Evaluation of the Effects of Lambda Cyhalothrin Insecticide Formulation "Ampligo 150 ZC" and Vitamins C and E on Rabbit Liver: Biochemical, Histological and Morphometrical Study

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Original Article

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ABSTRACT

Introduction: Chemical industry is currently developing new pesticides whose main objective is to overcome the reduction in yields of existing pesticides to which insects are becoming resistant gradually. At the same time, this permanent requirement must consider environmental issues, especially the potential risks for humans and animals. To this end, studies have shown that vitamins due to their antioxidant capacity can reduce the toxic risks of pesticides in *vivo*.

Aim of the Work: To investigate the possible ameliorative effect of vitamin C and E against hepatotoxicity of lambda cyhalothrin insecticide formulation Ampligo® 150 ZC (Chlorantraniliprole 9,3% and Lambda cyhalothrin 4,6%) in rabbit Oryctolagus cuniculus.

Material and Methods: Twenty-four male rabbits were divided into four groups : control (distilled water) , AP (12,24 mg/ kg lambda cyhalothrin), CE (200 mg/kg vitamin C+ 20 mg/kg vitamin E), and AP + CE group. Ampligo's effect was evaluated on the weight of the body and liver, food and water intake, biochemical parameters, liver histopathology, and morphometry.

Results: Ampligo reduces body weight gain, and feed intake, decreases liver weight, reduces total bilirubin level (2,14 mg/ L), and increases direct bilirubin serum level. Histopathological study on the liver shows structural disorganization in liver tissue, an increase in the central vein diameter (1209,32 µm) with a thickening of the central vein wall (253,44 µm), and sinusoidal dilatation. Contrarily, the addition of vitamins C and E improved the previous alterations.

Conclusion: Our study indicates that Ampligo 150 ZC causes various disorders in rabbit liver and supplementation with a combination of vitamin C and E reduces the insecticide toxicity.

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Key Words: Antioxidant; chlorantraniliprole; histopathological changes; lambda cyhalothrin.

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INTRODUCTION

As the world's population continues to grow, the world food demand is increasing exponentially. In response to this demand, modern societies are seeking to enhance food production, particularly agricultural food. However, insects compete with humans for food resources causing damage to the food industry[1]. To address this issue, many methods have been developed for this purpose to manage agricultural losses caused by insect pests. Among these methods, synthetic insecticides are the most widely used in the field[2]. Although these chemicals have proven their efficacity by increasing food production, an accidental exposure will be extremely dangerous to humans and the environment as they are known to be toxic[3]. Ampligo ® 150 ZC (AP) is a new Lambda Cyhalothrin (LCT) insecticide formulated from a combination of Chlorantraniprole (anthranilic diamide) and LCT (synthetic type II pyrethroid). The product proved to be very effective against a wide range of insect pests in vegetables, such as tomatoes, and even on cotton plantations[4,5]. However, the toxicological side against humans and the environment seems unknown. In fact, Chlorantraniliprole is claimed to be non-toxic to humans. On the other hand, many studies

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have been demonstrated that LCT generates oxidative stress[6–8], it is metabolized like other pyrethroids in the liver via hydrolytic ester cleavage and oxidative pathways by the cytochrome P450 yield Oxygen Reactive Species (ROS) which is an indicator of oxidative stress[9]. Furthermore, LCT increases lipid peroxidation and affects the oxidative defense system of the host body[10]. In that case, an antioxidant supplementation could be beneficial.

Vitamin E (α tocopherol) is a lipophilic chain-breaking antioxidant and a well-known protector of membranes from lipid peroxidation by scavenging lipid peroxyl radicals[11]. While, vitamin C (ascorbic acid) is a hydrophilic antioxidant able to control the oxidative stress and, scavenge physiological ROS, thus protecting the tissue from damage[12]. Also, it has been demonstrated that vitamin C enhances the hepatic injury caused by LCT exposure[8]. Moreover, vitamin C regenerates the active form of vitamin E by the stabilization of tocopheryl radicals that are formed during the scavenging of ROS[13].

