AMELIORATIVE EFFECT OF POMEGRANATE MOLASSES ON DELTAMETHRIN INDUCED NEUROTOXICITY IN ADULT ALBINO RATS: BIOCHEMICAL, HISTOPATHOLOGICAL & IMMUNOHISTOCHEMICAL STUDY

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ABSTRACT

Background: Deltamethrin (DLM) is class II synthetic pyrethroid used worldwide as pesticides in agriculture, household pest control, protection of foodstuff, and disease vector control. Exposures occur mainly from the household application, contaminated food or water. Although initially thought to be least toxic, a number of recent studies revealed its toxic effects in different animal species. **Aim:** The current study aimed to evaluate oxidative stress effect due to DLM exposure on brain tissues of adult albino rats, and whether co-administration of pomegranate (PM) molasses can ameliorate this oxidative damage. **Materials & Methods:** Thirty adult experimental Albino rats were divided into five groups: -ve control group (6 rats), +ve control group (6 rats) (received 1ml corn oil once daily, orally), diluted PM molasses [(0.5ml (PM) molasses+(0.5ml) distilled water] treated group (6 rats), DLM (6mg/kg) treated group (6 rats), DLM (6mg/kg) + diluted PM molasses[(0.5ml (PM) molasses+(0.5ml) distilled water] treated group (6 rats). These doses were given once daily, orally for seven days. By the end of the expirement, blood sample were obtained for estimation of plasma cholinesterase (PCHE) level and oxidative stress parameters (malondialdehyde [MDA], glutathione [GSH], and catalase [CAT]), then rats were sacrificed. The brains were excised, prepared for estimation of oxidative stress parameters in tissue, histopathological changes and immunohistochemical examination. **Results**: revealed that DLM caused neurotoxicity in albino rats as there was a significant increase in serum & brain tissues MDA, reduction of both GSH & CAT, decrease in PCHE level & pathological changes in brain included, neuronal degeneration, apoptotic bodies, neuropil vacuolizations, proliferated and dilated blood vessels beside strong positive immunreaction for bax when compared with both control groups & PM molasses treated groups. While, there was significant reduction in serum & brain MDA, significant increase in both GSH &CAT and also decrease in PCHE level. Mild pathological changes in brain of albino rats beside mild positive immunreaction for bax in DLM + PM molasses treated group as compared to DLM treated group. **Conclusion:** deltamethrin can induce oxidative damage in the experimental albino rat brain & pomegranate molasses as an antioxidant has an ameliorative effect against this damage.

Keywords: Deltamethrin, neurotoxicity, histopathology, immunohistochemistry, pomegranate

INTRODUCTION

For centuries, pesticides have been used in agriculture to improve food production by controlling disease vectors and eradicating unwanted insects. One of the popular pesticides is organophosphorus compounds that are widely used in agriculture, industry & medicine. The high effectiveness even in low concentration, photostability, easily dissosciations & less toxic effect in animals are main advantages of pyrethroids that made it successively replacing organophosphate (**Bradbury and Coats, 1989; Storm et al., 2000; Prakasam et al., 2001).**

Deltamethrin (DLM) is one of the most common synthetic insecticides pyrethroids of class II that is widely used in crop production, veterinary products and public health programs. Moreover; it is considered the most potent neurotoxic pyrethroid. Exposure originates mainly from the household application of insecticides, contaminated food or water **(Soderlund et al., 2000; Tu et al., 2007).**

The mode of action of deltamethrin is to interact with ion channels on the axons of target. The principle reaction is broken of ester bonds by hydrolysis and/or oxidation then oxidation of resulted acid & alcohol. The acid is mainly conjugates in a glucuronide form, excreted in urine and hydrolyzed by liver microsomal enzymes **(Anand et al., 2006).**

The basic pathophysiological insecticidal effects of DLM is thought to be resulted from binding to a specific receptor site on voltage-gated sodium channels and prolonging the open state via inhibiting channel inactivation **(Soderlund et al., 2002; Du et al., 2010).**

Deltamethrin reported to be most toxic, because it is neither fully metabolized nor quickly detoxified and hence creates serious problems due to residue accumulation especially in fatty tissues as brain **(Ansari and Razdan, 2001; Erdogan et al., 2006; Rehman et al., 2006).**

Neurotoxicity of deltamethrin induced by modification of sodium channels kinetics **(Dong, 2007)**, inhancing release of neurotransmitter **(Hossain et al., 2004)** induction of both cytochrome P450s & oxidative damage **(Dayal et al., 2003; Yousef et al., 2006**) & S100β upregulation **(Patro et al., 2009)**. Also, apoptosis suggested to have an important role in deltamethrin induced neurotoxicity **(Hossain and Richardson, 2011)**.

The body is always under the protection of antioxidant systems which pevent the incidence of oxidative stress, however, the antioxidants systems are overcomed in sever exposure to oxidative challenge, like in pesticide poisoning **(Saxena and Garg, 2010).**

Polyphenols are a large group of plant, which have high antioxidant activity **(Tapiero et al., 2002; Mennen et al., 2005).**

Pomegranate fruit, juice, and peel extracts is a natural rich source of polyphenols and hence posses a strong antioxidant effect. It is one of the most popular antioxidants, because of its potent antioxidant criteria **(Gil et al., 2000; Murthy et al, 2002).**

Pomegranate (Punica granatum L.) is a popular fruits used in folkloric medicine for management of numerous diseases and represent a main source of vitamin C anthocyanins,hydrolysable tannins punicalagin, punicalin ellagic and gallic acids**(Afaq et al., 2005; Lansky and Newman, 2007).**

Hence, the current study aimed evaluate possible protective effects of PM molasses adminstration against

deltamethrin toxicity on levels of oxidative stress parameters including malondialdehyde (MAD), reduced glutathione (GSH) & catalase (CAT) in both serum and brain tissues of albino rats, pseudocholine esterase plasma level (PCHE), in addition to histopathological & immunohistochemical studies of cerebral tissues.

MATERIALS & METHODS

A) Materials:

1) Chemicals:

Deltamethrin powder (98% purity) was obtained from Sigma Pharmaceutical Company.

