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Protective Effects of Royal Jelly against Hepatorenal Toxicity Induced by Deltamethrin in Male Albino Rats: Biochemical and Histopathological Studies

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Abstract

Deltamethrin (DM) is one of the most environmental and industrial pollutants that are toxic to humans, animals, fishes, and birds. The most common sources of human and animal exposure to deltamethrin (DM) are polluted water and food**.** This study was done to evaluate the nephrohepatic toxicity of deltamethrin. Twenty-four male rats were used. The first group was used as a control. The second and third groups were given deltamethrin orally in a dose of 1/10 % of the LD50 equal to 0.6mg\kg bwt alone plus royal jelly (RJ) at a dose of 100 mg/kg/day for two months, respectively. Oral administration of DM-induced biochemical and histopathological alterations. DM toxicity exhibited changes in the liver and kidney function tests manifested by an increase in AST, ALT, urea, uric acid and creatinine with no changes noticed in plasma proteins when compared to the control group. Giving RJ ameliorated the hepatorenal toxicity by causing recovery in both liver and kidney functions in comparison to DM given group. Pathologically, severe degenerative and necrotic changes in livers and kidneys were present in the deltamethrin group, where it improved to moderate to mild lesions with a protective royal gel substance. This study concluded that royal gel substance has been shown to benefit in lower down the side effects and increasing the rate of improvement of injury induced by deltamethrin.

Keywords:

Biochemicals, Deltamethrin, Hepatorenal, Histopathology, Royal Jelly, Toxicity.

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Introduction

Deltamethrin (DM) is a synthetic pyrethroid compound widely used for many purposes include (agricultural, veterinary and public health) to control and eradicate insects. The wide use of DM as a highly effective insecticide and other applications resulted in high concentrations of DM in the air, agriculture products, and surface waters. Therefore, DM has become one of the most environmental and industrial pollutants**.** Exposure to DM products may occur directly or indirectly through skin contact, inhalation, or food/water ingestion **(**Chrustek et al., 2018; Bouzar et al., 2020). Moreover, it was proved that DM has toxicological effects not only on the target organism but also on RBCs, neurons, hepatocytes, genotoxicity and male and female reproductive damages as well as pulmonary disorders that threaten the health of livestock, poultry, fish stocks and human beings **(**Shi et al., 2019). Exposure to DM has great health impacts on the liver and kidneys. The liver is the place of DM metabolism and detoxification after absorption. Additionally, DM was excreted and removed through the renal tubular epithelium (Abdel-Daim et al., 2013). During DM intoxication the concentration of reactive oxygen species (ROS) increased because of reactional oxidization of the DM by cytochrome P450 enzymes in the hepatocytes (Rehman et al., 2017). Moreover, poisoning by DM induced apoptosis in many cells and organs in addition to the oxidative stress which can lead to mitochondrial damage and alterations that end with liver tissues injury (Kumar et al., 2015).

Royal jelly (RJ) is a naturally thick and milky viscous material. It is soluble in water whitish to yellow color. RJ is secreted by the hypopharyngeal and mandibular glands in the heads of nursing worker honeybees which is the primary food for young larvae during their first three days of life and for the queen honeybee (Chi et al., 2021). RJ was used in traditional medicine for human health care. Nowadays, several researchers are highlighting the therapeutic properties of RJ. RJ has a wide range of biological and pharmacological impacts including immunomodulatory, anti-inflammatory, antibacterial, antioxidant and anti-tumor activities, which might be of high value in the recent medicine for the development of new drugs **(**El-Guendouz et al., 2020). Also, RJ in old Chinese history was used as a food supplement and medicine agent (Abdelnour et al., 2020). It was proved that the regular intake of RJ exhibits a beneficial effect on many disorders, such as infertility, digestive problems, neuronal disorders and inactive immune system. In addition, it has antioxidant, anticancer, antimicrobial and anti-diarrheal properties (Zhang et al., 2019). Even if RJ is known since ancient times; research papers concerning its investigation are not this developed as compared to the other beehive, products such as honey or propolis (EL-Guendouz et al., 2020). Recently, the application of natural supplements is a promising therapy for some diseases and health risks (Mahgoub et al., 2019). The objective of the current study was to investigate the ameliorative effects of RJ on DM-induced hepatorenal toxicity in male albino rats.