The present study aims to evaluate the hepatoxicity of LCT insecticide formulation "Ampligo ® 150 ZC" and the protective effect of vitamins C and E combination on the liver of male rabbits.

MATERIAL AND METHODS

Chemicals

A commercial insecticide formulation, Ampligo ® 150 ZC encapsulated soluble concentrate, used in this study was manufactured by Syngenta, Switzerland. This insecticide is a mixture of Chlorantraniliprole 9,3% and Lambda cyhalothrin 4,6% ZC. Vitamin E (α-tocopherol) and C (ascorbic acid) were manufactured by Sigma Chemical Co. (St.Louis, France).

Animals

A total of 24 male rabbits weighing 2,4 – 2,9 kg and aged 4 to 5 months were obtained from the Technical Breeding Institute (ITELV, Baba-Ali) and moved to the CRD Saidal Algeria for experimentation. Acclimatization of the rabbits lasted for 3 weeks as well as the treatment period. Rabbits had free access to food and water ad libitum, and they were housed in cages at 23 ± 2 C° on a 12h light/dark cycle throughout the experimentation period. Animals were daily weighted using an electronic scale. Food and water intake were measured daily throughout the study.

Experimental design

Animals were randomly divided into four groups of six rabbits each. The first group served as a control and received daily 1 ml of distilled water by gavage. In the second group (CE), rabbits were given vitamin C 200 mg/kg + Vitamin E 20 mg/kg body weight by gavage. In the third Ampligo group (AP), rabbits were administered orally 12,24 mg/kg per day of LCT. While the fourth group (AP+CE), animals were given vitamins C and E 12h after the administration of the insecticide, with the same doses as previous groups.

Biochemical analysis

For biochemical analysis, blood samples were collected from the ear vein at the end of the experimental period and directly placed on ice. Plasma was obtained by centrifugation of samples at 3000 rpm for 15 min. The following biochemical parameters ALT (alanine transaminase), AST (aspartate transaminase), GGT (gamma-glutamyl transferase), PAL (alkaline phosphatase), glucose, bilirubin, and total protein were evaluated using an available commercially kits (Biolab, France) and analyzed by an auto-analyzer (Hitachi 912) instrument (Roche Diagnostics, Mannheim, Germany).

Histological examination

On day 21 after treatment, rabbits were sacrificed by decapitation, then small portions of liver were quickly removed and fixed at 10% neutral buffered formaldehyde solution. Afterward, tissue samples were sectioned (2-3µm) and stained with Hematoxylin, Eosin (H&E), and Masson's trichrome. For histological analysis, digital images of liver parenchyma were obtained by photomicroscope.

Morphometric examination

The histological glass slides with H&E and Masson's trichrome stain were randomly selected and photo-documented using a digital camera connected to a light microscope (Optika B 235, Italy) via "TS View" software (Microscopes America, Cumming GA, USA). Diameters of nuclei, cytoplasm, central vein (CV), and CV to triads, and the thickness of the CV were measured via "Image View" software (version x64, 4.10.17614.20200822). A total of 60 measurements for each parameter were taken at a magnification of x100 and x400.

Statistical analysis

The Data was statistically performed using Statistica version 10.0 (stat soft Inc., Tulsa, Oklahoma, USA). The values were presented as mean ± standard error of mean (SEM). The statistical significance was used a linear mixed model for repeated measures such as body weight, food, and water intake and one-way ANOVA followed by Duncan's post hoc test for the rest parameters. $p<0.05$ was considered statistically significant.

RESULTS

Body and liver weight

(Table 1) shows the evolution of body weight, food, and water intake during the acclimatization period (21 days). Rabbits were well adapted to the experimentation conditions. All animals survived the whole experimental period. A continuous increase in rabbits' body weight was noticed in all experiment groups (Table 2). Treatment with LCT formulation showed the lowest weight gain among groups, in the opposite treatment with a combination of Ampligo and vitamins CE revealed a higher body weight. However, a significant increase in body weight was observed between the control and vitamins CE-treated

group (Table 2). A significant difference in liver relative weight was observed in Ampligo treated rabbits (p<0,05). The addition of vitamins CE to LCT formulation resulted in normal liver weight.

