effects of honeybee solution, which used in this study; .Honeybee solution has the highest content of antioxidant enzymes catalyze, inhibit agent, and B_1, B_2, B_5, B_6 and C vitamins, which found to be useful in preventing the tissues injury caused by toxic agent. In addition, of considerable interest is the decrease and improved of all enzymes which studied in this study in the rats receiving honeybee solution and cadmium, it may testify to the possibility of honeybee solution chelating cadmium ions which in consequence may decrease the damages caused by this metal, after the cadmium accumulation in liver and kidneys results in functional changes and then in interstitial fibrosis of these organs. The significance of this study is in agreement with recommended by Ali *et al*. (1997) using honey solution in treatment of the gastric mucosal lesions. It has been known for a long time that cadmium mainly accumulates in liver and kidneys because these organs contain most of metallothionein binding toxic metals (Liu *et al.,* 1998; Yiin *et al*., 1999; Choudhury *et al.,* 2001 and Hollis *et al.*, 2001).

In conclusion, cadmium resulted in alterations in biochemical parameters, damage in liver and kidney functions. When honeybee solution and cadmium were given together, the enzyme activities and the other biochemical parameters improved showing that the honeybee solution used in this study is good to prevent cadmium toxicity.

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