Materials and methods

Ethical approval:

All experimental procedures in the present study were performed and approved in accordance with the Ethics Committee of the Faculty of Veterinary Medicine, South Valley University, Qena, Egypt. Approval number 29.

Materials:

a- Deltamethrin (DM):

Commercially grade deltamethrin–based pesticides (butox 5% Ec) were purchased from (internet Co. France).

b- Royal jelly (RJ):

Fresh RJ was obtained from the local market and stored at 4℃ in the refrigerator until use. About 100 mg\kg of RJ was dissolved in 1 ml distilled water (d.w.) and administrated to rats orally for 60 days according to Ghanbari et al. (2016).

c- Biochemical kits:

The biochemical kits were used for the determination of AST, ALT, Bilirubin, Total Protein, Albumin, Globulin, Creatinine, Urea and Uric acid. The kits are produced by Diagnostic Laboratories, Spectrum company, Dokki, Giza, Egypt.

d- Experimental Animals:

A total of twenty-four sexually mature healthy male rats at age (12-14) weeks with average initial body weight (of 150-250) g was purchased from the Egyptian Company for Production of Antisera, Vaccines and Drugs, Helwan, Egypt. Throughout the experimental period, every 3 rats were housed in plastic cages with stainless steel covers and provided with a standard diet and tap water *ad libitum.* Cages were kept in an air-conditioned room (23±3ºC) with a 12/12 hrs light/dark cycle. All rats were reared under the same managerial and hygienic conditions. Cages were cleaned regularly and disinfected.

Methods

Experimental design:

Twenty-four rats were randomly allocated into three equal groups (8 rats/each).

Group1, the rats were fed the basal diet and received physiological saline without any supplementation and were used as the control group.

Group 2, the rats received DM at dose 1\10 LD50 (0.6 mg/kg B.W.) orally using a stomach tube.

Group 3, the rats received DM at dose 1\10 LD50 (0.6 mg/kg B.W.) Plus royal jelly (100 mg\kg B.W.).

The animals were examined daily for two months. At the end of the experiment, the animals were euthanized, and the blood and tissues samples were collected from the heart by heart puncture. About 5 ml of whole blood was collected on plan tubes without anticoagulant and allowed to stand for clotting from 1-2 hrs at room temperature. The clot was detached from the wall of the centrifuge tube and then samples were centrifuged at 3000 rpm for 10 mins in order to separate the serum. Serum samples were then divided into aliquots in Eppendorf tubes and stored at -20˚C until further analysis.

Tissue samples:

The livers and kidneys, from each rat, were quickly removed, washed in a saline solution (0.9% NaCl) for biochemical examination and other pieces of each tissue were fixed immediately in 10% neutral buffered formalin, dehydrated, cleared embedded in paraffin wax blocks for histopathological investigation.

Biochemical analysis:

The biochemical measurements were performed manually using an Ultraviolet-visible spectrophotometer using commercial specific kits (Spectrum Company, Obour City, Egypt) at Faculty of Veterinary Medicine, South Valley University, Qena, Egypt.

Liver functions:

Serum ALT and AST were measured according to the method described by Breuer, (1996) using commercial specific kits purchased from (Spectrum Company, Egypt). Serum total protein and albumin were measured according to Tietz, (1994) and Tietz (1990), respectively, using commercial specific kits purchased from (Spectrum Company, Egypt).

Kidney functions:

The BUN, uric acid and serum creatinine were measured according to the method described by according to Tietz (1990) using commercial specific kits purchased from (Spectrum Company, Egypt).

Histopathological Evaluation.

Samples from the hepatic and renal tissues were processed according to the guide of Bancroft and Gamble (2008). After fixation with 10 % neutral buffered formalin, specimens were washed in water, dehydrated in ascending grades of alcohol, then in xylene. Then, samples were embedded in paraffin for preparation of 5 µm paraffin sections and then stained with hematoxylin and eosin for histopathological examination.

