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PROTICTIVE EFFECTS OF VITAMINE E AGAINST TESTICULAR ENZYMES TOXICITY INDUCED BY CYPERMETHRIN IN MICE

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ABSTRACT

Cypermethrin is a synthetic pyrethroid insecticide. It is known for its wide toxic manifestations. The present work was designed to evaluate the protective role of vitamin E on Cypermethrin intoxication in mice after 14 days. The weight of testis and activity of aspartate aminotransferase (AST), alanine aminotransferase (ALT), acid phosphatase (AcP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH were studied. Male mice were divided into four groups ~~of~~ 10 each: group I served as control and treated with corn oil; group II received cypermethrin (2.8 mg/kg BW) in corn oil. Group III received vitamin E (100 mg/kg BW) ;group IV received both cypermethrin and vitamin E (100 mg/kg BW) the animals were fed by feeding tube through the mouth. The data showed that the exposure of mice to cypermethrin caused a significant decrease in weight of testis and the activities of marker enzymes (AST), (ALT), (AcP) and (ALP) and a significant increase in LDH activity.Co-administration of vitamin E(100 mg/kg BW) to the cypermethrin group restored all the parameters cited above to near the control values. Therefore, this study revealed that vitamin E have beneficial effects against cypermethrin-induced toxicity.

KEYWORDS: **Cypermethrin, Vitamin E, Testicular, Enzymes, Mice.**

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INTRODUCTION

Using pesticides is an important procedure for enhancing agriculture yield. However, the great consciousness, brought back upon their deleterious effects on human, animal and environmental health, lead to shortage their use by imposing various rules [1- 3]. Cypermethrin (CYP)is an insecticide in the synthetic pyrethroid family. The chemical formula of CYP is alpha-cyano-3-phenoxybenzyl ester of 2,2 dimethyl-3-(2,2 dichlorovinyl)-cyclopropane-carboxilic acid,the most widely used type II pyrethroid pesticides. It is commonly used to control moths and pests of cotton, soybean and other crops[4]. It was thought CYP has low mammalian toxicity so, it was also used for controlling the household pests. However, a number of studies have proven that CYP and other pyrethroids have hepatotoxic, carcinogenic, neurotoxic and immunosuppressive potential in mammals[5-7]. As well as, Synthetic pyrethroids (also including sumithrin, fenvalerate, d-trans allethrin, permethrin and cypermethrin) have the ability to disrupt biochemistry, haematology and reproduction [8]. The toxicity of pyrethroid insecticides to mammalian animals has received much attention in recent years because animals exposed to these insecticides exhibited changes in their physiological activities beside other pathological features [9]. Recently, oxidative stress and reactive oxygen species generated from this stress as well as endocrine disturbance are among the most important effects in pestricide toxicology[10-14]. CYP may be induces of oxidative stress and endocrine disturbance by interfering with different pathway in organisms. For example, the activity of oxidative enzymes were increase significantly in the liver and kidneys of two fresh water species after exposure to 3µg/l CYP for 10 days [15]. Giray et al., (2001)[16] also reported that oral administration of CYP to rats induces a significant oxidative stress in cereberal and hepatic tissues. Recently, it was proven that exposure to CYP during lactation significantly decreased the layer of spermatogenic cells, increased the inside diameter of seminiferous tubules and disturb the array of spermatogenic cells in the testes of pups at postnatal day (PND) 21 [17].

Enzymes are one of the major targets for pesticide action. Measurement of certain patterns of cellular enzymes under different conditions of treatments with various types of toxicants could provide good evidence for the cytotoxicity and hence the impairment of cell function [18]. El-Demerdash *et al,.*2003 [19] indicated that administration of cypermethrin (24 mg/kg body weight) to male New Zealand white rabbits resulted in a significant decrease in the activities of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) in liver and testes and alkaline phosphatase (AIP) in the liver. However, the activities of AST, ALT and AlP were increased in plasma. Yousef and Zeitoun 1998 [20] found that there were negative correlation coefficients between sperm motility on one side and AST and ALT release on the other side. They reported that the activities of these enzymes could be used as an indicator of sperm integrity.

