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IMMUNOTOXIC EFFECT OF DELTAMETHRIN IN IMMUNIZED MICE WITH CLOSTERDIUM

Taghred Jabbar Humadai[1], Sabrin Ibraheem Mohsin[2] and Salema Lafta Hassan[3]

[1, 3]Department of Pathology and Poultry Diseases, Collage of Veterinary Medicine, University of Baghdad, Iraq.
[2]Department of Microbiology Collage of Veterinary Medicine, University of Baghdad, Iraq.

Abstract

This object aimed to investigation of the immunotoxic effects of deltamethrin and showed relationship between immunization by closterdium vaccine and administration Vitamin-E.

To achieve this goals, used a total one hundred mice of both sexes, aged 8 weeks, which divided equally into five groups and treated as follows: 1st group (20) mice were administrated orally with drinking water daily 1/10 LD50 (LD50 140 mg kg of deltamethrin for 4 weeks. Oral administrated of Deltamethrin to 2nd group (20) mice 1/10 LD50 with drinking water daily, for four weeks, then immunized by closterdium vaccine (0.1 ml) I/P two doses for two weeks interval.

The 2nd group (20) mice were administrated orally 1/10 LD50 of Deltamethrin with drinking water daily for four weeks and immunized by closterdium vaccine (0.1 ml) I/P two doses for two weeks interval. The 3rd group (20) mice have administrated both Deltamethrin and immunized with closterdium vaccine as 2nd group, at same time administrated (0.15 I.U./kg) of vitamin E. The 4th group (20) mice have immunized by closterdium vaccine. While the 5th group (20) mice were as control negative group. Collected blood samples from all groups for measuring IFN-γ. The result showed the effect of Deltamethrin to inhibition of Cell-mediated immunity. Therefore the mean value of skin thickness it is significantly ($P<0.05$) in group 3 at 24 hr. and 48 hr while lower significantly ($P<0.05$) in group 1.2. at 24hr. and 48 hr. The results showed a significant decreasing in the level of IFN-γ titer in serum by ELISA tests in the G3 than G1 and G2 compared to G4. The pathological lesions showed that the animals exposed to a toxic dose of deltamethrin characterized by an inflammatory reaction, hemorrhage, congested blood vessels, necrosis, fibrosis and multiple granuloma lesions in internal organs, while fewer lesions were recorded in the groups treated with deltamethrin and administration of vitamin E showed improvement against the toxic effect of deltamethrin.

***Key words*:** Deltamethrin, Vitamin E, IFN-γ, Histopathological changes, Internal organs.

Introduction

The use of pesticides by indiscriminate and injudicious lead to threat for community health due to exceeds the concentration of pesticide residue the maximum limit in the food chain, therefore, it is product effect to human health (McLachlan, 2001). For increase production and pest control now, being substituted Synthetic pyrethyroid that have harmful effect (Muthviveganandavel *et al.,* 2008). The extensively used for Deltamethrin (a synthetic pyrethroid) that have a potential insecticidal property in public health programmed and crop protection as an ectoparasiticide (McGregor, 2000). The major mechanism of Organophosphate pesticides it is inhibition of the acetylcholinesterase (ache), (Hzarika *et al.,* 2003) this lead to accumulates of acetylcholine (ach) in the nervous system, that resulting overstimulation receptors for nicotinic and muscarinic (Eddleston *et al.,* 2005). Toxicity of OP pesticides have negative effect on the body organs such as nervous system, kidney, liver, reproductive system and immune system (Aly and E l-gendy, 2000, Mansour and Mossa, 2011). This study aimed to determine the effect of deltamethrin on internal organs and immunotoxic effect on mice. IFN-γ is a type II class of interferon-a pleiotropic cytokine. (Gray and Goeddel, 1982). This cytokine (IFN-γ) is critical for adaptive and innate immunity against some protozoal, bacterial and viral infection. Chief functional of IFN-γ is the activator of macrophages and molecule expression of Class II major histocompatibility complex (MHC). This cytokine produced predominantly by natural killer (NK) and natural

killer T (NKT) cells that consider as part of the innate immune response and also produced by cells of response on adaptive immunity such as CD4 Th1 cells and CD8-cytotoxic T-lymphocyte (CTL) effector T cells (Schoenborn and Wilson, 2007). In addition, the IFN-γ is release from non-cytotoxic innate lymphoid cells (ILC), a family of immune cells first discovered in the early 2010s. Ustyugova, (2002) reported the effect of nitrate/ nitrite ingestion on the immune system. The present study was designed to investigate the effects of deltamethrin on the imunity and internal organs of mice.

Material and Methods

Experimental Design

To achieve these goals, used a total one hundred mice of both sexes, aged eight weeks, which divided equally into five groups and treated as follows: 1st group (20) mice were administrated orally with drinking water daily 1/10 LD50 (LD50 140 mg kg of deltamethrin for four weeks. The 2nd group (20) mice were administrated orally 1/10 LD50 of deltamethrin with drinking water daily for four weeks and immunized by closterdium vaccine (0.1 ml) I/P two doses for two weeks interval. The 3rd group (20) mice were administrated with deltamethrin and immunized with closterdium vaccine as 2nd group, at same time administrated (0.15 I.U./kg) of vitamin E. The 4th group (20) mice were immunized by closterdium vaccine. While the 5th group (20) mice were as control negative group.