Pomegranate (PM) molasses was obtained freshly prepared from local market. It is a concentrated product produced simply by boiling PM juice with the addition of sugar and lemon juice.

Experimental Animals: Thirty adult albino rats weighing 180-200 g were maintained on stock diet and kept under fixed appropriate conditions of housing and handling. The research were carried out according to with the research protocols of Ethics Committee of Scientific Research, Faculty of Medicine, Banha University that followed instructions of the National Institutes of Health Guide for Care and Use of Laboratory Animals (Publication No. 85-23, revised 1985).

Albino rats were animals of choice for experiments. This is because the anatomy as well as physiology of these animals is closely related to that of human and most of chemical and biochemical experimental studies were carried out with these animals often produce similar results with those conducted on human **(Ogunleye and Omotoso, 2005).**

Experimental protocol: 30 adult albino rats were equally divided into 5 groups as follow:

(1) Group I (control -ve group) 6 rats: lifted without intervention to measure the basic parameters.

(2) Group II (control +ve group) 6 rats: Each rat was treated with 1ml corn oil (vehicle of deltamethrin) once daily, orally for seven days.

(3) Group III (diluted PM molasses gavaged group) 6 rats: each rat was gavaged with 0.5ml (PM molasses) + 0.5ml distilled water once daily, orally for seven days.

(4) Group IV (deltamethrin (DLM) gavaged group) 6 rats: Each rat was treated with $^1/_5^{th}$ LD_{50} of DLM (6mg/kg dissolved in corn oil), once daily, orally for seven days. The dose was determined on the basis of LD_{50} of deltamethrin in peanut oil i.e. 30 mg/kg body weight **(Singh et al., 2007).**

(5) Group V (treated with DLM + PM molasses) 6 rats: Each rat was gavaged with DLM (6 mg/kg/ day) and PM molasses (0.5ml (PM) plus 0.5ml distilled water) once daily, orally for seven days.

All animals were received the drugs orally. The oral administration was via appropriate sized metallic cannula dressed with plastic cover that exceeds the tip by 2-3 mm to prevent injury of the esophagus.

A) Biochemical study:

Preparation of serum:

Blood samples were taken from their hearts by 5ml syringes, where it lefted to coagulate at room temperature, and then centrifuged at 986 g for 15 minutes; the clear non-hemolyzed supernatant serum was quickly removed and used for the estimation of malondialdehyde (MDA), reduced glutathione (GSH), and catalase (CAT). Blood samples were also taken for

estimation of plasma pseudocholine esterase (PChE) level.

Tissue Samples:

1- By termination of 7 days, the rats were sacrificed using decapitation. Brain tissues from each rat were removed, washed with saline solution, tissues were homogenized in ice-cold 50 mM sodium phosphate buffer (pH 7.4) containing 0.1 mM ethylene diamine tetraacetic acid (EDTA) to induce 10% (W/V) homogenate which was centrifuged at 10,000xg for 20 minute at 4C° and resultant supernatant was used for the estimation of MAD, GSH, & catalase by using ELISA kits that purchased from LifeSpan Biosciences companey (LSBio), North America for MDA and Shanghai BlueGene Biotech CO., LTD for GSH and CAT.

2- Another portion of the brain was dissected and settled in 10% formalin for histopathological& immune-histochemical examination.

Biochemical analysis

1– MDA, GSH & CAT:

The determination of MAD, GSH, and catalase level in serum & brain tissues were done by using ELISA kits that purchased from LifeSpan Biosciences companey (LSBio), North America for MDA and Shanghai BlueGene Biotech CO., LTD for GSH and CAT according to the manufacturer's instructions.

2-Pseudocholine esterase:

Pseudocholine esterase plasma activity was measured spectrophotometrically using the commercial kit of cholinesterase SGM ITALY, with Spinlab (Spinreact companey, Spain) by the kinetic butyrylthiocholine method **(Panteghini et al., 2006).**

Histopathological analysis:

(A) Light microscope technique:

The brain was fixed in 10% formalin saline. After fixation, brain was embedded in paraffin & prepared for 5µ thickness sections, which stained with Hematoxylin & Eosin stains then examined by light microscope (OLYMPUS, Japan) **(Bancroft&Layton, 2019).**

(B) Immuno-histochemical study:

Immediately after dissection, immunohistochemical reactions were carried out on sections of brain of adult albino rats using Bax according to **(Wu et al., 2000; highly and Sullivan, 2019),** then it fixed in paraformaldehyde in 0.1 M phosphate buffer for 20 min and treated with 0.3% Triton X-100 for 30 min. After 30 min of 0.3% treatment of H_2O_2 for blocking endogenous peroxidase activity, sections were incubated in 2% normal goat serum at 37oC for 1 h, followed by 48 h incubation at 4oC with primary anti-Bax at a dilution of 1:100 respectively, then it incubated with biotinylated link antibody (1:100) and in streptavidin-horseradish peroxidase solution (1:100) at 37oC for 2 h, respectively. After being stained with DAB, sections were dehydrated, and examined under light microscopy. The specifcity of the immunoreactivity was confrmed by omission of the primary antibody. The site of antigen was clearly identified by presence of brown color in cytoplasm.

Statistical Analysis:

The measured parameters were organized, tabulated and statistically analyzed using SPSS software statistical computer package version 16 (SpssInc, Chicago, ILL Company). Data were expressed in form of mean ±standard deviation and range. They were tested for normality using

Shapiro-Wilks test assuming normality P>0.05. Differences among groups were tested by ANOVA for normally distributed variables, or Kruskal Wallis test for non parametric ones. Significant ANOVA or Kruskal Wallis tests were followed by post hoc multiple comparisons by Bonferroni tests to detect the significant pairs. The level of significance was stated at 0.05 ($P \leq 0.05$ was considered significant).

RESULTS

The Findings obtained from acute toxic effects of deltamethrin (DLM) and uses of pomegranate (PM) molasses as an antioxidant on the rats (Plasma cholinesterase enzyme [PChE] level and oxidative stress parameters (Malondialdehyde [MDA], catalase [CAT] and reduced Glutathion [GSH] in both serum and brain tissue) as compared with those of control groups and with each others have been statistically analyzed, outlined, and graphically illustrated.