Some studies have shown that both vitamin C and vitamin E are used as experimental studies in pesticide toxicity [21-23]. Vitamin E is a potential antioxidant, and a liposoluble antioxidant present in biological membranes and inhibit free radical formation in biological system [24]. High levels of vitamin E are found in selected mammalian tissues including testes [25]. In many studies,vitamin E neutralizes lipid peroxidation and unsaturated membrane lipids because of its oxygen scavenging effect [26-29] . While vitamin E was showing a protective effect on some biochemical indices in short period cypermethrin and OP insecticides fenthion and diazinon toxicities, it did not show effect on some biochemical indices [30-31]. Ogutcu *et al.* 2008 [32] found that feeding mice vitamin E with pesticide dichrvos for seven weeks showed a significant increase in liver enzymes AST, ALT, AlP and LDH compared with a group that was given dichorvos alone without vitamin E.

Also feeding male mice vitamin E with diazon for 14 days led to a significant increase in liver enzymes AST, ALT, AlP and LDH compared with a group that fed diazon alone. El-shenawy *et al.* 2010 [33]showed that vitamin E has a preventive and reducible role against the oxidative stress induced by a toxic substance in the testis. The aim of this study is to investigate the effectiveness of vitamin E as an antioxidant against the toxicity of the pesticide cypermethrin represented in the testis weight and testicular enzymes. It is well known that the use of pesticides in agriculture causes health problems, that need to be solved.

2. MATERIALS & METHODS

2.1.MATERIAL

2.1.1.ANIMAL

In this study 40 male strains of the albino mice (MF1), obtained from King Fahd Medical Research Center, King Abdulaziz University in Jeddah, were used. The animals were in good health having average weights (33± 2 g). The mice were placed in the laboratory of the Department of Biology of the Faculty of Science – King Abdulaziz University for 14 days for acclimatization prior to the experiment at a temperature of (25± 2 g). The animals were placed in a special medium sized cages, at a rate of 3 individuals per cage, and provided with food and water and the food contains a balanced diet of vitamin A, amino acids , fibers , folic acid, salts of calcium, phosphourus, iron and potassium. The animals were set to breed under two systems of lighting (12L - 12D), white fluorescent and red light, because mice are nocturnal animals to red light.

2.1.2. CYPERMETHRIN

The chemical pyrethroid is an insecticide used to combat many of the agricultural and public health pests and it is used in controlling insects, ticks, beetles, butterflies and larvae and is used in crops, cotton, grain, ornamentals, potatoes and other vegetables. It activates the ingredient pesticide by 10% and was obtained from one of the stores in Jeddah and imported by the Saudi Company, Delta chemical industries.

2.1.3. VITAMIN E

It is a semi-liguid substance, stored in dark glass bottle because it is sensitive to light and under 2-8 °C. It was obtained from Ballna Trading Co. Ltd. In Jeddah.

2.2. EXPERIMENTAL DESIGN

Mice were divided into four groups, each group contains 10 animals as follows: The first one is the control group which was fed with corn oil only throughout the experiment; the second group is the cypermethrin group (CYP): which was fed 2.8 mg/ kg body weight of cypermethrin dissolved in corn oil orally through a feeding tube [34]. The third group is vitamin E group: in which the animals were fed vitamin E (100 mg/kg b.wt.) in corn oil orally through a tube [35]; and the fourth group is the animals given vitamin E with cypermethrin (CYP+Vit.E) , at a dose of 100 mg / kg b.wt. vitamin E and 2.8 mg / kg cypermethrin dissolved in corn oil, orally throughout the duration of the experiment.

2.3. MEASURMENTS OF TESTIS WEIGHT

Testis weights of the control and treated rats were measured at the end of 14 days with an automatic balance (AND GX-600, Japan). Mice were anesthetized with diethyl ether and were removed and weighed immediately.

2.4. TISSUE PREPARATION AND ENZYMES ANALSIS.

Testis was removed from The mice had been anesthetized by using ether and washed by cold saline solution buffer after 14 days.Washed tissues were immediately stored at - 80 ° C. The tissue were homogenized in cold sodium phosphate buffer (50 mM, pH 7.0) containing0.1m Methylene diaminetetraacetic acid (EDTA) to yield 10% (W/V) homogenate. The homogenates were then centrifuged at 1000 rpm for 10 min at 4 ° C. The supernatants were separated and used for enzyme determination of ALT, AST, AcP, ALP and LDH which were expressed in International Units per liter (IU/g of tissue) and protein. Biomarkers for

testis damage were determined using UV kinetics methodology of the commercial diagnostic kit (Stanbio Co., Spain).