Treatment

- **Chemicals:** Dimethoate:O,O-dimethyl s-(nmethyl carbamoylmethyl) (40% EC)

Phosphorodithioate (IUPAC). is an OP pesticide that has a chemical formula: SCH3NHCOCH2SP(OCH3)2

- **Vitamin E preparation:** The optimal dose of Vitamin E (α-tocopherol) in mice equal to 15 I.U./kg B.W. (The Journal of Nutrition, 1982). 400 I.U. Vitamin E (Capsule form) completed to 40 ml with Olive oil (stock solution 1) each 1ml of stock solution contain 10 I.U. of Vitamin E, so 1.5 ml of stock solution contain 15 I.U. Vitamin E. This 1.5 ml completed to 10 ml by Olive oil (stock solution 2) each 1ml of stock solution contain 1.5 I.U. of Vitamin E. The final dose given to the mice 0.1 ml /10 gm B.W. of mice.

Clostrdia vaccine preparation

We prepared of Ag of Clostridia that used for immunizing animals according to (Saleh, 1999).

Immunological tests

- **Skin test-Delayed type hypersensitivity:** This test was carried out at the 28 days of immunization animals groups according to the procedure of authors Hudson and Hay (Hudson and Hay, 1980).

Table 1: Difference Skin thickness (mm) of different immunized mice groups at 24 and 48 hours post examination.

Groups	24 hmean± SE	48 hmean± SE
G1 deltamethrin	C 0.19.22±0.11	C 0.21±0.17
G2 deltamethrin+ vaccine	A 0.31±01.16	B 0.33±0.04
G3 deltamethrin+ vaccine+vit E	B 0.40±0.06	A 0.71±0.15
G4 vaccine	B 0.64±0.07	A 0.87±0.07
G5 control	0	0

Different capital letter in the same row refers to the present a significantly different (P<0.05).

IFN-γ concentration (ELISA) Kit

ELISA Kit obtained from Elabscience. (U.S.A.) Used for detected concentration serum IFN-γ in mice as pictogram/millilitre (Pg/mL) and this test carried out according to the protocol of the company.

Statistical analysis

Statistical analysis has applied by two ways ANOVA and the mean difference was significant at the ($P \leq 0.05$) level by SPSS.

Results and Discussion

Skin test-Delayed type hypersensitivity

The results of skin test at 24 hr post-test, showed the mean values of skin thickness was high significantly ($p \leq 0.05$) in the group 4 (0.64 ± 0.07) mm, group 3 and group 2 against *closterdium* compared with the group 1 (0.19.22 ± 0.11) and negative control group G5 (0) mm. while the result of skin thickness at 48 hr. post-immunization showed the mean values were increased in the G4, G3, G2 as revealed in table 1.

IFN-γ concentration

The result of concentration IFN-γ (pg./ml), showed higher significantly of group 4 (570.76±32.40) at 30-day

Table 2: Means & a stander error of serum INF-γ concentration at 30-day post-immunization mice for different groups.

Groups	Means & a stander error of INF-γ (pg./ml)
G1 deltamethrin	450.23±11.70 D
G2 deltamethrin+ vaccine	517.38±14.970 C
G3 deltamethrin+vaccine+vit E	534.88±55.16 B
G4 vaccine	570.76±32.40 A
G5 control	0

Different capital letter in the same row refers to the present a significantly different (P<0.05).

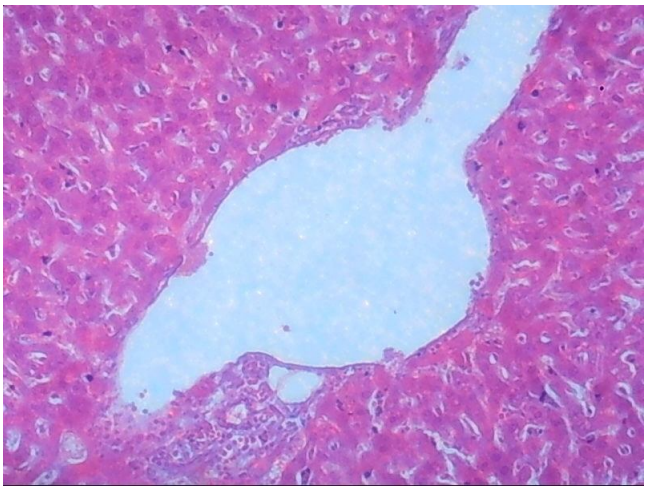

Fig. 1: Histopathological section of liver at 4 weeks in 1st group shows sever areas of vacuolar degenerative changes of hepatocytes (H and E stain 100X)

post-immunization than those values in the G3, G2, G1 (534.88±55.16), (517.38±14.970), (450.23±11.70) and negative control groups G5 (0) respectively, as shown in table 2.