Food and water intake

A continuous increase in food intake was observed throughout the study (Table 2). However, the quantity consumed was the least in the AP group with a significant *p-value* (<0,05) in the third week compared to the control group. On the other hand, an accentuated increase was noticed in the CE group during the three weeks as well as the rabbits treated with the combination of AP and vitamins E and C in the first week. Regarding water consumption, a progressive increase was seen with no special features among the groups (Table 2).

Biochemical parameters

The effects of different treatments on biochemical parameters in male rabbits are given in (Table 3). Relative to the control, the plasma level of AST showed a normal variation. A non-significant decrease in plasma ALT levels was observed in the three groups of treatment. There was a non-significant change in plasma GGT level in all experimental groups. PAL parameter shows an increase in the three groups of treatment (p>0,05). In AP treated rabbits, total bilirubin level indicates a non-significant decrease, however, direct bilirubin level was significantly (P < 0.05) elevated. A low level of glucose was observed in the AP+CE group (p<0,05) and a stable level of total protein in all groups of the experimentation.

Histopathological examination

(Figures 1,2) show liver histology with different magnifications in control, CE, AP, and AP+CE groups. Normal cellular architecture of hepatocytes, central vein (CV), sinusoids, and liver lobules were observed in the control group (Figures 1 A,B). The same architecture of liver parenchyma was observed in the CE group. However, the treatment with AP revealed several changes such as dilatation and congestion of the CV and thickening of the connective tissue, necrotic areas, and sinusoidal dilatation were observed. The addition of vitamins C and E to AP avoided the histopathological damage.

Morphometrical study

The diameter of the nuclei was increased to 46, 11 µm in the CE group and 45,85 µm in the AP+CE group (p< 0,05) (Table 4). As a result, a decrease in the diameter of the cytoplasm was noticed in the CE group (p<0,05). The nucleus to cytoplasm ratio was significantly higher in CE. A highly significant increase in CV diameter in AP treated rabbits (p<0, 0001), and a significant increase in the AP+CE group. A strong thickening in the CV of AP rabbit liver (p<0, 0001). The distance of CV to triads has reduced significantly in the AP group (p< 0, 0001) (Table 4).

Table 1: Body weight, average food and water intake in rabbits from control, CE, AP, and AP+CE treated groups throughout 3 weeks of acclimatization period.

Acclimatization period	Control (n=6)	CE (n=6)	AP (n=6)	AP+CE (n=6)
Body weight (kg)				
Week 1	2,48 ± 0,02	2,45 ± 0,05	2,42 ± 0,04	2,49 ± 0,02
Week 2	2,47 ± 0,09	2,46 ± 0,04	2,45 ± 0,04	2,58 ± 0,02
Week 3	2,69 ± 0,02	2,66 ± 0,04	2,67 ± 0,04	2,72 ± 0,02
Body weight gain (%)	7,8%	7,8%	9,3%	8,4%
Food intake (g)				
Week 1	32,71 ± 0,07	32,89 ± 1,43	33,38 ± 2,42	37,57 ± 1,45
Week 2	49,49 ± 4,03	55,31 ± 3,98	81,6 ± 4, 38^{a}	54,11 ± 3,81
Week 3	138,04 ± 5,06^{a}	118,38 ± 5,35 ^{b}	121,96 ± 7,55^{a}	121,66 ± 6,21^{a}
Water intake (ml)				
Week 1	96,4 ± 4,54	88,67 ± 3,42	100,25 ± 2,34	119,82 ± 8,04
Week 2	130,4 ± 1,05^{a}	108,78 ± 5,17^{b}	166,98 ± 15,3^{c}	142,87 ± 3,79^{a}
Week 3	164,52 ± 4,81	174,33 ± 9,73	186,22 ± 7,82	159,55 ± 5,46

^{a,b,c} Means within columns with different subscripts are significantly different at P<0,05.