1- Biochemical study:

1- As regard to both control groups (negative & positive) and pomegranate [PM] molasses treated group:

All the studied biochemical parameters of control negative, control positive and pomegranate [PM] molasses treated group revealed statistically insignificant differences between them by ANOVA test (F test) regarding:

1- Plasma cholinesterase enzyme (PChE) level **(Table 1 & Figure 1).**

2- oxidative stress parameters

a- Malondialdehyde [MDA] level in both serum and brain tissues **(Table and Figure 1 & 2).**

b- Antioxidant parameters (catalase [CAT] and reduced Glutathion [GSH]) in both serum and brain tissues **(Table and Figure 1 & 2).**

So the negative control group was chosen as a representative group to be compared with the Biochemical results of the other treated groups; [deltamethrin treated group (group IV) and deltamethrin and pomegranate molasses (group V) treated group].

2- As regard to deltamethrin (DLM) and deltamethrin + pomegranate (PM) molasses (DLM + PM molasses) treated groups:

1) **Comparison between studied groups regarding to Plasma cholinesterase enzyme (PChE) Level:**

The mean value of PChE activities among DLM treated group (302.5±156.4.6 U/L) and DLM + PM molasses treated group (485.8±161.9U/L) were significant lower as matched with those of control. However, there was insignificant reduction in mean values of PChE when compared DLM treated group with DLM + PM molasses treated group **(Table 1&Figure1)**.

2) **Comparison between studied groups according to oxidative stress parameters:**

a- **Comparing regarding to MDA in both serum & brain tissues:**

In comparision of MDA of rats in DLM and DLM + PM molasses treated groups with those in control, they depicted signifcantly higher level of serum MDA (39.1±2.1 ng/ml and 26.8±2.1ng/ml, respectively). Moreover, when DLM & DLM + PM molasses gavaged groups matched with each other, DLM gavaged animals revealed significant higher level of MDA production than DLM + PM molasses treated group **(Table 1& Figure 2).**

The present study showed that MDA level was highly signifcant increased in brain tissues in both DLM

and DLM + PM molasses treated groups with mean values [12.28 ± 0.76 & 7.06 ng/g ± 0.39 ng/g respectively] as compare with control. However, administration of pomegranate molasses resulted in significance reduction in elevated MDA in brain tissues in DLM + PM Molasses treated group when compaed with DLM treated group (**Table 2 & Figure 3)**.

***b*- Comparing regarding to antioxidants parameters (CAT & GSH) in both serum and brain tissue:**

Mean serum levels of CAT & GSH in DLM gavaged rats [25.8±3.14U/L & 49.3±2.97 pg/ml respectively] and in DLM + PM molasses treated group [42.3±2.52 U/L &99.8±1.37pg/ml respectively] illustrated significance decreases as matched with those of control group. Furthermore, in comparision between rats in DLM group & those in DLM + PM molasses regarding to serum level of CAT & GSH levels there were significantly reduction in their concentrations in DLM treated animals **(Table 1& Figure 2).**

The present study illustrated that the brain CAT level in DLM treated group [3.68 ± 0.23 U/g] and in DLM + PM molasses treated group [8.86 ± 0.30U/g] as well as brain GSH level in both DLM & DLM + PM molasses treated groups [12.2 ± 0.96 pg/ g and 28.1 ± 1.59 pg/g respectively] were significantly lower than those of control group. Furthermore, reduction of brain CAT & GSH in DLM treated group were statistically different as compared with those of DLM + PM molasses treated group **(Table 2 & Figure 3).**

2-Histopathological results:

a- H & E light microscopic examinations:

1- In –ve control, +ve control & pomegranate (PM) molasses treated group (group I, II & III respectively):

The light microscopic examinations of both control negative & positive (I&II) groups as well as PM molasses treated group (group III) revealed similar results. Thus, we choose control negative (group I) as a representative group in the histopathological & immunohistochemical images.

In the light microscopic examinations with hematoxylin and eosin (H&E) stain of group I, II & III; the cortex of the cerebrum showed normal granular and pyramidal layer with large and small pyramidal (neuronal) cells contianed darkly stained cytoplasm and processes with vesicular nuclei, neurofibrillar network & surrounding neuropil contained nerve fibers, glial cells & blood vesssels **(Image I; A).**

2- In deltamethrin (DLM) treated group (group IV):

Histopathological examination of stained section in the brain of DLM treated rats showed; neuronal cell degeneration (pyknosis) in form of diffuse apoptotic body (scanty dense esinophilic cytoplasm with deeply stained shrunked or even absent nucleus) and a highly proliferative dilated blood vessels with widening perivascular Virchow–Robin space were present also **(Imag I; B-B2).**

3- In DLM + PM molasses treated group (group V):

Histopathological examination of stained section in the brain of DLM + PM molasses treated rats showed the same histopathological disruption seen in the DM treated group with decreased number of apoptotic bodies and congested blood vessels **(Imag I; C & C1).**

b- Immunohistochemical examinations:

The BAX expression was evaluated according to intensity of positively stained neural cells into; negative, positive and strong positive reaction.

2- In deltamethrin [(DLM) treated group (group IV):

The Immunohistochemical examination of the brain of DLM treated group showed many nerounal cells with strong positive expression of BAX antibody appears as diffuse strong brownish cytoplasmic staining (I**mage II;B).**

3- In DLM + PM molases treated group (group V):

The immuno-histochemical examination of the brain tissues in the DLM + PM molasses treated rats also showed low cytoplasmic expression to Bax antibody when compared to DLM group **(Image II; C).**

Table (1): ANOVA one way statistical analysis of studied groups regarding to [Plasma cholinesterase enzyme and oxidative stress parameters (MDA, Catalase and GSH)] in serum.