The histopathological changes

1. The histopathological changes of Mice in 1st group

- **Liver:** Vacuolar degenerative changes of hepatocytes (Fig. 1), congestion of blood vessels with infiltration of mononuclear inflammatory cells. In addition for newly formed bile ductules, infiltration of mononuclear inflammatory cells as well as degenerative vacuolar changes of hepatocytes (Fig. 2), in other sections the changes showed a widespread hemorrhage, cloudy swelling of hepatocyte with a severe thick fibrous connective tissue observed in the liver.

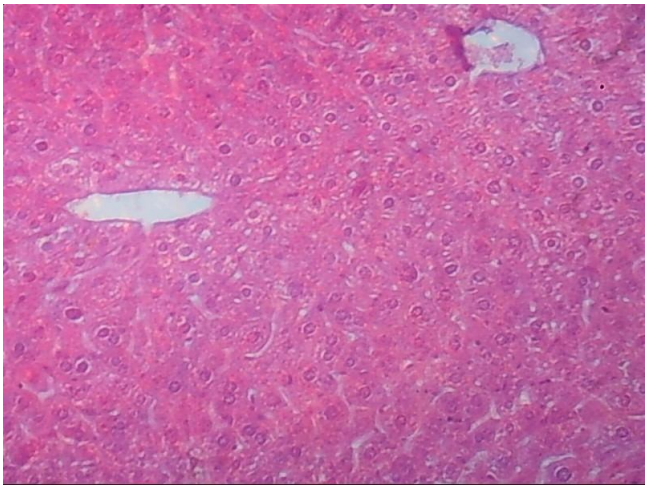

Fig. 2: The histopathological lesions in the liver at 4 weeks in 1st group shows newly formed bile ductules, infiltration of mononuclear inflammatory cell black arrow sever areas of vacuolar degenerative changes of hepatocytes (H and E stain 100X)

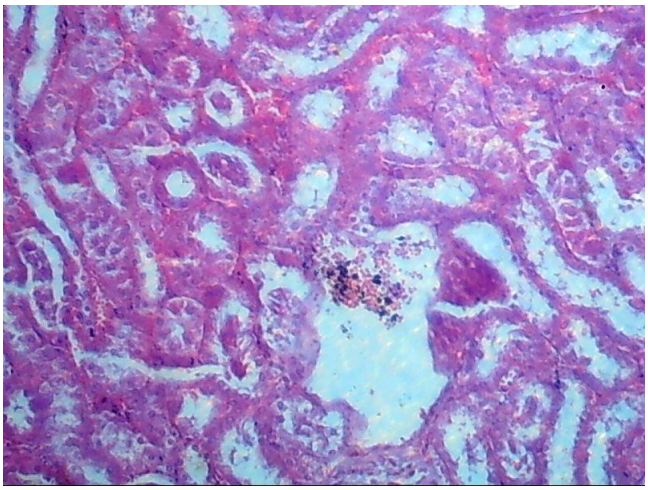

Fig. 3: The histopathological changes of the kidney at 4weeks in 1st group shows: hyaline casts with cellular debris in the lumen of renal tubules in addition to acute cellular degeneration. (H and E stain 100X)

- **Kidney:** Histopathological changes of kidney showed hyaline casts with cellular debris in the lumen of renal tubule in addition to acute cellular degeneration (Fig. 3), in addition, hemorrhage appeared in the intertubular spaces and severed areas of degenerative changes of renal tubules (Fig. 4), also singes of periglomerular edema and necrosis of some renal tubules lining cells in addition to congested blood vessels. The intertubular spaces were infiltrated by inflammatory cells. The walls of Bowman's capsule was eroded and the glomeruli were fragmented and atrophied.
- **Spleen:** The spleen showed inflammatory cells infiltration in the red pulp with depletion of the white pulp as well as an increase in the thickness of the

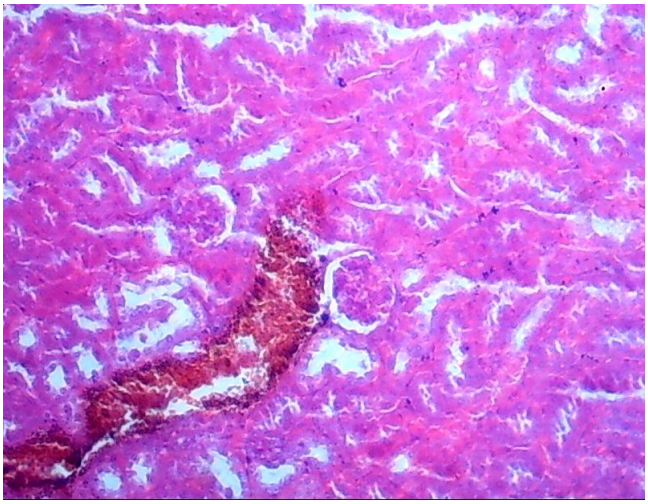

Fig. 4: Histopathological section of kidney at 4weeks in 1st group shows: hemorrhages and sever areas of degenerative Changes of renal tubules (H and E stain 100X)

