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Research Article

Haematological Characteristics and Oxidative Stress Indicators in Pregnant Rabbit does (*Oryctolagus cuniculus*) Exposed to Lambda Cyhalothrin

Mahamat Tahir Markhous Adam[1,3], Chongsi Margaret Mary Momo[1]*, Vemo Bertin Narcisse[1], Tchoffo Hervé[1], Djuissi Motchewo Nadège[1], Dongmo Nguedia Arius Bauland[1], Kouamo Justin[2] and Ngoula Ferdinand[1]

[1]Department of Animal Science, Faculty of Agronomy and Agricultural Sciences, University of Dschang, Dschang, Cameroon

[2]Department of Surgery and Medical Pathology, School of Sciences and Veterinary Medicine, University of Ngaoundere, Ngaoundere, Cameroon

[3]Department of Biology, Faculty of Science and Techniques, University of Adam Barka of Abéché, Abéché, Chad

***Corresponding Author:** Chongsi Margaret Mary Momo, Department of Animal Science, Faculty of Agronomy and Agricultural Sciences, University of Dschang, Cameroon.

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Abstract

The present study was undertaken to evaluate the effects of lambda cyhalothrin on haematological characteristics and oxidative stress indicators in pregnant rabbit does. Fifteen nulliparous and sexually mature rabbit does, aged 8 months and weighing 2.80-3.00 kg were divided into three groups of five animals, comparable in terms of body weight (bw). After mating, group T0 received distilled water, while groups T1 and T2 were administered doses of 4.16 and 8.32 mg/bw of lambda cyhalothrin respectively. On the 28th day after mating, animals were given anesthezier (ether vapor) and dissected. Blood samples were collected into tubes for dosages of biochemical characteristics and with anticoagulant (EDTA) for dosing haematological characteristics and oxidative stress markers.

Results showed that catalase (CAT), superoxide dismutase (SOD) and total peroxidase (POD) activities as well as malondialdehyde (MDA) concentration registered a dose-dependent significant ($p < 0.05$) increase in ovaries of lambda cyhalothrin-exposed does, with a significant decrease in total ovarian protein levels in comparison to those given distilled water.

Haematology revealed comparable ($p > 0.05$) values among groups except in monocytes and granulocytes where a significant ($p < 0.05$) increase was recorded in females treated with lambda cyhalothrin as opposed to control.

Moreover, nephrotoxicity analysis showed that Kidney weight, creatinine and urea levels significantly ($p < 0.05$) increased with the highest values observed in the lower dose (4.16 mg/kg bw) of lambda-cyhalothrin with respect to the distilled water-receiving group. Nevertheless, a non-significant ($p > 0.05$) difference was noted in kidney volume. Hepatotoxicity registered a dose-dependent significant ($p < 0.05$) increase in liver weight and alanine aminotransferase (ALAT) activity, with a significant ($p < 0.05$) decline in liver volume and total proteins concentration in lambda cyhalothrin-exposed animals with respect to control group. Meanwhile, aspartate aminotransferase (ASAT) activity, albumin and globulin levels were comparable ($p > 0.05$) among all groups.

From these results, it can be concluded that lambda cyhalothrin when found in tissues may bring about the production of reactive oxygen species, which are concerned with haematological, kidney and liver toxicity in pregnant rabbit does.

Keywords: *Lambda Cyhalothrin; Oxidative Stress; Pregnancy; Rabbit Does; Toxicity*

Introduction

Pesticides (insecticides, herbicides and fungicides) constitute the major potential environmental hazard to humans and animals as they are present and concentrated in the food chain. World Health Organization has prohibited the use of pesticides having acute toxicity, but pyrethroids use is extensive [1]. The pyrethroid pesticides been shown to be replacing other insecticides at a very fast rate the fact that they are known to be less harmful to animals, poultry and the environment than other insecticides [2].

They are used all over the world as insecticides in pest control and act by disrupting the normal function of sodium channels. However, they have now become an environmental issue due to excessive use in agriculture, livestock production, leather industry and shampoos etc. Pyrethroid pesticides have also been found in environmental samples, like water and sediments [3]; food [4] and can equally be found in urine and breast milk in human samples. Their metabolites have been reported to produce adverse consequences on different physiological functions in the body [5].

Moreover, some investigators [6] have registered oxidative stress consequences brought about by pyrethroids. An increasing number of studies have shown that oxidative stress plays great roles in various toxicities that have to do with pyrethroid insecticides [7].

Earlier studies have reported that pyrethroids exposure change antioxidant defense mechanisms and increase lipid peroxidation [8]. Rats administered a single dose of the pyrethroids, cypermethrin (25 μg kg^{-1}) and fenvalerate (4.5 μg kg^{-1}), decreased the activities of the antioxidant (AO) enzymes SOD and CAT, leading to both lipid peroxidation and reduced values of GSH in erythrocytes [9].