Table 2: Body weight gain, average food and water intake in rabbits from control, CE, AP, and AP + CE treated groups, throughout 3 weeks of treatment.

Treatment period	Control (n=6)	CE (n=6)	AP (n=6)	AP+CE (n=6)
Body weight (kg)				
Week 1	2,84 ± 0,02[a]	2, 76 ± 0,03[b]	2,68 ± 0,04[c]	2,94 ± 0,01[d]
Week 2	2,89 ± 0,01[a]	2,95 ± 0,02[a]	2,7 ± 0,04[b]	3,07 ± 0,02[c]
Week 3	3,09 ± 0,01[a]	2,98 ± 0,04[a]	2,79 ± 0,04[b]	3,14 ± 0,03[ab]
Body weight gain (%)	8,09 %	7,38 %	3,94 %	6,36 %
Food intake (g)				
Week 1	136,64 ± 3,20[a]	125,71 ± 4,32[a]	126,97 ± 4,37[a]	145,87 ± 2,42[b]
Week 2	159,85 ± 4,61	168,88 ± 7,91	155,65 ± 9,23	165,08 ± 10,02
Week 3	175,14 ± 4,40[a]	185,68 ± 11,97[b]	159,22 ± 10,65[c]	179,8 ± 13,17[ab]
Water intake (ml)				
Week 1	135,85±2,01	129,57±4,28	123,74±6,27	134,71±2,88
Week 2	149,4±4,03	146,68±7,05	138,51±8,17	157,11±3,68
Week 3	161,35±4,3	165,25±8,66	169,3±7,55	179,05±6,05
Liver weight (g)				
Absolute liver Weight (g)	79,70 ± 1,38	72,01 ± 2,95	62,19 ± 0,99	82,72 ± 1,12
Relative liver Weight (g)	2,57 ± 0,05[a]	2,41 ± 0,21[a]	2,22 ± 0,12[b]	2,70 ± 0,14[ab]

[a,b,c,d] Means within columns with different subscripts are significantly different at $P<0,05$.

Table 3: Effects of Ampligo and vitamins C and E on biochemical parameters in rabbits.

	Control	CE	AP	AP + CE
AST (IU/L)	31,36 ± 3,03	29,33 ± 2,08	33,46 ± 1,56	30,7 ± 1,72
ALT (IU/L)	34,4 ±4,06	28,3 ±3,6	31,68 ±3,09	28,63± 2,33
GGT (IU/L)	31,05± 0,87	31,5 ±8,54	31,83 ±3,11	32,72± 7,79
PAL (IU/L)	8,35±0,46	10,73±3,02	9,61±0,70	12,65±5,32
Total bilirubin (mg/L)	5,68±3,74[a]	4,35±4,10[a]	2,14±0,87[b]	5,19±2,21[a]
Direct bilirubin(mg/L)	0,47±1,52[a]	0,45±1,67[a]	0,83±0,65[b]	0,6±0,90[a]
Glucose (mg/dL)	1,34 ±0,00	1,4 ±0,03	1,41 ±0,06	1,29 ±0,03
Total protein (g/l)	63,54±1,28	65,79±1,53	65,38±1,46	64,96±1,18

[a,b] means within columns with different subscripts are significantly different at $p<0,05$.

Table 4: Variation of different morphometric parameters after treatment on rabbit liver.

	Control (µm)	CE (µm)	AP(µm)	AP+CE (µm)
Nuclei (N) x400	43,29 ± 0,57[a]	46,11 ± 0,62[b]	43,91± 0,63[a]	45,85 ± 0,56[b]
Cytoplasm (C) x400	136,37 ± 3,12[a]	110,43± 2,11[b]	140,96 ±4,23[a]	152,33± 4,13[a]
N/C x400	0,32± 0,006[a]	0,42± 0,008[b]	0,32 ±0,01[a]	0,31± 0,008[a]
CV diameter x100	232,49 ±9,58[a]	189,41± 5,30[a]	1209,32 ±41,41[b]	502,9 ±38,44[c]
Thickness of CV x400	35,58± 1,64[a]	29,52 ±2,33[a]	253,44 ±9,56[b]	89,35± 4,004[c]
CV to triads x100	687,91± 18,54[a]	678,08 ±20,16[a]	462,36± 25,26[b]	712,82 ±18,26[a]

[a,b,c] means within columns with different subscripts are significantly different at $p<0,05$.