2.5. STATISTICAL ANALYSIS

The program used to beStatistcal package For Social Science (SPSS 15). The student' s t-test was used to study the difference in weights and testis enzymes. One – way random statistical analysis was used and the results were written as Stander Erro± Mean.

3. RESULTS

3.1. TESTIS WEIGHTS

The results in table (1) showed significantly lower testicular weight (P <0.05) in mice treated with cypermethrin compared to control, while the decline in testis weight was less pronounced in the group that received treatment with vit.E + cypermethrin and vit.E group did not show any significant difference in testis weight compared to control (Table 1).

Table 1

Means of the testis weight under the different treatments cypermethrin, Vit. E or their combination (Cypermethrin +Vit. E).

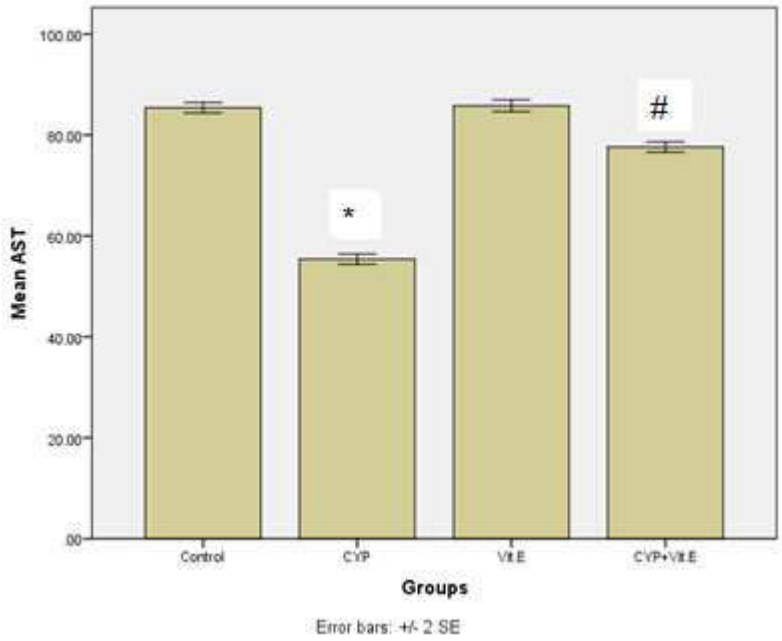
Group / Organ	Control	CYP	Vit.E	CYP+Vit.E
Testes	0.250 ± 0.002	* 0.193 ± 0.005	0.246 ± 0.002	# 0.225 ± 0.002

*Significant differences:Values are mean ± S.E.M(n=5). * P<0.05,vs. Control group; (cypermethrin +Vit.E) group vs. Cypermethrin group; # P<0.05*

3.2. ASSESSMENT OF BIOCHEMICAL CHANGES

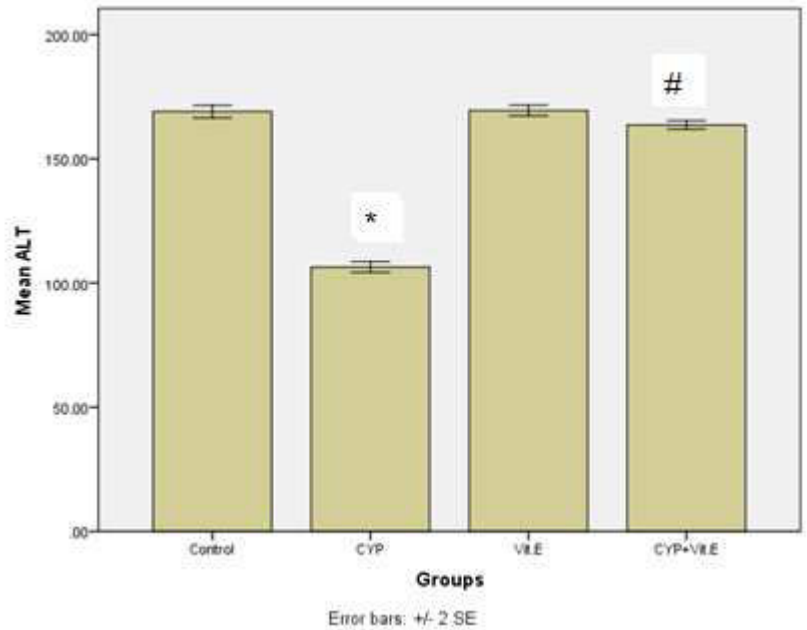
To determine the testicular damage caused by cypermethrin and the protective effect of vitamin E, the activities of some testis enzymes (ALT, AST, AcP, ALP and LDH) were used as biomarkers of the testis. After 14 days of cypermethrin administration, several changes of the parameters have been observed to indicate the occurrence of testicular injuries by comparing to control group. The results of the current study, fig (1, 2, 3, 4, 5) in cypermethrin group showed significant decrease (P <0.05) in the activities of testicular enzymes AST, ALT, AcP and ALP and significant increase in LDH. However, this effect is completely recovered by the treatment cypermethrin with vit.E where significant increase in the activities of the enzymes ALT, AST, ALP and AcP and a significant decrease in LDH were observed compared with the cypermethrin group alone, while no change were observed in the activities of enzymes in vit.E group.