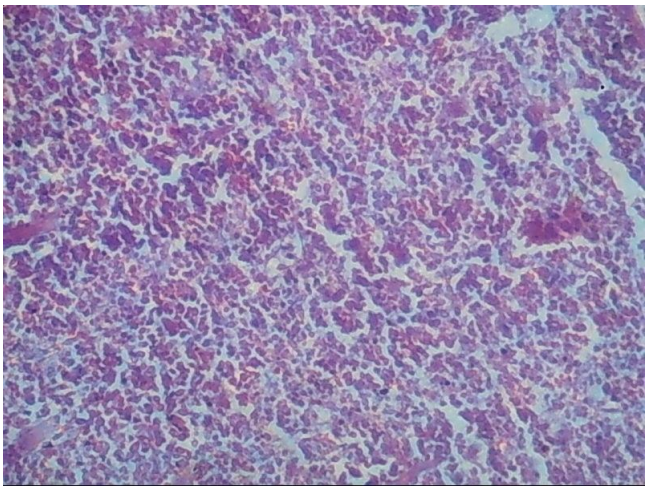

Fig. 5: Histopathological section of spleen at 4 weeks in 1st group shows: inflammatory cells particularly neutrophils infiltration in the congested red pulp with depletion of white pulp (H and E stain 100X).

capsular region (Fig. 5).

- **Lung:** The microscopic section revealed RBCs and neutrophils in the alveolar space, in addition to granulomatous lesion consisting of an aggregation of macrophages and lymphocytes in the interstitial tissue (Fig. 6). In other animals, the lung showed severe suppurative inflammation characterized by neutrophils filled the lumen of bronchioles and alveolar spaces in addition to multiple abscesses in the lung parenchyma and alveolar emphysema.

2. The histopathological changes of Mice of 2nd group

- **Liver:** Histopathological examination showed a granulomatous lesion in the liver parenchyma with congested sinusoids and vacuolar degeneration of hepatocytes, in addition to neutrophils and mononuclear cells aggregation in one side of the central vein. In

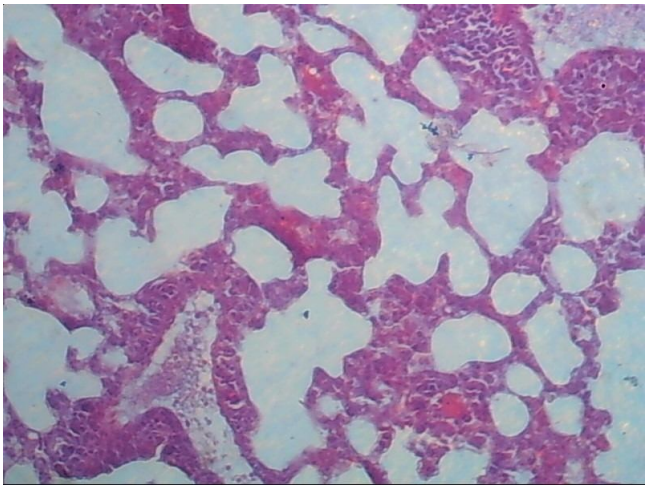

Fig. 6: Histopathological section of lung at 4 weeks in 1st group shows: multiple abscess in the lung parenchyma with emphysema and neutrophil (H&E stain 100X).

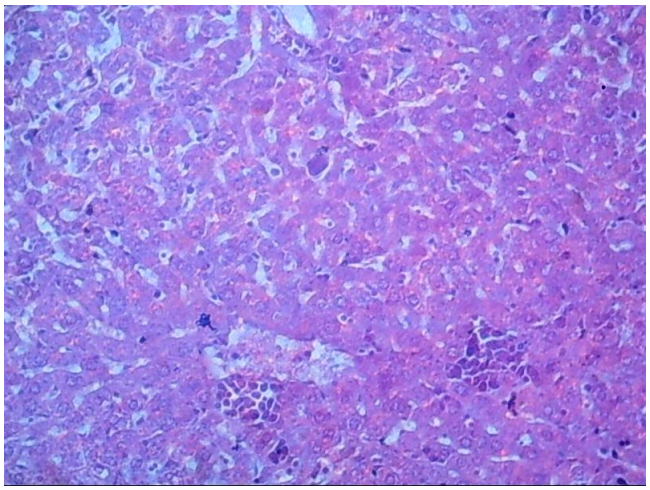

Fig. 7: The histopathological changes of the liver at 4 weeks 2nd group shows proliferation of kupffer cells with aggregation of mononuclear cells in liver paranchyma (H & E stain 100x)

other animals. It was reported mononuclear cells aggregation around blood vessels. (Fig. 7) and coagulative necrosis of hepatocytes characterized by pyknotic and disappearance of nuclei in addition to marked vacuolar degeneration of hepatocytes.