Statistical Analysis:

One-way analysis of variances (one-way ANOVA):

One-way ANOVA was conducted to examine the effect of our independent variables (the group) on the studied traits under this study. One-way ANOVA revealed significant difference was followed by a post-hock test (Duncan's test) for multiple comparisons among experimental conditions. The results were expressed as the mean ± standard error of the mean (SEM). Statistical analysis was performed with IBM® SPSS® (SPSS Inc., IBM Corporation, NY, and USA (2012) Statistics Version 21 for Windows.

Results

Liver function tests:

To evaluate the liver function's response to DM exposure, we determined the activities of serum AST and ALT as well as total protein, albumin, and globulin in different groups. The present data showed that in the DM group, significant increases in AST and ALT activities were detected as compared with the control and RJ plus DM groups (Table 1). The enzymes' activities were declined in the RJ plus DM group as compared to the deltamethrin group. On the contrary, co-administration of rats with RJ with DM prevented a DM-induced increase in the enzyme activities when compared to control and DM groups. From Table (1), we observed also that the DM did not affect the total protein, albumin, and globulin concentrations as compared to the control group and DM+ RJ group.

Kidney Function test:

In kidney function tests; there was a significant increase in levels of creatinine in the deltamethrin intoxicated group as well as the increase in the serum urea and uric acid in comparison to the control group (Table 2). From (Table 2) a significant decrease in the concentration of mentioned parameters was reduced when RJ was given with deltamethrin in comparison to the DM group.

Histopathological Findings:

Histopathological findings, kidneys and livers in the rats in groups (2, 3) which administrated deltamethrin drugs and treated with royal gel, respectively compared with a control group (1). The control group showed normal structures in both livers and kidneys (Fig. 1a, 1b). The rats in (group. 2) suffered from degenerative and necrotic changes of cortical tubule epithelial cells are characterized by cloudy swelling of epithelial cells and pyknosis of the nuclei, besides congestion in the all renal blood vessels. In addition, degenerative changes manifested by angiogenesis in blood vessels in the medulla pressured on collecting tubules lead to necrosis with dilation in the lumen of the others. In comparison with (group 3), which was treated with royal gel

displayed moderate degenerative and necrotic changes with few casts in renal tubules in most rats (Fig. 2a, 2b, 2c, 2d). Moreover, the livers in (group. 2) showed hepatitis manifested with severe congestion in the portal vein, periportal fibrosis and newborn bile ducts in the portal triads, besides coagulative necrosis and degenerative changes in hepatic cells, in comparison with (group 3) which appeared normal hepatic cells with few inflammatory cells around portal areas (Fig. 3a, 3b, 3c, 3d).

Table 1. Liver functions differences between the control, deltamethrin and deltamethrin combined with royal jelly groups.

Parameter	Groups			P-Value
	Control	DM	DM+RJ	
ALT UI/L	29.35±1.55	47.96±2.74[a]	38.78±2.04[b]	<0.001**
AST UI/L	50.31±1.52	76.06±1.82[a]	66.08±2.37[b]	<0.0001***
Total protein	12.66±2.01	12.57±1.38	11.77±1.45	<0.916
Albumin g/dl	4.61±0.76	5.13±0.55	5.11±0.53	<0.803
Globulin g/dl	7.89± 1.60	6.93± 1.40	6.20± 1.60	<0.1865
A/G ratio	0.68± 0.19	0.95± 0.23	1.42 ± 0.73	<0.1523

Table 2. Kidney functions Differences between the control, deltamethrin and deltamethrin combined with royal jelly groups.

Parameter	Groups			P-Value
	Control	DM	DM+RJ	
Creatinine(mg/dl)	1.16±0.18	1.69±0.20[a]	1.36±0.05[b]	<0.05*
Urea(mg/dl)	42.11±4.44	54.93±2.81[a]	47.92±1.96	<0.05*
Uric acid(mg/dl)	3.71±0.50	5.62±0.28[a]	4.02±0.28	<0.01**

Data are represented as Mean ±SE. The P-values reported are for one-way ANOVA test. The used symbols *, **, and *** to represent significance at $P \leq 0.05$, $P \leq 0.01$ and $P \leq 0.001$ respectively for ANOVA test. The letters are used to denote the significant differences based on Duncan test at 0.05 significance level as follows: **a** for Control vs. DM, **b** for Control vs. DM+RJ, **c** for DM vs. DM+RJ.