Figure 1
AST (IU/g) levels in testicular tissues of male mice



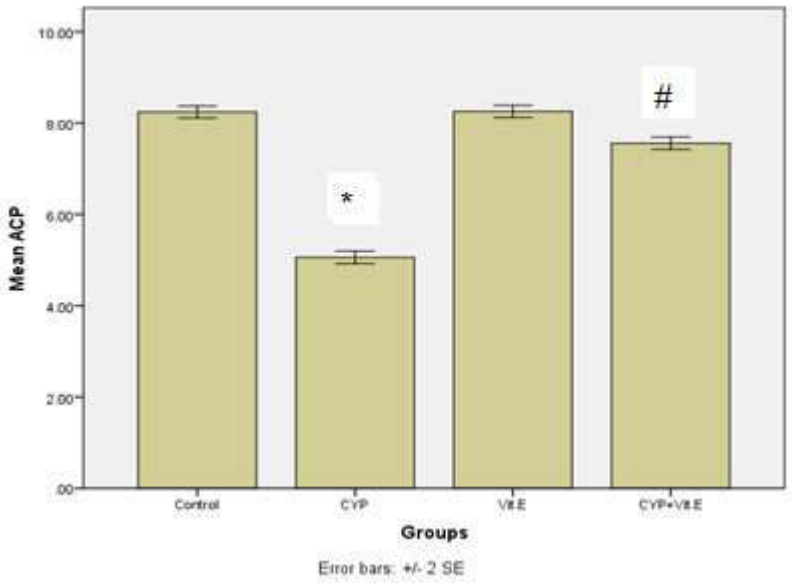
Results are expressed as means ± S.D. n= 10 for each treatment group.* Statistically different from the control group. P<0.05 and # Statistically different from the CYP group. P<0.05.

Figure 2
ALT (IU/g) levels in testicular tissues of male mice



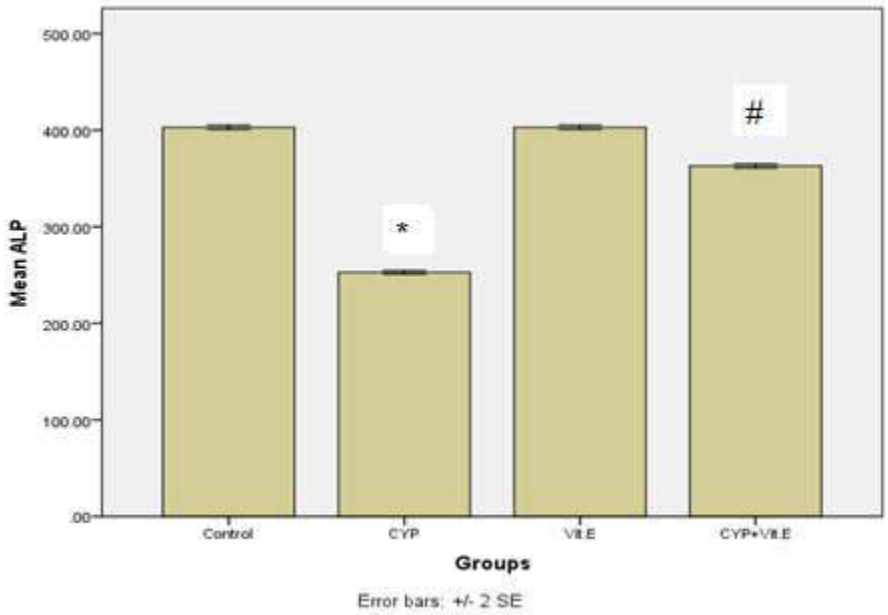
Results are expressed as means ± S.D. n= 10 for each treatment group.* Statistically different from the control group. P<0.05 and # Statistically different from the CYP group. P<0.05.

