Amelioratory effects of vitamin E against biochemical toxicity induced by deltamethrin in male rats
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Background/aim
Deltamethrin (DLM) is a synthetic pyrethroid insecticide known for its wide toxic manifestations. The present experiment pertains to the protective role of vitamin E (vit E) against biochemical toxicity following pesticide exposure during 30 days.

Materials and methods
Male albino rats were divided into four groups of six each: Group I served as control rats (0 mg (vit E) and 0 mg DLM/kg body weight), Group II received deltamethrin (7.5 mg/kg body weight), Group III received vit E (100 mg/kg body weight), Group IV received both deltamethrin (7.5 mg/kg body weight) plus vit E (100 mg/kg body weight).

Results
Exposure of rats to DLM induced significant increase in the levels of hepatic markers enzymes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP); while acetylcholinesterase (AChE) was inhibited. Significant decrease in catalase (CAT) and glutathione S-transferase (GST) enzyme activities were observed in treated rats. Furthermore, renal markers such as urea and creatinine were increased in deltamethrin treated rats. Additionally, serum cholesterol, triglycerides, low-density lipoprotein (LDL) and the level of high-density lipoprotein (HDL) were significantly increased and decreased, respectively. Co-administration of vit E restored all the parameters cited above to near-normal values.

Conclusion
Our investigation showed that vit E acts as an effective antioxidant for DLM pesticide toxicity in reducing oxidative stress burden.

Keywords:
deltamethrin, enzyme activities, lipids, rats, vitamin E

Introduction
The use of pesticides is an important procedure for enhancing the agricultural 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].

There are three types of pyrethroid insecticides: type I (T syndrome) pyrethroids produce abnormal sensitivity and coarse tremors leading to prostration. Type II (CS syndrome) pyrethroids produce ptyalism and coarse tremors progressing to twisting movements of the neck and tail, whereas type I/II or TS pyrethroids produce signs of both whole-body tremors and salivation [2].

Previous studies have reported data indicating that these pyrethroids, which are widely used insecticides, induce oxidative stress through the generation of free oxygen radicals. Abnormal production of free radicals leads to damage of some macromolecules including proteins, lipids, and nucleic acids, and this is believed to be involved in the etiology of many chemicals and diseases [3–5].

Some experimental studies have shown that vitamins C and E (vit C and vit E) can be used to counteract pesticide toxicity [6,7]. Several biological defense mechanisms against intracellular oxidative stress are present in the organism such as antioxidant enzymes [superoxide dismutase, catalase (CAT), glutathione reductase, and glutathione transferase], and nonenzymatic antioxidants such as caratenoids, Vit E, vit C, and glutathione can also act to overcome the oxidative stress of the pesticides [8].

Antioxidant vitamins are the most important free radical scavengers in extracellular fluids, trapping radicals in the aqueous phase and protect biomembranes from peroxidative damage [6,9]. Some investigators have reported that the administration of vit E may be useful in controlling the toxic effect of insecticides and chemicals [10].

Therefore, the aim of the present study was

(1) To evaluate whether deltamethrin (DLM) induced biochemical perturbations in rats.
(2) To investigate the possible protective effects of vit E on deltamethrin induced toxicity and its role as inhibitor for free radicals generated following pesticide exposure during 30 days.
Materials and methods

Chemicals
DLM is a synthetic pyrethroid insecticide (Fig. 1) (purity over 98%) that was synthesized in the Laboratory of Applied Organic Chemistry, Chemical Industries Division, National Research Centre (Egypt) according to a known method [11]. DLM was administered orally at 1/20 LD$_{50}$ (7.5 mg/kg). Vit E ($\alpha$-tocopheryl acetate) was supplied by Kahira Pharmacy and Chemistry (Cairo, Egypt).

Animals and drug administrations
Male albino Wister rats, 6 weeks old and weighing 120–160 g, were selected from an inbred colony maintained in the Animal House of the National Research Centre (Giza, Egypt) under controlled conditions of a temperature of 25 ± 2°C, and a normal photoperiod (12 h dark: 12 h light). Animals were housed in cages throughout the experiment (with each cage housing six animals), fed on pellet diet and water ad libitum, and allowed to acclimatize to the laboratory environment for 7 days.