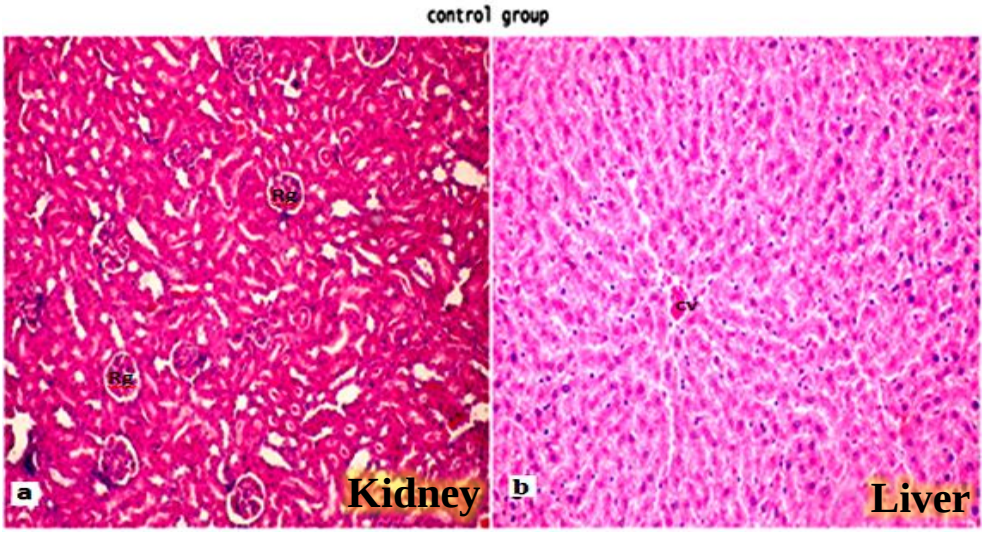

Fig. 1. Showing kidney and liver of the rats of **control group** showing **a)**. Nephron consisted from normally renal glomerulus (Rg), primary and distal renal tubules **b).** The hepatic lobules noticed in normal architecture around central vein (cv). (H& E. x 150)