- **Kidney:** The lesions in the kidney showed shrinkage of glomerular tuft with a widening of bowman space in epithelial lining urinary tubules (Fig. 8).
- **Spleen:** It was noticed inflammatory cells particularly neutrophils infiltration in the congested red pulp with depletion of white pulp (Fig. 9).
- **Lung:** Neutrophils infiltration and RBCs in the alveolar spaces were the main lesions in the lung (Fig. 10)

3. The histopathological changes of Mice in 3rd group

- **Liver:** Histopathological changes showed

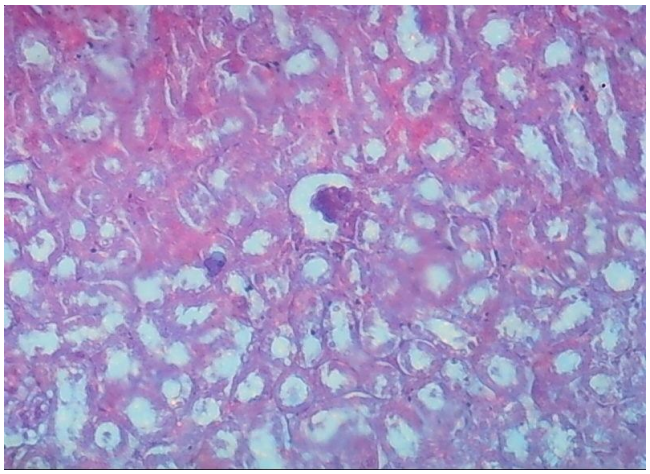

Fig. 8: Histopathological section of kidney at 4 weeks in 2nd group shows shrinkage of glumarular tuft with widening of bowman space in epithelial lining urinary tubules (H and E stain 100X).

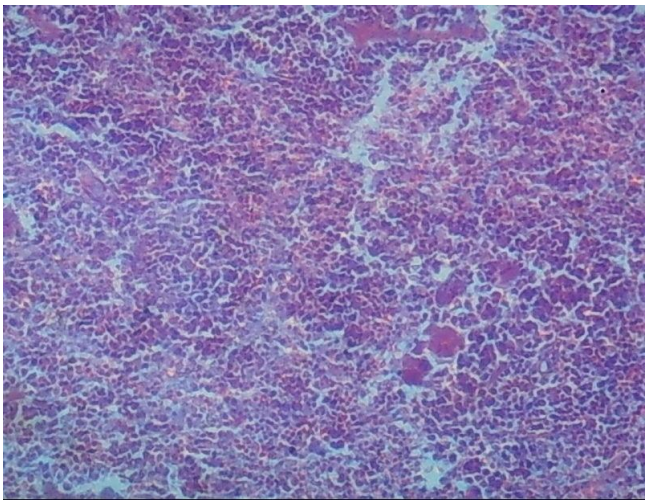

Fig. 9: Histopathological section of spleen at 4 weeks in 2nd group shows inflammatory cells particularly neutrophils infiltration in the congested red pulp with depletion of white pulp and proliferation of megakarocyte (H & E stain 100X).

microabscess lesion consisting from activated macrophage in the liver parenchyma, lymphocytes and hypercellularity of kupffer cells (Fig. 11), in addition to marked perivascular mononuclear cells aggregation at the portal area and central vein with necrosis of hepatocytes.

- **Kidney:** Histopathological section of the kidney explained congested blood vessels with neutrophils and mononuclear cells in their lumens (Fig. 12).
- **Spleen:** Moderate hyperplasia of white pulp was the main lesion in the spleen (Fig. 13).
- **Lung:** Neutrophils infiltration and RBCs in the alveolar spaces were the main lesions in the lung (Fig. 14).

4. The histopathological changes of Mice in 4th group

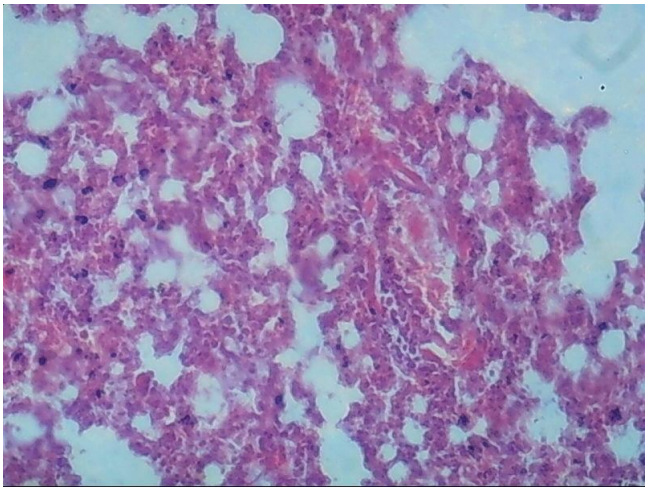

Fig. 10: Histopathological section of lung at 4 weeks in 2nd group shows Neutrophils infiltration and RBCs in the alveolar spaces (H & E-stain 100X).