Groups	Pseudocholine estrase Mean ± SD (range)	Serum MDA Mean ± SD (range)	Serum catalase Mean ± SD (range)	Serum GSH Mean Mean ± SD (range)
–ve control group (group I)	1336.1±200.6 (1103-1607)	15.3±0.82 (14.1-16.1)	60.9±2.72 (57.3-65.2)	139.4±8.04 (129.6-149.5)
+ve control group (group II)	1346.1±177.8 (1109-1560)	14.7±0.75 (14-15.9)	60.7±3.37 (57.1-65.1)	138.3±8.47 (128.3-149.3)
PM molasses treated group (group IIII)	1335.0±176.2 (1132-1600)	15.6±0.83 (14.4-16.7)	61.5±3.60 (57.2-65.0)	139.6±7.97 (129.4-149.2
DLM treated group (group IV)	302.5±156.4 (102-497)*†‡	39.1±2.1*†‡ (36.5-41.2)	25.8±3.14 (22.9-30.2) *†‡	49.3±2.97 (45.3-52.1)*†‡
DLM & PM molasses treated (groupV)	485.8±161.9 (219 - 663)*†‡	26.8±2.1*†‡Δ (24.3-29.5)	42.3±2.52 (39.5-45.3) *†‡Δ	99.8±1.37 (98.3-101.3) *†‡Δ
ANOVA (F test)	53.1	314.4	157.1	223.2
P	<0.001 (HS)	<0.001 (HS)	<0.001 (HS)	<0.001 (HS)

Table (2): ANOVA one way statistical analysis of studied groups regarding to oxidative stress parameters (MDA, Catalase and GSH) in the brain tissues.

Groups	Brain MDA Mean ± SD (range)	Brain catalase Mean ± SD (range)	Brain GSH Mean Mean ± SD (range)
–ve control group (group I)	3.83 ± 0.35(3.4-4.2)	13.4 ± 0.96 (12.3-14.6)	50.6 ± 3.11 (47.6-54.1)
+ve control group (group II)	3.83 ± 0.25 (3.5-4.2)	13.6 ± 0.68 (12.7-14.6)	50.4 ± 2.93 (47.4-54)
PM molasses treated group (group IIII)	3.86 ± 0.35 (3.4-4.3)	13.0 ± 1.13(12-14.5	47.3 ± 9.88 (27.9-54.1)
DLM treated group (group IV)	12.28 ± 0.76 (11.3-13.2) *†‡	3.68 ± 0.23 (3.4-4.0) *†‡	12.2 ± 0.96 (11-13.2) *†‡
DLM & PM molasses treated (groupV)	7.06 ± 0.39 (6.5-7.6) *†‡Δ	8.86 ± 0.30 (8.4-9.2) *†‡Δ	28.1 ± 1.59 (26.4-30.2) *†‡Δ
ANOVA (F test)	387.7	196.4	KWT=21.5
P	<0.001 (HS)	<0.001 (HS)	<0.001 (HS)

KWT→Kruskal Wallis test
***→ Significant in comparison with control group.**
†→ Significant in comparison with corn oil group.
‡→ Significant in comparison with PM group.
Δ→ Significant in comparison with DM group.

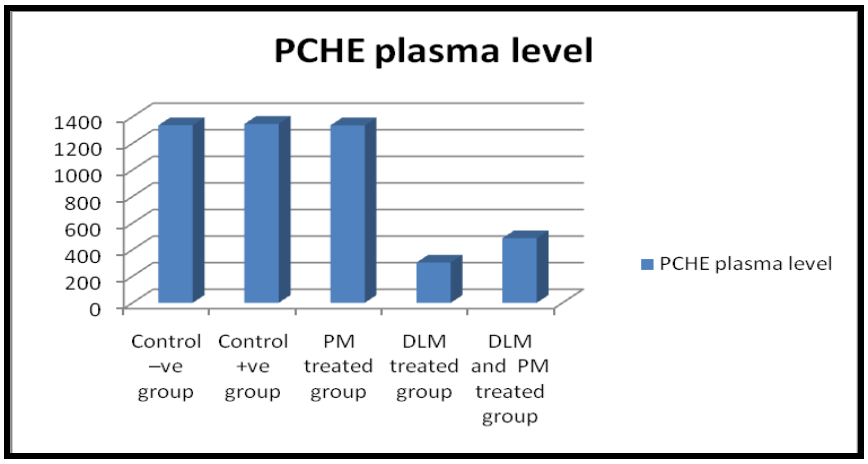

Figure (1): Distribution of the studied groups according to mean plasma cholinesterase enzyme (PCHE).

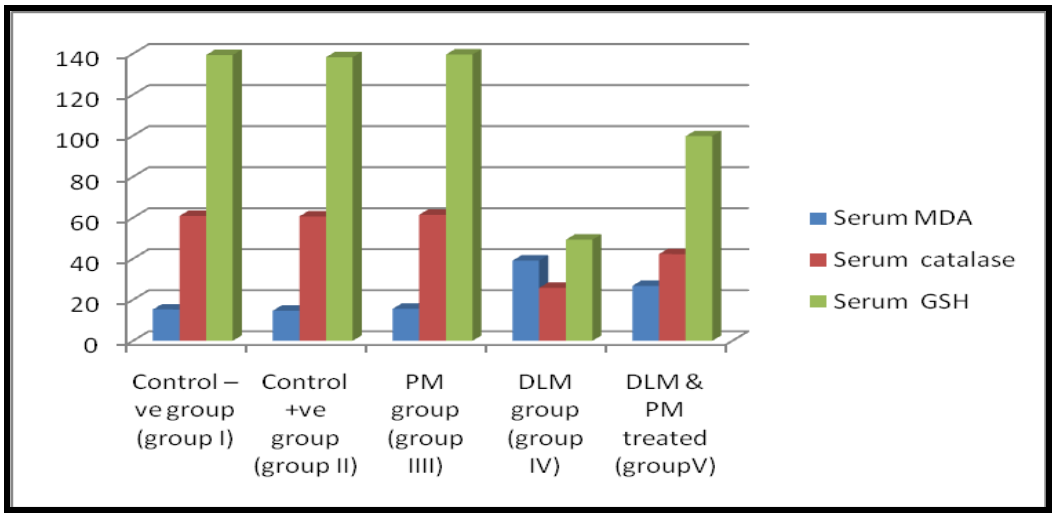

Figure (2): Distribution of the studied groups according to oxidative stress parameters (MDA, Catalase and GSH)] in serum.