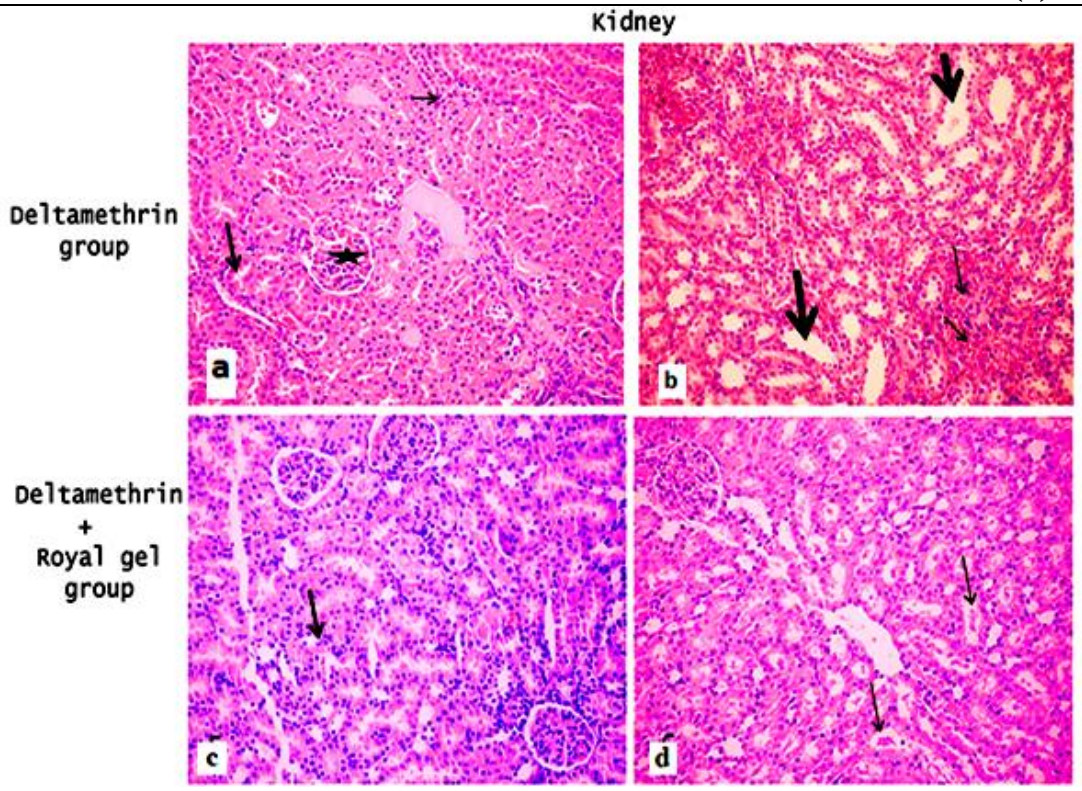

Fig. 2. Showing effect of deltamethrin administration on kidney of the rats**; a)** Showing cloudy swelling (thick arrow) and necrosis in cortical renal tubules (thin arrow) with congestion in glomerular capillaries and renal blood vessels (star). **b)** Angiogenesis (thin arrow) in blood vessels pressured on some collecting tubules leading to compensatory dilation in others (thick arrow). After royal jelly co administrated with deltamethrin **c)** Moderate degenerative changes (thick arrow) with **d)** Renal casts in cortex (thin arrow). (H& E., x 150)

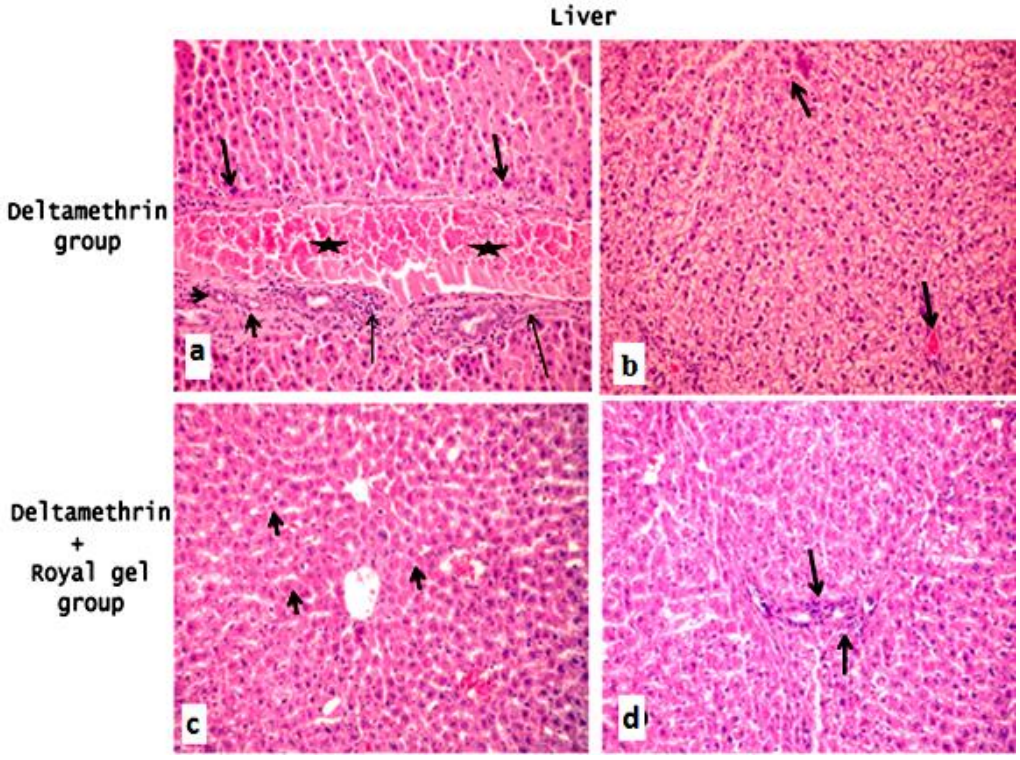

Fig. 3. Showing effect of deltamethrin administration on liver of the rats**; a)** Showing coagulative necrosis (thick arrow) in the hepatic cells with severe congestion in portal vein (star), periportal fibrosis