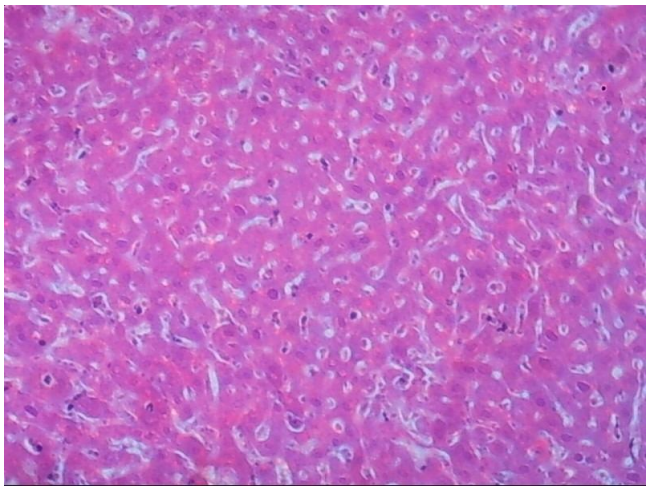

Fig. 11: The histopathological section of the liver at 4 weeks of 3rd groups shows microabscess lesion consisting from activated macrophage in liver parenchyma, lymphocytes and hyper cellularity of kupffer cells (H & E stain 100X).

Histopathological change of immunized animals for internal organs showed as following Infiltration of mononuclear cells and proliferation of megakaryocyte in the spleen (Fig. 15), also mononuclear cells infiltration between renal tubules (Fig. 16), in addition to hyperplasia of lymphoid tissue (Fig. 17).

5. The histopathological changes of Mice in 5th group

There were no significant macroscopic findings.

Discussion

The present research showed higher of skin thickness in immunized animals and this result may indicate that *clostridia vaccine* Ags stimulated cell-mediated immunity and this result is agreed with Nonnecke *et al.,* (2012) who suggesting stimulate and maturation of

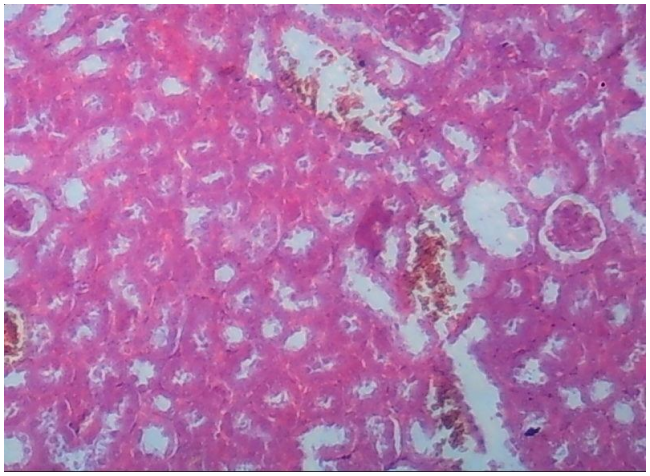

Fig. 12: Histopathological section of kidney at 4 weeks in 3rd group shows congested blood vessels with neutrophils and mononuclear cells in their lumens (H and E stain 100X).

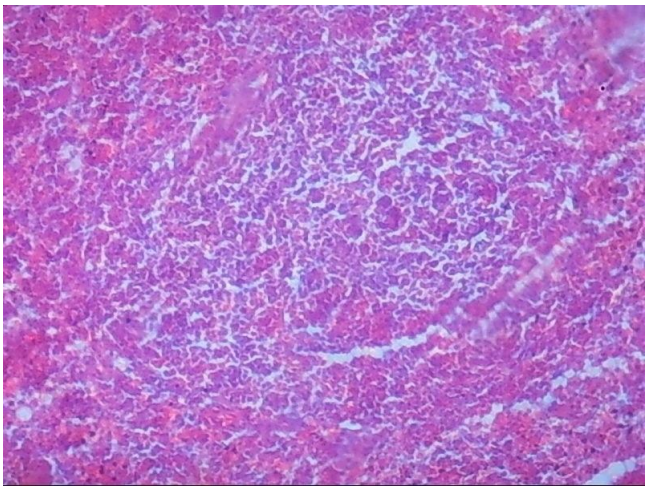

Fig. 13: Histopathological section of spleen at 4 weeks 3rd shows Moderate hyperplasia of white pulp (H and E stain 100X).

cell-mediated immune a colostrum-independent and this response to a predominant new calf. Higher proliferative of T-cell subsets that responses to antigen-stimulated at week seven versus week 0 this relived to development and maturation of responses of lymphocyte for specific antigen in early vaccination. The current research revealed that the mean values of skin thickness in immunized animals treated with Deltamethrin were lower than those value in immunized animals only, this result may show that *clostridia vaccine* Ags stimulated cell-mediated immunity and Deltamethrin diminished the immune response elicited by this Ags, this observation also may give indication that treatment with Deltamethrin associated with decreased activity of vaccine program against brucellosis in animals. The end result of skin test is contracted with that of serum levels of INF-γ supported the idea that Deltamethrin can cause immunotoxic and genotoxic effects of Deltamethrin in immunity cells, that

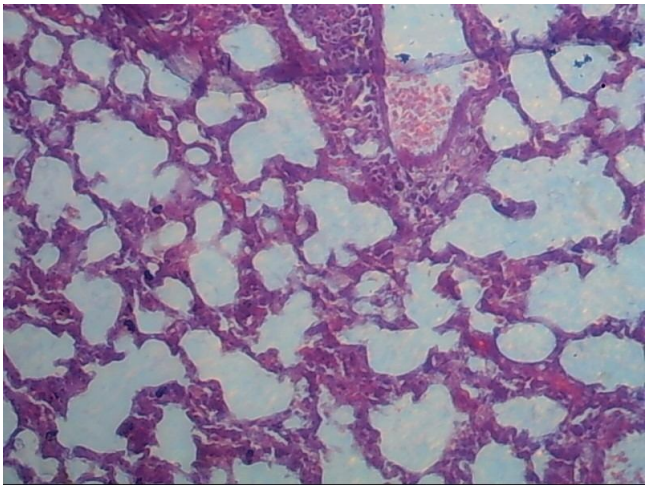

Fig. 14: Histopathological section of lung at 4 weeks in 3rd grop shows Neutrophils infiltration and RBCs in the alveolar spaces (H and E stain 100X).