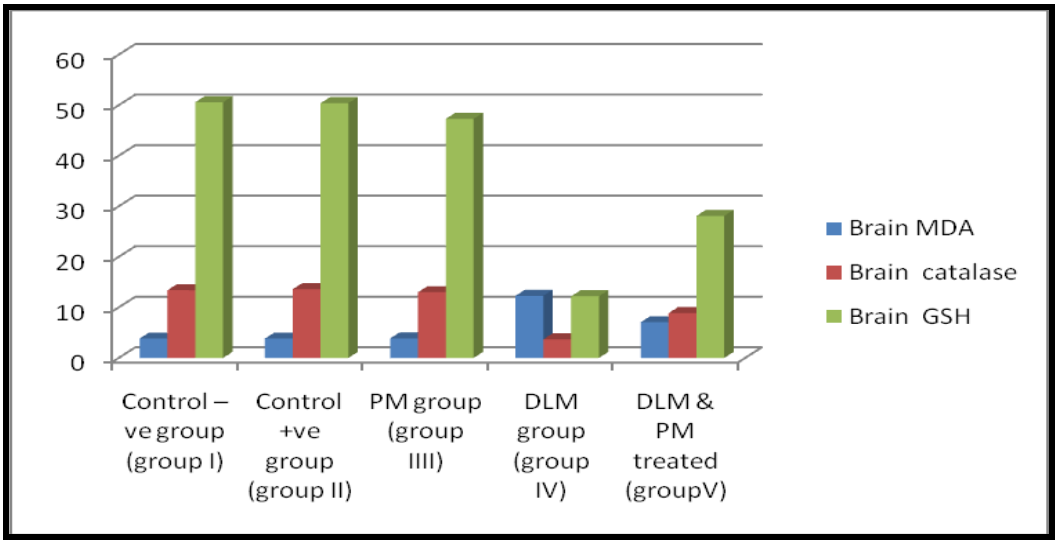

Figure (3): Distribution of the studied groups according to oxidative stress parameters (MDA, Catalase and GSH)] in the brain tissues.

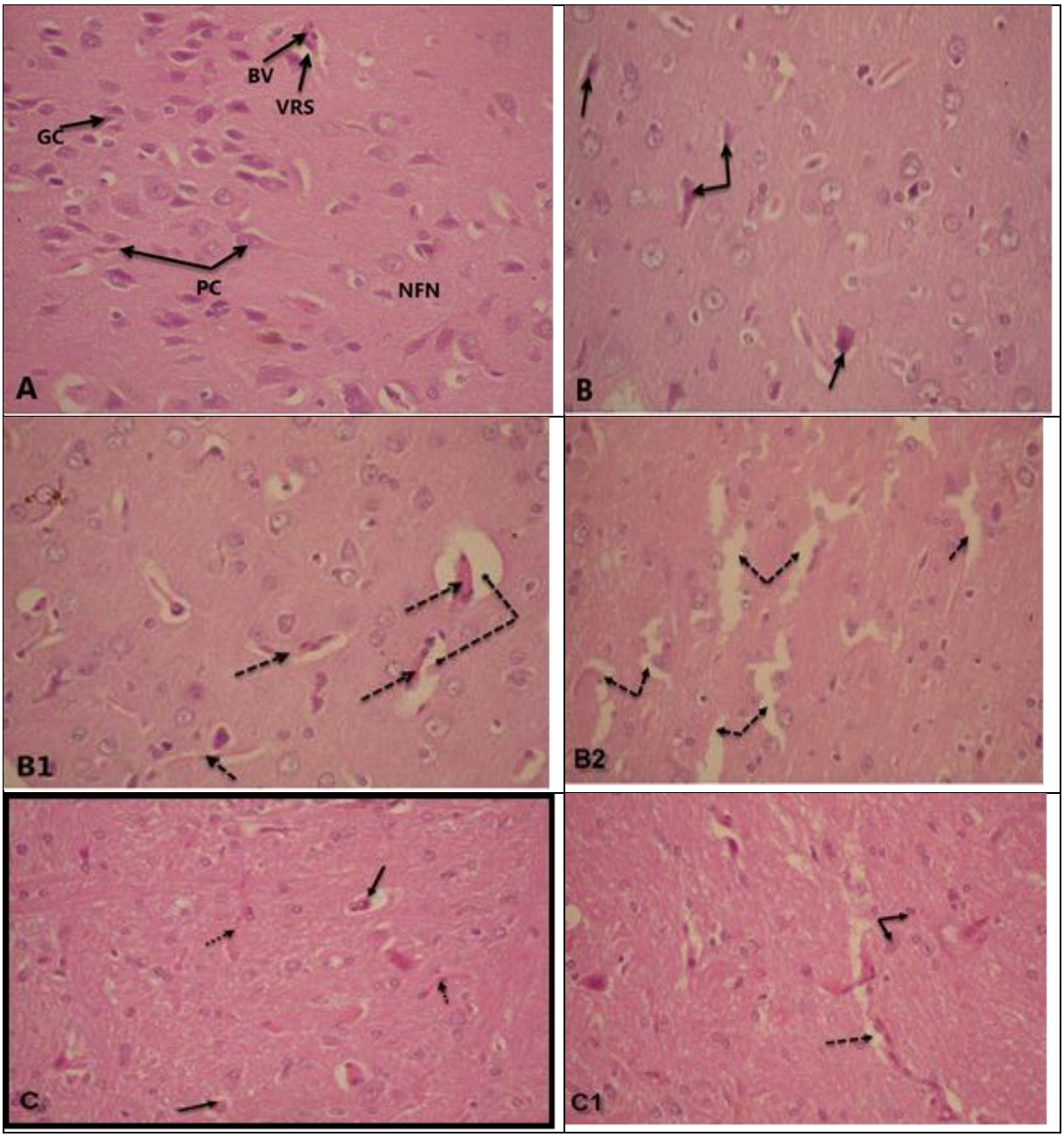

Image (I): A photomicrograph sections of the brain tissues of studied rats. All (H& E staining X 400) in original magnification), histopathologcal findings as follows:

- **Image (A);** a section from the brain of -ve Control group showing normal appearance of the cerebral cortex. It illustrates pyramidal cells (PC) with vesicular nuclei and darkly stained cytoplasm and processes, granular cells (GC) (astrocyte), neurofibrillar network |(NFN) and normal blood vesssels (BV) surrounded by normal perivascular [Virchow–Robin (VRS)] space.
- **Image (B–B2);** a section from the brain of deltamethrin (DLM) treated rats showing diffuse distorted cells with deeply stained shrunken nuclei and scanty dense esinophilic cytoplasm vacuolation (⟶), a highly proliferative and dilated blood vessels (⇢) and widening Virchow–Robin (⇢) space.
- **Image (C&C1);** a section from the brain of DLM &PM molases treated rats showing less diffusion of both apoptotic body with vaculization (⟶) and proliferative dilated blood vessels (⇢**).**

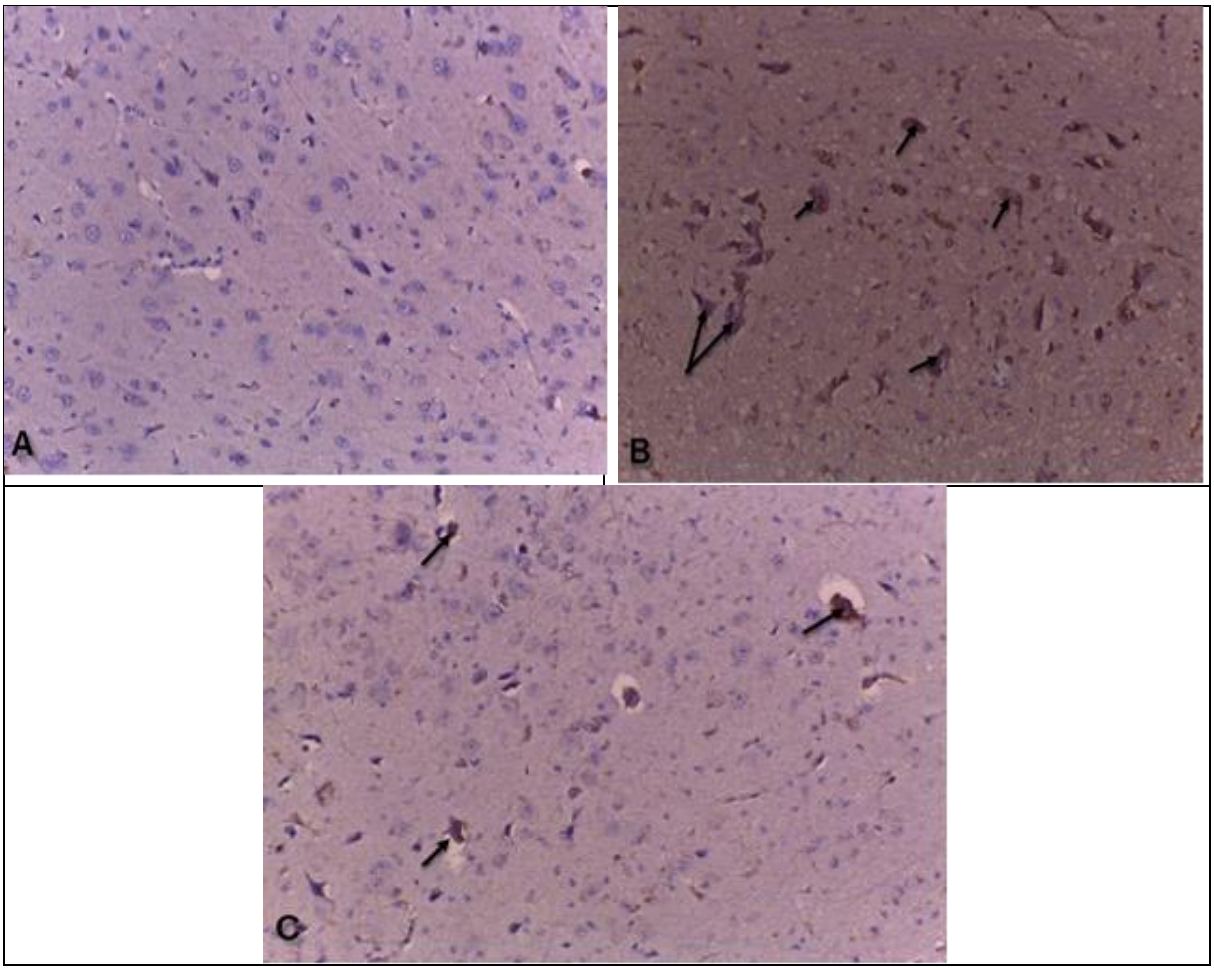

Image (II): A photomicrograph sections of the brain tissues of studied rats. Immunostain x 400, histopathologcal findings as follows:

- **Image (A);** a section from the brain of -ve Control group showing negative expression of immune reaction for Bax.
- **Image (B);** a section from the brain of deltamethrin (DLM) treated rats showing Astocytes with strong immunostaining cytoplasm (a highly diffuse brownish cyroplasmic expression) of Bax antibody.
- **Image (C);** a section from the brain of DLM &PM molases treated rats showing positive immune reaction with low expression of Bax antibody.

DISCUSSION

Organophosphphorous compounds and pyrethroids act mainly on the nervous system and used broadly in agricultural and veterinary applications **(Flaskos et al., 2007).**

Deltamethrin is an imperative pesticides that used in cultivation and indoor for control of houseflies **(Hassanin and El Asely, 2015).**

Apoptosis is a programmed cell death, in which has basic role in both physiological & pathological situations. Deltamethrin was found to produce neurodegeneration and apoptotic cell death in cerebral tissues of albino rats **(Aksalal et al., 2010).**

A numerous of protective antioxidant enzymes and molecules are continuously produced in vivo to compate toxic free radicals. The delicate balance between the production and catabolism of oxidants is critical for maintenance of the biological function **(Klaunig and Kamendulis, 2004)**.