(thin arrow) and newborn bile ducts in the portal triads (arrowhead). **b)** Vascular degeneration in hepatic cells (arrow). Due to administration of royal jelly **c)** The liver appeared with normal structure (arrow). **d)** Few inflammatory cells showed in portal areas (arrowhead). (H&E x150).

Discussion

In the present study, we investigate the toxic effects of DM in the rats via examination of some biochemical parameters and histopathological examinations. According to many previous studies and reports, deltamethrin is fastly metabolized in the hepatic cells which resulted in a great concentration of DM metabolites accumulating in the liver causing oxidative stress on the hepatocytes (Saoudi et al., 2017). In our study, administration of DM to albino rats increased the liver enzymes activity AST, ALT and ALP which return to over generation of ROS and free radicals that changes the oxidative system status and cause disruptions to the integrity of the cell membrane leading to release of the hepatic enzymes from the injured hepatocytes into the blood circulation (Khalaf et al., 2019; Tewari et al., 2018). An increase in the serum concentrations of AST and ALT activities after exposure to DM has been reported in several reports (Abdel-Daim et al., 2013; Gunduz et al., 2015; Maalej et al., 2017). ALT is a highly specific enzyme as an indicator marker for hepatic damage by increasing its level in the serum. No significant difference in serum total protein, albumin and globulins values due to exposure to DM in comparison to the control group. Similar results to our findings were reported by Tewari et al., (2018). However, some other previous studies have come opposite to our results (Abdel-Daim et al., 2013; Uchendu et al., 2017). these studies reported that DM toxicity induced decreased total protein and albumin concentrations. The differences between our results and other previous studies may be due to different doses, time of exposure to DM as well as the study's experimental conditions. Liver injuries end with the improper function that is manifested by its failure to remove red blood cells' life span. in the same exposure to DM affects kidney function leading to high levels of urea and creatinine. Physiologically creatinine results from creatine metabolism in muscles then it is processed by the kidney and eliminated via the urine. While during kidney malfunction because of any exogenous and endogenous elements, its concentration gets increased directly (Harvey et al., 2006). Our results were confirmed by the alteration seen in the hepatic tissues due to DM exposure leading to cellular disruption in the hepatocytes ending with raises in ALT and AST.

Exposure to DM not only affects the liver but also affects the renal tissues. In this study exposure to the DM induced increase in serum urea and creatinine concentrations in comparison to (DM+RJ) and control groups; this was associated with disrupted glomerular filtration. These findings agreed with the observations of Wahlang et al. (2013). High concentrations of urea indicate the impairment in the renal tubular reabsorption, while the increased serum creatinine level reflects impairment of glomerular filtration rate (GFR) (Adedara et al., 2012). Thus, high levels of urea and creatinine in the DM exposure animals revealed renal tissue injury (Tewari et al., 2018).

Co-treatment of DM with Royal jelly in this study was able to decline the elevated activities of AST and ALT in the DM plus RJ group. This recovery may be due to the antioxidant effects of RJ, which ameliorates the effects of DM toxicity by removal of ROS and free radicals (Kohno et al., 2004). This was confirmed by the observed recovery in the biochemical analyses and histopathological findings.

Conclusion

It could be concluded that deltamethrin is a toxic substance-induced impairment of hepatorenal functions with toxicity lesions. Meanwhile, the royal gel substance was declared beneficial in lower down the side effects and increasing the rate of improvement of injury induced by the deltamethrin.

Conflict of interest statement

The authors declare that they have no conflict of interest.

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