Experimental design
After 1 week of acclimation, rats were randomly divided into four groups, each containing six animals, and the route of administration selected for the study was oral (using oral feeding needles). The animals were grouped as follows: the rats in group I (control) received dismethylsulfoxide (1 ml); the rats in group II were administered DLM dissolved in dismethylsulfoxide (1 ml) at a dose of 7.5 mg/kg body weight corresponding to 1/20 LD$_{50}$; and the rats in group III received vit E only (100 mg/kg b.w.). Previous studies have shown that this dose was effective against the toxicity of DLM [7]; the rats in group IV received DLM at a dose 7.5 mg/kg b.w. plus vit E, respectively. Treatment duration was once a day daily for 1 month.

Biochemical analysis
At the end of the experimental period, animals were sacrificed by cervical decapitation, blood was collected from the arbitral plexus, and divided into two parts: the first part was collected in a dry test tube, left at room temperature to clot, and then centrifuged at 3000 rpm for 10 min to separate the serum that was used for the assay of biochemical parameters. The other part was collected in heparinized tubes for the assay of cholinesterase activity in plasma. Plasma acetylcholinesterase enzyme activity was examined using acetylthiocholine iodide as a substrate according to Ellman et al. [12]. Blood parameters were determined using kits from Bio diagnostic Company, Egypt.

In serum, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured according to Reitman and Frankel [13]. Serum alkaline phosphatase (ALP) activity was measured by Kind and King [14]. CAT and GST enzyme activity was determined according to Achi [15] and Habig [16], respectively. Serum samples were analyzed for the total protein (TP) concentration by the biuret method [17]. Serum albumin (ALB) concentration was determined using the Sigma diagnostics [18]. Blood urea nitrogen (BUN) concentration was determined according to urease-modified Berthelot reaction [19]. Serum creatinine determination was carried out according to Jaffe reaction [20]. Also, plasma was assayed for cholesterol, triglycerides by the method Carr et al. [21]. HDL and LDL were determined according to the methods of Warmick et al. [22] and Bergmeyer [23], respectively.

Statistical analysis
The obtained data from serum biochemical and enzymes analysis were statistically evaluated for the mean and standard error of the mean of each group. The significance of the changes between the tests and the control group was evaluated by the “t” test according to Sendecor and Cochran [24].

Results
The effects of DLM, vit E, and their combination on serum enzymes in the rats are shown in Table 1. The results indicated that the activities of ALT, AST, and ALP were significantly ($P$<0.01) increased, whereas the activities of CAT, GST, and AchE were significantly ($P$<0.05) decreased in the serum of rats treated with DLM for 30 days compared with the control group. However, treatment with vit E alone did not induce any significant change in the enzyme activities in the serum, whereas vit E in combination with DLM alleviated its negative effect on the activities of the above-measured enzymes (Table 1).

Renal profile biomarkers such as blood urea and creatinine showed a significant ($P$<0.01) increase in the group of rats treated with DLM compared with the control rats at the end of the experiment. In addition, the presence of vitamin plus DLM led to a reduction in the elevation of urea and creatinine, and maintained normal values compared with the control group at the end of 30 days of treatment. In terms of the changes in total protein and albumin, a significant decrease was found in rats treated with DLM, whereas insignificant changes were found when these
groups of rats were treated with Vit E alone and in combination with DLM (Table 2).

The present data showed that plasma cholesterol, triglycerides, and low-density lipoprotein concentrations were significantly ($P < 0.01$) increased by DLM treatment, whereas the high-density lipoprotein level was decreased compared with the control animals (Table 3). Vit E alone caused an insignificant decrease in the lipid profile and minimized the toxic effects of DLM. Vit E in combination with DLM reduced the elevation in serum lipids and minimized the toxic effects of deltamethrin.