Figure 3
AcP (IU/g) levels in testicular tissues of male mice



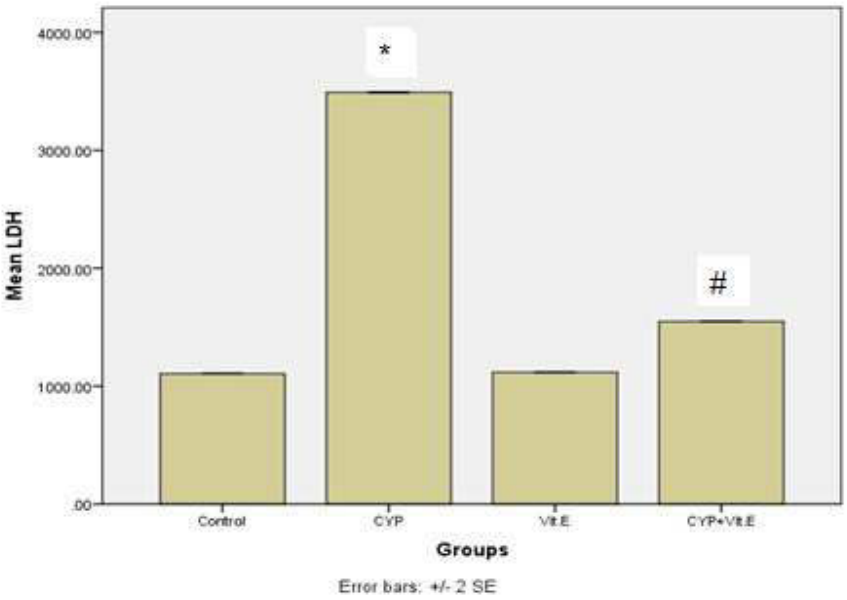
Results are expressed as means ± S.D. n= 10 for each treatment group.* Statistically different from the control group. P<0.05 and # Statistically different from the CYP group. P<0.05.

Figure 4
ALP (IU/g) levels in testicular tissues of male mice



Results are expressed as means ± S.D. n= 10 for each treatment group.* Statistically different from the control group. P<0.05 and # Statistically different from the CYP group. P<0.05.

Figure 5
LDH (IU/g) levels in testicular tissues of male mice



Results are expressed as means ± S.D. n= 10 for each treatment group.* Statistically different from the control group. P<0.05 and # Statistically different from the CYP group. P<0.05.

4. DISCUSSION

The data of the present study showed a significant decrease (*P* <0.05) in testicular weight (Table 1) in the cypermethrin treated group. The decrease in testicular weight returns to the toxicity of cypermethrin, perhaps by malabsorption of nutrients induced by effects on the gastro-intestinal tract or inhibition of protein synthesis. And the occurrence of a toxic effect on the hormonal system.Also, cypermethrin can act as antagonists in various male sexual differentiation disorders such as hypospadias, cryptorchidism, low sperm count and quality [36]. One of the most proven interperitation of the effect of the cypermetherin is that the ability of this chemicals to binding to androgenic receptors and preventing transcription of androgen-dependant genes [37-40]. The results of this work are in agreement with the findings by Abd El-Aziz *et al.* 1994 [41] and Anderson *et al.* [42],who mentioned that testicular weight of wistar rats treated by deltamethrin was reduced at the dose of 4.0 mg/kg bwt from day 1 of pregnancy to day 21 of lactation. Also these results are in agreement with the findings in many animals model such as in rats [43] and in rabbits (8) after feeding the animals with cypermethrin. And Similar results have been found in animals exposed to different pyrethroid compounds (deltamethrin, fenvalerate and diazinon) [29, 44]. Ogutcu *et al.,* 2008 [32] found a decrease in testis weight after feeding mice dicholorovs for 4 or 7 weeks. Wang *et al.* 2009 [45] reported that a high dose (20 mg / kg) CYP beta led to a decrease in the weight of the reproductive system, including the eipididymides and the testis and seminal vesicles, prostate and decreased sperm count. Oda and El-Maddawy 2012 [46] found that feeding rats deltamethrin for 60 days caused a significant reduction in reproductive organs weights, sperm count, sperm motility percent, a live sperm percent, testosterone level and testicular serum . In the present work, it was noticed that, there is a significant reduced (P< 0.05) in the activities of a measured testicular enzymes AST,ALT,ACP and ALP (Fig. 1-4) whereas the activity of LDH enzyme shows a significant increase (Fig., 5). This finding may