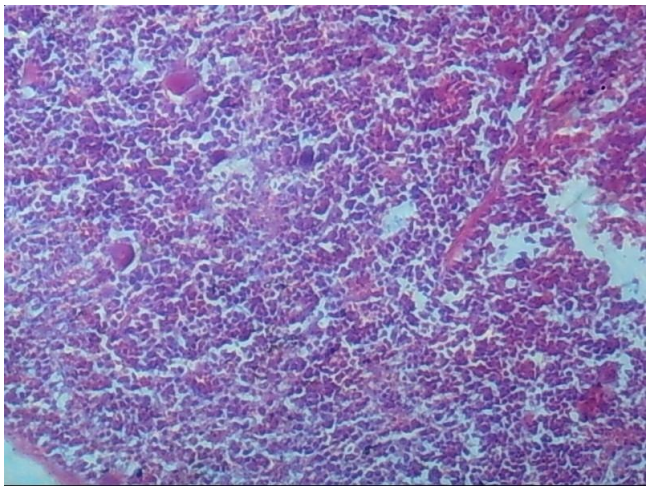

Fig. 15: Histopathological section of spleen at 4 weeks in 4th group shows mononuclear cells infiltration and proliferation of megakarocyte (H and E stain 100X).

led to decreased of defence mechanism and increase bacterial invasion of host, which occurred to release many endogenous antioxidant enzymes, this indicated that Deltamethrin maybe release ROS and endogenously that react with amides and amines to produce free radicals and nitrosamines (Raina *et al.,* 2010), ROS have been recognized as contributing in dysfunction of blood vascular due to endothelial dysfunction, inflammation, lipid and growth cell of muscle of vascular smooth (Touyz *et al.*, 2004), these result of our study agreement with (Yousef *et al.,* 2006) who reported that oral exposure of Deltamethrin for 30 days in male rate induce change in enzyme activities, changes levels in biochemical parameters and oxidative stress. The present study showed that immunized animal treated with Deltamethrin expressed significantly low levels of INF-γ as compared with immunized animals only, this result may indicate that Deltamethrin also induced suppression of cellular immune

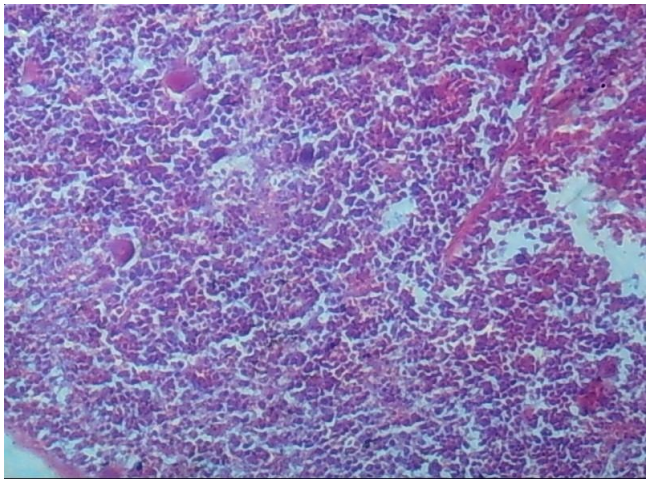

Fig. 16: Histopathological section of kidney at 4 weeks in 4th group shows hyperplasia of lymphoid tissue (H and E stain 100X).