**Discussion**

Insecticides are chemicals used widely in agriculture, environmental, human and animal health fields. Exposure to insecticides has been associated with many hazardous effects [25]. Determination of the common mechanism of toxicity in mammals is complicated by the number of potential biological target sites and effects exerted by various pyrethroid insecticides on these targets [26]. In the present study, we observed a significant increase in AST, ALT, and ALP activities in DLM-treated rats. ALT and AST are important indicators of liver damage in clinical finding. The increase in the activities of these enzymes may be because of the increase in the secretory activities of the hepatocyte cells, which were in agreement with the findings of El-Demerdash et al. [27] and Yousef et al. [7]. Biochemical analysis carried out by Tuzmen et al. [28] and El-Maghraby et al. [29] showed that administration of the chlorpyrifos and DLM caused damage in rat liver. The decrease in the activities of GST and SOD (Table 1) is in agreement with the results of Yousef et al. [7], who found oxidative stress and alteration in antioxidant enzymes in erythrocytes of

### Table 1 Change in enzyme activities of rats after daily oral administration of deltamethrin, vitamin E, and deltamethrin plus vitamin E for 30 days

<table>
<thead>
<tr>
<th>Enzymes</th>
<th>Control</th>
<th>DLM</th>
<th>Vitamin E</th>
<th>DLM + vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT (U/l)</td>
<td>34.67 ± 2.58</td>
<td>52.50 ± 3.00***</td>
<td>36.50 ± 2.63</td>
<td>38.00 ± 2.98</td>
</tr>
<tr>
<td>AST (U/l)</td>
<td>91.30 ± 4.80</td>
<td>123.00 ± 5.60**</td>
<td>99.50 ± 4.85</td>
<td>106.30 ± 5.30</td>
</tr>
<tr>
<td>ALP (U/l)</td>
<td>62.67 ± 3.95</td>
<td>80.50 ± 3.48**</td>
<td>58.80 ± 3.40</td>
<td>63.50 ± 4.23</td>
</tr>
<tr>
<td>CAT (U/mg protein)</td>
<td>0.466 ± 0.03</td>
<td>0.27 ± 0.02**</td>
<td>0.50 ± 0.04</td>
<td>0.423 ± 0.02</td>
</tr>
<tr>
<td>GST (μmol/mg protein)</td>
<td>1.44 ± 0.08</td>
<td>0.95 ± 0.05*</td>
<td>1.55 ± 0.09</td>
<td>1.39 ± 0.06</td>
</tr>
<tr>
<td>AChE (μmol/min/ml)</td>
<td>2.20 ± 0.13</td>
<td>1.68 ± 0.28*</td>
<td>2.19 ± 0.25</td>
<td>1.96 ± 0.18</td>
</tr>
</tbody>
</table>

All data are expressed as means ± SD.

AChE, acetylcholinesterase; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CAT, catalase; DLM, deltamethrin; GST, glutathione S-transferase.

*Significant at $P < 0.05$ compared with the control.

**Significant at $P < 0.01$ compared with the control.

### Table 2 Blood biochemistry of rats after daily oral administration with deltamethrin, vitamin E, and deltamethrin plus vitamin E for 30 days

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>DLM</th>
<th>Vitamin E</th>
<th>DLM + vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urea (mg/dl)</td>
<td>40.67 ± 2.58</td>
<td>74.25 ± 3.00**</td>
<td>41.00 ± 2.63</td>
<td>49.25 ± 2.98</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.897 ± 0.08</td>
<td>1.11 ± 0.60**</td>
<td>0.72 ± 0.05</td>
<td>0.73 ± 0.30</td>
</tr>
<tr>
<td>TP (g/dl)</td>
<td>7.45 ± 0.95</td>
<td>5.65 ± 0.48**</td>
<td>7.78 ± 0.40</td>
<td>6.99 ± 0.23</td>
</tr>
<tr>
<td>ALB (g/dl)</td>
<td>3.79 ± 0.03</td>
<td>2.71 ± 0.02**</td>
<td>3.7 ± 0.04</td>
<td>3.59 ± 0.02</td>
</tr>
</tbody>
</table>

All data are expressed as means ± SD.

ALB, albumin; DLM, deltamethrin; TP, total protein.