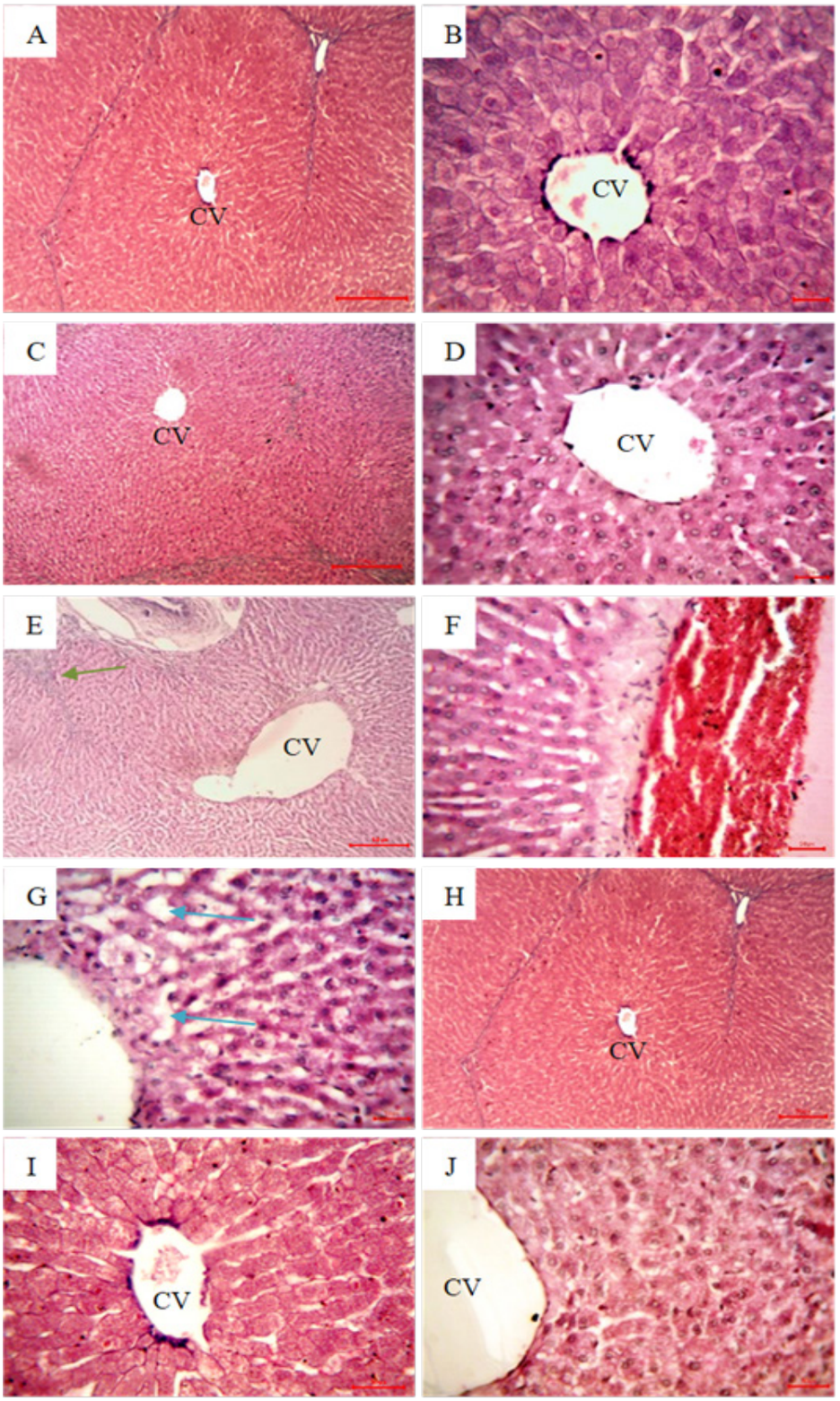

Fig. 1 : Effect of different treatments on liver rabbit. Control (A & B) (x100; 400) normal appearance of liver lobule and the central vein (CV) ; Vitamins C and E administrated (C & D) (x100; 400) with normal architecture of liver parenchyma; AP administrated (E;F&G) showing CV dilatation, inflammatory areas (→), vascular congestion and sinusoids dilatation (→) (x100;400;1000);co-administration of AP and CE (H;I;J) (x100;400) showing restored liver parenchyma with normal CV lobule tissue. HE stained.