response, according to result of DTH reaction and serum levels of INF-γ in this group, these result in agreement with Jolanta and Jerzy, (1992), who reported Deltamethrin exhibits an immunosuppressive on the female BALB/c mice in oral administration two doses daily (15 mg/kg for 14 day and 6mg/kg 84 days) However, immunized animals administration orally with Vitamin E expressed high value of thickness of skin and INF-γ as comparing with those values in immunized animals only, this result supported the idea that Vitamin E plays a role in the stimulation immune response, this result supported the idea mentioned by (McDowell, 2000). Who reported a chief functional of Vit-E is neutralizing free radicals, a chain-breaking antioxidant and Considered first line of defense to preventing peroxidation of phospholipids and lipid within membranes. However, the α-tocopherol is principal form of Vit-E for immune functions and antioxidant, tocotrienols and non α-tocopherol have important functions But there are few studies on these forms. While the α-tocopherol is Superior effective of inhibitor mechanisms of peroxy nitrite-induced lipid peroxidation (McCormick and Parker, 2004). Also it is inhibiting to inflammatory reactions. Schaffer *et al.,* (2005) who suggested the Tocotrienols more suppress to ROS because more than efficiently from tocopherols as antioxidant activity *in vitro*. As well as Vit-E is alleviated effects of Deltamethrin (Raina *et al.,* 2010). Vit-E considers as an antioxidant and have an important role in immunity by increasing of cell-mediated immunity, TNF production by T-lymphocytes, humoral antibody protection, inhibition of mutagen formation, resistance to bacterial infections, blocking micro cell line formation and repair of membranes in DNA (Sokol, 1988). Hence Vit-E may be stimulation of immune mechanism to inhibition carcinogenesis and cancer prevention. The production of ROS is associated with toxic by pesticides response to chronic, permanent damage and oxidative stress in the body tissues (Abdollahi *et al.,* 2004). Such damage occurs in cases of excessive formation of ROS or insufficient of protective antioxidants. Therefore, the harmful effects of ROS are balanced by the antioxidant action of nonenzymatic and enzymatic antioxidants. Antioxidants are molecules that contain an unshared electron (Verhagen *et al*., 2006), confirm documented induce oxidative stress when acute exposure to pesticides in humans (Verhagen, 2006) and animals (Mansour and Gamet-Payrastre, 2006, Mansour and Mossa, 2010). Increased lipid peroxidation (LPO) may be one of the Adverse effects involved in the toxicity of body tissues (Sayeed, 2003). The pesticides and many substances lead to oxidative damage (*e.g*. lipid peroxidation), can be determined indirectly for LPO by the measure of Malondialdehyde (MDA) that end product of LPO. Decrease oxidative stress and free radicals that product from oxygen-derived by SOD that considers the first line against the effect of dismutation O2-. The decline of antioxidant enzyme activity by DEL could be attributed to the direct effect on SOD either by reduction of the enzyme substrates and/or by downregulation of transcription and translation processes (McCord and Fridovich, 1960). The histopathological changes induce internal tissue organs due to OP insecticides exposure (Gokcimen *et al.,* 2007). Earlier studies on the rate that exposure to dimethoate shown in acute and chronic period for exposures alter in brain and liver tissue and antioxidant status (Sayim, 2007b). The target organ to toxic impact it is life as regards in the function of excretion of xenobiotics and biotransformation (Roganovic and Jordanova, 1998). Therefore present study agreement with Selmanoglu and Akay, (2000), who recorded similar lesions in the liver that including congestion, hepatocellular damage, mononuclear cell infiltration in tissue and hydropic cellular degeneration due to the toxic effect of dimethoate in male rats. In addition to Sharma *et al*., (2005), who reported the effects of exposure to dimethoate in liver of rate at doses 6 and 30 mg/kg included hepatocyte necrosis, inflammation in portal regions and congestion in centrical (Muthuviveganandave *et al.,* 201). Also may occur in the liver the following lesion inflammatory cell infiltration and hemorrhage. Histopathological examination of kidney tissue vacuolar degenerative changes in the epithelial cells lining renal tubules and scattered glomerular tufts with hypercellularity together with mesangial cell proliferation. Hettwer's, (1975) in similar experiments reported fatty degeneration. Also, Zaleska-Freljam *et al.,* (1983), showed that organophosphate induced stellate shape lumen of the proximal convoluted tubules and vacuolation degenerative changes in the wall of these tubules. The obtained histopathological changes due to intercellular hypoxia (Hettwer, 1975), inhibition of kidney esterase (Rajini *et al*., 1989) and/or to decrease of mucoid kidney content (Awasthi *et al.,* 1984). On the other hand, these changes may occur as an outcome of direct tubular cytotoxicity and/or oxidative stress at the tubular level (Poovala *et al*., 1999). Histopathological changes in kidney tissue. These changes were vacuolation of epithelial lining renal tubules and glomerular tufts. Such could be due to interference with metabolic activities (Kackar, 1997).

The pathological change of internal organs of immunized animal including lymphoid tissue hyperplasia, aggregation of mononuclear cells around blood vessels and this may due to good immune stimulation and proliferation of Ags to lymphocyte This was compatible with the authoress (Kathaperumal *et al*., 2008). Who

study vaccination with identified protective protein antigens inducing strong Th1-type immune responses could be an ideal strategy to surmount the limitations associated with whole-cell-based vaccines. In addition to Singh *et al*., (2012). Who mention the vaccinated animals by S19 vaccine showed higher continuity of immune response and indicated for that extended CD4+ memory cells MHC Class II + CD4(+) cells and higher a significant response of IFN-γ later than vaccination and revaccination. We recorded in the present study when examined of internal organs of animals treated with Vit-E moderate Histopathological changes may be the Vit-E protect tissue as Antioxidant from damaging by free radicals that formed by exposure to heavy metals that lead to toxicity (Hamadoche *et al.,* 2012). Furthermore, Flora *et al.,* (2012), recorded the clear role of Vitamins as co-administration with chelating agents against effects of lead intoxication. In other hande Vit-E delivering an H atom to free radicals and a radical scavenger (Lide, 2006).

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