**Significant at $P < 0.01$ compared with control.

### Table 3 Blood lipid and lipoprotein profiles of rats after daily oral administration with deltamethrin, vitamin E, and deltamethrin with vitamin E for 30 days

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Control</th>
<th>DLM</th>
<th>Vitamin E</th>
<th>DLM + vitamin E</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol (mg%)</td>
<td>103.33 ± 5.60</td>
<td>123.75 ± 6.74**</td>
<td>112.5 ± 5.32</td>
<td>98.75 ± 4.66</td>
</tr>
<tr>
<td>Triglycerides (mg%)</td>
<td>84.76 ± 4.98</td>
<td>135.50 ± 7.46**</td>
<td>93.75 ± 5.83</td>
<td>90.50 ± 5.00</td>
</tr>
<tr>
<td>HDL (mg%)</td>
<td>22.33 ± 1.67</td>
<td>14.50 ± 1.30**</td>
<td>25.75 ± 1.46</td>
<td>23.75 ± 1.80</td>
</tr>
<tr>
<td>LDL (mg%)</td>
<td>64.06 ± 2.38</td>
<td>80.90 ± 3.45**</td>
<td>68.00 ± 2.80</td>
<td>56.85 ± 2.34</td>
</tr>
</tbody>
</table>

All data are expressed as means ± SD.

DLM, deltamethrin; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

**Significant at $P < 0.01$ compared with control.
pyrethroid-intoxicated rats. (Pyrethroids [30] and other pesticides [31–33] have been reported to cause oxidative damage in studies conducted in various animals species by using at various doses for various periods. Dichlorvos causes subacute and subchronic hepatotoxicity, and vitamins C and E decreased dichlorovos toxicity, but did not confer complete protection [34]. Modulatory effects of DLM were recorded on antioxidant defense mechanisms and lipid peroxidation in fish liver and intestine [35]. In general, pesticide intoxication produces oxidative stress by the generation of free radicals and induced tissue lipid peroxidation in mammals and other organisms [36]. Reduced activities of antioxidant enzymes (CAT, SOD) after treatment of pesticides are important indicators for the toxicity of these chemicals [37]. Rahman et al., [4] determined that MDA was a significant increase in the group treated with vit E plus DLM when compared to group II (only deltamethrin) suggests protective potential of vitamin E. The decrease in AChE activity could be due to the decrease of the enzyme synthesis by the inhibitory nature of toxicant. Accumulation of pesticides in the liver is reported to disrupt lipid metabolism and increase serum cholesterol levels [38]. Significant increase in total cholesterol, triglycerides and LDL and a significant decrease in HDL in the toxic control indicate hepatopathy, cardiac damage as well as renal failure [39], which could be probably due to free radical-induced oxidative damage. In group 4, supplementation of vitamin E revealed a significant alternation in the antioxidant property of vitamin E [40]. In this study, the blood urea and serum creatinine levels were significantly increased in group 2 at the end of 4th wk, which could be attributed to the free radical induced oxidative damage by deltamethrin on kidney. Serum levels of creatinin and urea were used as indicator of renal function. Elevated blood urea is known to be linked with an increased protein catabolism to urea as a result of increased synthesis of arginase enzyme involved in urea production [41]. It can be concluded that vitamin E, as an antioxidant, has protective effect against deltamethrin adverse effects by scavenging free radicals generated following pesticides exposure and supplementation of vitamin E might be beneficial to deltamethrin exposed populations.

In our study, the blood urea and creatinine levels were significantly increased in the group treated with vit E plus DLM at the end of 30 days, which could be attributed to the free radical induced oxidative damage by DLM on the kidney. Elevated blood urea is known to be linked to an increased protein catabolism to urea as a result of increased synthesis of arginase enzyme involved in urea production [34]. It can be concluded that chronic exposure to DLM causes hepatic and renal toxicities which may be due to the release of free radicals and the lipid peroxidation that it induces. The use of vit E was found to reduce the harmful effects of DLM in the mentioned parameters. Supplementation of vitamin E might be beneficial to diazinon-exposed populations [35]. Our findings show that DLM exerted adverse effects on some hematological and biochemical parameters. Vit E was observed to improve the hematological and biochemical changes induced by DLM. It can be concluded that vit E, as an antioxidant, may protect against the adverse effects of DLM by scavenging the free radicals generated following pesticide exposure.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

References

19. Charles J, Crouch SR. Spectrophotometric and kinetics investigation of the heme protein catabolism to urea as a result of increased synthesis of arginase enzyme involved in urea production [34]. It can be concluded that chronic exposure to DLM causes hepatic and renal toxicities which may be due to the release of free radicals and the lipid peroxidation that it induces. The use of vit E was found to reduce the


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