Elevated reactive oxygen species (ROS) levels caused damage to cellular macromolecules like proteins, lipids and DNA with induction of oxidative stress state and redox imbalance **(Circu and Aw, 2010).**

1- Regarding the biochemical results:

a) As regard plasma choline esterase level:

Organophosphate and carbamate poisoning lead to reduction in plasma cholinestrase activity which considered as a marker of this toxicity, however, nowadays resereaches have emerged that reduction is not exclusive to them, as it is also occur with other environmental contaminants, such as pyrethroid insecticides.**(Ali et al., 2017).**

In the current study, the mean pseudocholinestrase plasma level was significantely decreased among DLM & DLM+PM molasses treated groups regarding to their comparison with both control and pomegranate (PM) molasses treated groups.

This finding agrees with **El-Demerdash (2007)** who demonstrated that pyrethroids cause a decrease of acetyl choline esterase (AChE) activity in the erythrocytes, plasma and brain of expiremental animal.

Also, in experimental study carried by **Gokcimen et al. (2007); KEREM et al. (2007); Ela et al. (2008); Lu etal (2010);** the results showed significant decrease in the activities of cholinesterase enzymes by the different types of OP compounds (e.g. methadithion, diazinon, methyl parathion, fenthion and omethoate) treated rats compared to control group.

The decrease in plasma AChE activity following DLM could be as a result of increasing of lipid per oxidase (LPO) which indirectly affect membrane bound enzymes such as AChE **(Lo´pez et al., 2007).**

b) As regard oxidative stress parameters:

The findings in present study revealed that, DLM produced neurotoxicty by oxidative stress mechanism as there was significant increase in serum & cerebral tissues Malondialdehyde of deltamethrin treated group as compared with rats in both control and pomegranate (PM) molasses treated group.

Manna et al. (2005), demonstrated that DLM administered to female rats provoked a significant increase of plasma MDA concentration. Also, **Varol et al. (2016),** reported that delatmetrin intoxication caused significance elevation in total oxidant state (TOS) & significance reduction in superoxide dismutase [SOD] & GSH reductase in rat brains. Furthermore, results of studies conducted by **Abdelkhalek et al. (2015) and Gündüz et al. (2015)** were in agreement with those findings.

The previous findings of oxidative effect produced by deltamethrin could be explained by its lipophilicity and hence ability to penetrate the cell membrane where it causes generation of numerous free radicals which lead to destructive effect matches with oxidative stress **(Celik and Suzek, 2009)**.

In comparison of deltamethrin treated animals with both control and pomegranate (PM) molasses treated groups as regard antioxidant activities, there were a significant reduction in serun and brain GSH & CAT in DLM treated rats.

Also, **Al-Afifi et al. (2017)** demostrated that GSH levels decreased in the testis of the DLM-treated mice, reflecting their consumption through

the oxidative stress. Similary decreases in glutathione (GSH) level were reported in broiler chicks treated with deltamethrin **(Jayasree et al., 2003).**

Additionally, **Wang et al. (2009)** found that B-Cypermethrin decreased the activity of both SOD and CAT & **Ben Slima et al. (2013)** documented that testicular SOD activity declined significantly in DLM treated mice.

In study carried by **El-Maghraby et al. (2010)** repeated dose of deltamethrin altered the biochemical parameters, decreased content of cytochrome P450 and antioxidant state (GSH, catalase, SOD) in many organs such as lungs, liver, kidneys, hippocampus and cerebellum which correlated with histological changes induced by deltamethrin in these organs and agree with the current work.

Also, **Ali et al. (2017),** revealed a significant rise in plasma MDA levels & reduction in biological activity of catalase [CAT] & glutathione S-transferase [GST] in dimethoate exposed group.

The reduction in these antioxidant activities might be due to utilization of antioxidant enzymes to challenge the prevailing oxidative stress under the influence of free radicals generated from DLM and/or inhibition of enzyme synthesis by DLM **(Slaninova et al., 2009; Zhang et al., 2013)**.

2) Regarding the histopathological results

As regard to histopathological analysis, of the brain tissues of DLM treated rats of the present study showed apoptotic bodies where cells were disturbed containing scanty eosinophilic cytoplasm with deeply stained shrunken or even absent nuclei, neuropil vacuolization and highly proliferated & dilated blood vessels as compared to to both control and pomegranate (PM) molasses treated groups.

These findings are in accordance with **Varol et al. (2016)** who found that, oral administration of single dose 35 mg/kg of DLM resulted in neuronal cell degeneration in the cerebral tissue & dilated congested blood vessels.

Moreover, **Wu and Liu (2000) and Ogaly et al. (2015)** revealed that repeated oral administration of different doses of deltamethrin showed neuronal cell degeneration with vacuolization, degenerated glial cells and necrosis which supported findings in current work .

These histopathological results may be due to the lipid nature of cerebral tissues which may allow to DLM accumulation causing increase in production of ROS and causing destruction of cells **(Oikawa et al., 2007; celik and suzak, 2009; Ogaly et al., 2015).**

3) Regarding the immune-histochemical results:

Bax is a proapoptotic Bcl-2 family protein that resides in the cytosol and translocats to mitochondria upon induction of apoptosis. It blocks the anti-apoptotic effect of Bcl-2 **(Cartron et al., 2003; Xu et al., 2012).**

Bax to Bcl-2 ratio determines the cell fate; where increased Bcl-2 responsible for survival of cells, while Bax produced programmed cell death **(Kroemer, 1999; Crompton, 2000)**.

Immunohistochemical staining of brain of deltamethrin treated rats showed many neurons with strong positive immune reaction to Bax antibody in their cytoplasm indicated by brownish cytoplasmic deposits comparing to control and pomegranate (PM) molasses treated groups.

Finding of current study are confirmed by those obtained by **Wu et**

al. (2000) who reported that immunohistochemical staining of rats brain treated by deltamethrin show exess of P53 and Bax with decrease of Bcl-2 expression in cortex and hippocampus comparing to control, leading to an elevation of Bax to Bcl-2 ratio, which may lead to apoptotic cell death of cerebral tissues of rats receiving deltamethrin.