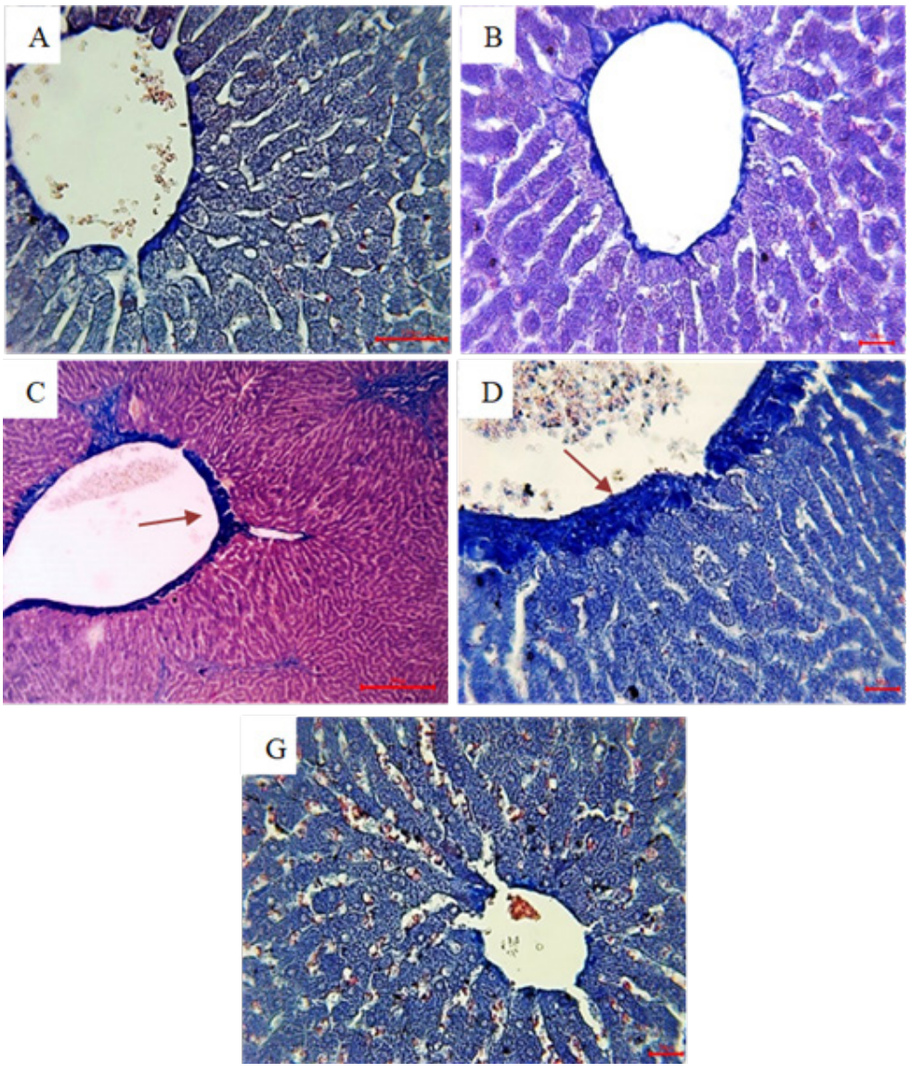

Fig. 2: Effect of different treatments on liver rabbit. Control (A) and vitamin C&E (B) administrated showing normal architecture of liver parenchyma; AP administrated (C&D) showing thickening of the connective tissue around the CV (→); co-administration of AP and CE showing a normal aspect of connective tissue around the CV. Masson's trichrome stained magnification x 400.