be return to the damaged tubules and leydig cells due to the effect of cypermethrin on the composition of amino acids making up the cell plasma membrane proteins, leading to leakage of their contents to the outside of cells. These results are in agreement with the findings by El-Demerdash *et al.* 2003 [19] who indicated that administration of cypermethrin (24 mg kg body weight) to male New Zealand white rabbits resulted in a significant decrease in the activities of AST and AST in liver and testes, and AlP in liver. Another study investigated the in vitro toxicity of cypermethrin at different concentrations (100, 200 ,400 and 800 ng / ml) when incubated in a primary culture of rat hepatocytes, cypermethrin was cytotoxic to rat hepatocytes at concenteations of 200 ng / ml or greater, toxicity was measured by a decrease in cell viability and leakage of AST and ALT enzymes into the culture medium [47] . More recent studies found that the enzymatic activities of AST and ALT, phosphatases (AcP and AlP), lactate dehydrogenase (LDH) in plasma were significantly increased in male rats treated with 1.28 mg deltamethrin per kg body weigh for 30 days [48].

Treatment of vitamin E with cypermethrin caused a significant (P<0.05) increase in testis weight (Table 1). The beneficial effects of vitamin E can be attributed to the antioxidant effects of this vitamin; it is scavenger of oxygen-free radicals which are toxic byproducts of many metabolic processes [49]. Oda and El-Maddawy 2012 [46] reported that the beneficial effect of vit E is mostly due to its antioxidant properties. Vitamin E protects critical cellular structures against damage caused by oxygen-free radicals and reactive products of lipid peroxidation. It has been reported that lipid peroxidation was prevented by vitamin E [50,51]. Vit E as a lipid soluble antioxidant plays a major protective role against oxidative stress and prevents the production of lipid peroxides by scavenging free radicals which are toxic byproducts of many metabolic processes in biological membranes[52]. Moreover, vit E is essential in maintaining the physiological integrity of testis, epididymis and accessory glands [53]. Conversely, deficiency of vit E may lead to detrimental effects on the reproductive organs, such as degenerative spermatogonium, testicular damage and degeneration of the seminiferous tubules [49,54]. Treatment with vitamin E alone caused a significant (P < 0.05) increase in body weight and relative testes and epididymis weights. Also treatment of vitamin E with cypermethrin caused a significant (P < 0.05) increase in activity of testicular enzymes AST, ALT, AcP and AlP and decrease in LDH (figs 1,2,3,4 and 5). These results are in agreement with the findings by Yousef *et al.,* 2003[8] who found that the New Zealand white rabbits vitamin E and vitamin C in drinking water fed for 12 weeks faced a reduction in the production of free radicals and a decrease in the activities of aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase (LDH), and an improvement in the sperm quality and standards of the blood and the improvement was more of vitamin E. Feeding of mice by dichlorovs with vitamin E and vitamin C for a period of seven weeks showed a significant increase in liver enzymes AST, ALT, AlP and LDH [32] . El-Shenawy *et al.* 2010 [33] found that feeding mice vitamin E with diazinon for 14 days showed a significant increase in liver enzymes AST, ALT, AlP and LDH. The present study showed that vitamine E treated group did not show any significant difference in the weight and testicular enzymes from the control indicating the role of this article as an antioxidant.

5. CONCLUSION

From the current results,it can be concluded that concurrent administration of vitamin E to cypermethrin treated animals ameliorated the induced weight and testicular enzymes damage. This is consistent with a vital role of vitamin E in antioxidant systems that protect against cypermethrin damage, possibly by preventing oxidative damage to testes. The present study suggest therapeutic effects of vitamin E to minimize the testes toxicity of cypermethrin exposure.

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