As regard PM+DLM treated group, finding of current work illustrated a sigmificant decrease of PCHE in plasma, excess in MDA, & reduction of GSH & CAT in serum & brain tissue as compared with control & pomegranate (PM) molasses treated groups. Furthermore, there was insignificant increase in PCHE in plasma, sigmificant decrease in MDA, and significant increase in GSH & CAT in serum & cerebral tissues when compared with DLM treated animals.

These finding are agreed with (**Khan, 2006; Gawish and Elhalwagy, 2009)** who used phenolic compounds as antioxidant in OPC poisoning.

Kaur et al. (2006), demonstrate that pretreated rats by pomegranate for 7 days produced a protection against free radical damages in liver which initiated by Ferric nitrilotriaacetate through modulation of LPO levels & GSH as well as CAT & GST.

Mahmoud and Abdel Moneim (2013) reported that CCl4 enhanced MAD generation and decreased GSH content in brain tissues of rats was improved after administration of pomegranate juice alone. More over, the same results have been obtained by **Murthy et al. (2002)** who proved that PM peel extract lead to protection against lipid per oxidation damage against CCl4**.**

The finding of current work are in accordance with **Cekmen et al. (2013)**, who found that pomegranate extract has strong antioxidant properties against gentamicin induced nephrotoxicity, as it increased the level of GSH and decreased level of MAD in kidney cortex tissue.

The results of the present showed an improvement in histopathological & immunohistochemical studies in DLM+ PM treated group as compared with DLM treated group.

These results were in line with the study of **Abdel Moneim (2012),** who cocluded that PM peel methanolic extract could inhibit aluminum-induced oxidative stress and histopathological changes in brain of female rats & these may be due to antioxidant activity.

These results may be explained by antioxidant effect of PM due to its high contents of polyphenols which may suggest its role as an electron donor in scavenging free radicals **(Seeram et al., 2005**).

CONCLUSION

- Administration of (6 mg / kg) of deltamethrin orally produced neurotoxicity via affecting oxidant /antioxidant balance in cerebral tissues of albino rats that proved by biochemical, histopathological& immunohistochemical changes.
- Co-administration of PM molasses ameliorated this oxidative stress effects.

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التأثير الملطف لدبس الرمان على السمية العصبية الناجمة عن الدلتامثرين فى الجرذان البيضاء البالغة: دراسة بيوكيميائية , نسيجية و مناعية

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الملخص العربى

الدلتاميثرين هو بيرثرويد مصنع من الفئة الثانية يستخدم فى جميع أنحاء العالم كمبيد فى الزراعة، مكافحة الآفات المنزلية، حماية المواد الغذائية ، ومكافحة ناقلات الأمراض. ويحدث التعرض به بشكل رئيسى من الاستخدام المنزلى ، الأغذية أو المياه الملوثة. على الرغم من أن فى البداية أعتقد أنه الأقل سمية، فقد اظهرت عدد من الدراسات الحديثة آثاره السامة فى أنواع مختلفة من الحيوانات. هدفت الدراسة الحالية إلى تقييم تأثير الاكسدة الناتجة عن التعرض للدلتاميثرين على أنسجة مخ الجرذان البيضاء البالغه، وعما إذا كان إضافة دبس الرمان يمكن أن يلطف هذا الضرر التأكسدى. تم تقسيم ثلاثون من جرذان التجارب البيضاء إلى خمس مجموعات: المجموعة الضابطة السالبة (6 جرذ)، المجموعة الضابطة الموجبة (6 جرذ) تلقت 1مللى من زيت الذرة مرة واحدة يوميا ، بالفم، المجموعة التى عولجت بدبس الرمان المخف [(0.5 مللى) دبس الرمان + ماء مقطر(0.5 مللى)] (6 جرذ) ، المجموعة التى عولجت بالدلتاميثرين(6 ملليجم /كجم) (6 جرذ) والمجموعة التى عولجت بالدلتاميثرين (6 ملليجم /كجم) + دبس الرمان المخفف [(0.5 ملل) دبس الرمان + ماء مقطر(0.5 مللى)] (6 جرذ) . هذه الجرعات أعطيت مرة واحدة يوميا، بالفم لمدة سبعة أيام. بنهاية التجربة ، تم الحصول على عينة دم لتقييم مستوى الكولينستريز فى البلازما ومعاملات الاكسدة (المالونديالدهيد، الجلوتاثيون، الكاتاليز) ثم تم ذبح الجرذان واستئصال المخ وإعداده لتقييم معاملات الاكسدة فى أنسجته، فحص التغيرات النسيجية والمناعية. أوضحت النتائج أن الدلتاميثرين قد تسبب فى السمية العصبية فى الجرذان البيضاء حيث كان هناك زيادةً ذو دلالة احصائية فى المالونديالدهيد فى السيرم وانسجة المخ ، انخفاض فى كلا من الجلوتاثيون والكاتاليز ، انخفاض فى مستوى انزيم الكولينستريز فى البلازما وقد شملت التغيرات فى مخ الجرذان: التنكس العصبى، الأجسام الإستماتية، فجوات عصبيية، الأوعية الدموية المتكاثرة والمتوسعة إلى جانب تفاعل مناعى ايجابى قوى للباكس فى المجموعة التى عولجت بالدلتاميثرين عند مقارنتها بالمجموعتين الضابطتين والمجموعة التى عولجت بدبس الرمان. فى حين كان هناك انخفاض ذو دلالة احصائية فى المالونديالدهيد فى السيرم وانسجة المخ، زيادة ذو دلالة احصائية فى فى كلا من الجلوتاثيون والكاتاليز وأيضا انخفاض فى مستوى الكولينستريز فى البلازما. تغيرات مرضية معتدلة فى أنسجة مخ الجرذان البيضاء بجانب تفاعل مناعى ايجابى معتدل للباكس فى المجموعة التى عولجت باالدلتاميثرين مع دبس الرمان مقارنة بالمجموعة التى عولجت بالدلتاميثرين. وهكذا، يمكن للدلتاميثرين أن يحدث ضرر تأكسدى فى أنسجة مخ فئران التجارب البيضاء ودبس الرمان كمضاد للاكسدة له تأثير ملطف ضد هذا الضرر.