DISCUSSION

Pesticides are parts of xenobiotics and it is known that there is a strong link between xenobiotics and the immune system causing immunotoxicity[14], reproductive toxicity[15], nephrotoxicity, and hepatotoxicity[16]. Moreover, the main target of the xenobiotics in the body is often the liver, which plays a crucial role in the metabolism and detoxification of pesticides. Therefore, the liver can be used as an indicator of their toxicity[17,18]. The present study aimed to evaluate the effect of repeated exposure to an insecticide formulation of lambda cyhalothrin Ampligo on the liver of rabbit "Oryctolagus cuniculus".

A progressive increase in body weight was observed during the experiment in all groups, however, the lowest weight gain was noticed in AP treated rabbits. Similarly, the average feed intake was lower and a significant decrease in liver relative weight was observed in AP treated rabbits. Variations in body and relative organ weights are critical elements for evaluating organ toxicity in toxicological investigations and have been used as a strong indicator of insecticide-related organ damage[19]. In the present study, reduced weight gain appeared as a lesser feed intake in Ampligo treated rabbits. Many studies proved that LCT reduces the body weight of rabbits and rats[8, 20, 21]. Also, it has been demonstrated that LCT reduces rabbit food intake[22], and pyrethroids insecticides reduced relative and absolute liver weights[17,23]. Supplementation of vitamins C and E allows for preserving the stability of rabbit body weight. On the other hand, the combined effect of vitamin C and E enhances food intake but maintains stable body weight. The co-treatment of AP and vitamins elevate both body weight gain and food intake, this was expected since the separate effect of the two molecules was previously demonstrated. No significant changes were observed in water intake; thus, we can say that Ampligo has no impact on water consumption.

In the present study, no change was observed in AST and ALT activity. Being liver specific enzyme, transaminase is often used as an indicator of liver injury. Moreover, exposure to LCT was found to produce hepatic damage and elevate serum AST and ALT activities in rabbits and rats[8,24–26]. Serum GGT, PAL, and total protein values varied insignificantly in all treatment groups. However, a significant decrease in direct bilirubin (p<0,05) was noticed in the AP treated group in contrast to total bilirubin values. The decrease in serum value of direct bilirubin could be explained by the destruction of liver enzymes responsible for the conversion of conjugated bilirubin to direct bilirubin. Being part of the pyrethroids family, LCT is used in various insecticide formulations to improve its effectiveness. In this context, the addition of Chlorantraniliprole to LCT seems to reduce its toxicity since the serum level of these biochemical parameters was not much disrupted. The combination of vitamin C and E improved all possible alterations of the tested parameters. This improvement was shown in a previous study which confirmed the corrective role of vitamin C and E against pesticide alteration[27].

Histopathological changes resulting from Ampligo's administration, as well as CV congestion and dilatation, hepatic necrosis, sinusoids dilatation, and thickening of the connective tissue, allow us to confirm its toxicity. The morphometric study correlates with the results of the histological examination showing an accentuated thickening of the wall of the CV as well as an increase in its diameter due to treatment with Ampligo. Several studies have demonstrated histopathological damages in the liver induced by LCT like hepatic necrosis, congestion of the central vein, infiltration with inflammatory cells, and hepatocytes degeneration[8,25,28]. The thickening of the central vein proved to be an indicator of liver damage[29,30]. Also, it has been proved that LCT induces a high level of ROS in rate liver[8] thus improving liver injury. On the other hand, the toxic effect of Chlorantraniliprole on liver parenchyma seems unclear. In our study, the addition of vitamins C and E to AP enhanced the immune system to eliminate the insecticide toxins in the liver and restore its damage.

Numerous studies have shown the potent effect of combined vitamins C and E on reducing the oxidative stress caused by toxic substances such as insecticides[31–35].

CONCLUSION

our study provides new information about the low hepatotoxicity of the association of two types of insecticides, LCT and Chlorantraniliprole, on rabbits and the corrective effect of combined vitamin C&E. However, further studies are needed to evaluate the degree of toxicity of Chlorantraniliprole in the first place then to investigate deeply on the effect of Ampligo insecticide to improve this hypothesis and promote the supplementation of vitamins to minimize its damages on human and environment.

ETHICAL STATEMENT

The animals were kept and treated following welfare legislation and the guide for the care and use of laboratory animals from the local Algerian CRD Saidal, at route d' El Khmis Miliana. BP 33.Oued Harbil, Medea, Algeria.

CONFLICT OF INTERESTS

There are no conflicts of interest.

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الملخص العربى

تقييم تأثيرات تركيبة المبيد الحشري لامدا سيهالوثرين "امبليجو ١٥٠ زس " وفيتامينات ج و هـ على كبد الأرانب: دراسة المؤشرات البيوكيميائية والنسيجية والقياسات الشكلية

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مقدمة: تعمل الصناعة الكيميائية حاليًا على تطوير مبيدات حشرية جديدة هدفها الرئيسي هو التغلب على انخفاض إنتاجية المبيدات الحشرية الموجودة والتي أصبحت الحشرات مقاومة لها تدريجيا. وفي الوقت نفسه، مع هذا التطور يجب الاخذ بعين الاعتبار القضايا البيئية، ولا سيما المخاطر المحتملة على البشر والحيوانات. وفي هذا الصدد، أظهرت الدراسات أن الفيتامينات نظرًا لقدرتها على مكافحة الأكسدة يمكن أن تقلل من المخاطر السامة للمبيدات في الجسم.

الهدف من البحث: البحث في التأثير التحسيني المحتمل لفيتامين ج وهـ على السمية الكبدية الناتجة عن المبيد الحشري امبليجو ١٥٠ ز س الذي يحتوي على اللامبدا سايهالوثرين (كلورانترانيليبرول ٩,٣٪ ولامبدا سايهالوثرين ٤,٦٪) في الأرانب.

المواد والطرق: تم تقسيم أربعة وعشرون أرانب ذكور إلى أربع مجموعات: مجموعة شاهدة (ماء مقطر)، مجموعة الأمبليجو (١٢,٢٤ ملغ/كغ لامبدا سايهالوثرين)، مجموعة فيتامين ج و هـ ٢٠٠) ملغ/كغ فيتامين + ج ٢٠ ملغ/كغ فيتامين (، ومجموعة أمبليجو + فيتامين ج و هـ. تم تقييم تأثير أمبليجو على وزن الجسم والكبد، وتناول الطعام والماء، ومستوى المؤشرات البيوكيميائية في الدم، ونسيج الكبد، بالإضافة الى دراسة القياسات الشكلية.

النتائج: أظهر أمبليجو تقليلًا في زيادة وزن الجسم وتناول الطعام، وانخفاضًا في وزن الكبد، وتقليلًا في مستوى البيليروبين الكلي (٢,١٤ ملغ/لتر)، وزيادة في مستوى البيليروبين المباشر في المصل. أظهرت الدراسة النسيجية للكبد اضطرابات في البنية النسيجية للكبد، وزيادة في قطر الوريد المركزي (١٢٠٩,٣٢ ميكرومتر) مع تضخم في جدار الوريد المركزي (٢٥٣,٤٤ ميكرومتر)، وتوسيع الأوعية الدموية الجيبية. على النقيض، قامت إضافة فيتامينات ج وهـ بتحسين التغيرات السابقة.

الاستنتاج: تشير دراستنا إلى أن أمبليجو ١٥٠ ز س يسبب اضطرابات متنوعة في كبد الأرانب والإضافة المكملة بمزيج من فيتامين ج وهـ تقلل من سمية المبيد الحشري.