Lambda-cyhalothrin (LCT) is a manufactured pyrethroid insecticide which is used in home pest control, agriculture, protection of food and disease vector control [10]. Agriculturally, it is applied on cotton, cereals, various vegetables and fruits with applications made to control aphids, Colorado beetles and lepidopteran larvae, and was found in milk, the blood of dairy cows and cattle meat [11].

However, subsequent studies have shown that lambda-cyhalothrin, is quite toxic to mammals and humans [12]. Its degree depends on the dose, method and duration of administration. Many reports have been made on lambda-cyhalothrin toxicity to mammals and its ability to induce oxidative stress *in vivo* and *in vitro* [13].

The exposure of rats to LCT led to hepatotoxicity and severe injury of renal structure due to its toxicity [14]. It was also demonstrated that renal activities, tissue malondialdehyde (MDA), histopathology, protein carbonyl levels, reduced glutathione levels and AO enzyme activities were altered significantly by lambda-cyhalothrin [10]. LCT increased the production of reactive oxygen species and DNA damaged levels, leading to harmful immune effects [15]. Equally, other results indicated that LCT caused significant rise in the kidney, brain and liver weight and plasma alanine aminotransferase (ALAT) and aspartate aminotransferase (ASAT) levels. Nevertheless, the plasma content of bilirubin, urea, creatinine, and glucose were significantly raised. On the contrary, plasma total protein and albumin was reduced [16].

However, studies available are mostly on males or on Pyrethroids in general. Keeping in view the scarcity of information on LCT toxicity in females, this study was designed and executed to investigate the ability of Lambda-cyhalothrin to induce oxidative pressure and changes in haematological characteristics and oxidative stress indicators in pregnant does.

Materials and Methods

Animal material

Healthy fifteen adult fertile rabbit-does (New Zealand breed) of 8 months old, weighing 2.8 - 3.0 kg, produced at Teaching and Research Farm of the University of Dschang were used. They were treated against external (exo) and internal (hemo) parasites by sub-cutaneous injection of an ivermectin solution (0.1 ml/kg bw), repeated after two weeks.

Lodging and feeding

Animals were housed in a cement block building with sheet metal roof, plastered and open 1/3 upper section. They were kept individually in wire cages (galvanized metal, 96 cm long, 40 cm wide and 15 cm high). Each cage was equipped with a feeder and a drinker (800 ml capacity). The building was previously disinfected with a solution of javel water and cresyl (1/2 l each mixed in 20 l water) which was sprayed in the building and in all the cages. Animals were introduced in the cages two weeks after disinfection. Throughout the trial period, animals received *ad libitum* a commercial complete feed from SPC (*Société des Provenderies du Cameroun*) and water. Table 1 presents the chemical characteristics of this feed.

Chemical characteristics	Values
Fats (% DM)	6.50
Calcium (% DM)	1.20
Crude fiber (% DM)	7.00
Crude protein (% DM)	16.00
Metabolisable energy (Kcal/kg DM)	2350.00
Humidity (% DM)	12.00
Vitamins	+
Oligo-elements	+
Antioxidants	+
Anti-moisture	+

Table 1: *Chemical characteristics of the feed.*

DM: Dry Matter.

Preparation of lambda-cyhalothrin solutions

Doses of Lambda-cyhalothrin used were 0, 1/100 and 1/50 of the LD_{50} of LCT (416 mg/kg body weight reported in rabbit doe by Morgan and Osman [17]. That is 0, 4.16 and 8.32 mg/kg body weight. Lambda-cyhalothrin solutions were prepared by diluting known

volumes of KILLAM 15 EC (Lambda-cyhalothrin 15 g/L) from INTRADE LTD SAS- France, in distilled water in such a way to obtain final solutions at required concentrations.

Ethical consideration

Experimental protocols used in this study were approved by the Ethical committee of the Department of Animal Science of the University of Dschang (ECDAS-UDs 23/02/2015/UDs/FASA/DSAES) and was in conformity with the internationally accepted standard ethical guide lines for laboratory animal use and care as described in the European Community guidelines; EEC Directive86/609/EEC, of the 24thNovember1986.

Experimental design

Fifteen fertile rabbit-does were mated with untreated sexually mature males, with sex ratio 1:3 (1♂ for 3 ♀), and randomly divided into 3 groups of 5 rabbit-does each, comparable in terms of body weight (bw). The 3 groups were assigned different treatments for 28 days *post-coïtum*.

Lambda-cyhalothrin was administered by gavage using a syringe of 2.5 ml. The animals of the control group (T0) received 0.5 ml/kg bw of distilled water daily. Groups T1 and T2 were given doses of 4.16 and 8.32 mg /kg bw respectively. At 28th day *post-coïtum*, animals were sacrificed for evaluation of hematological characteristics and oxidative stress indicators.

Biochemical and haematological analysis

Samples of blood were collected into tubes without anticoagulant through cardiac puncture for dosing biochemical characteristics like aspartate aminotransferase, alanine aminotransferase, albumin, globulin, urea, creatinine, and total proteins, performed with Chronolab kits (Barcelona, Spain); and with anticoagulant (EDTA) for dosing haematological characteristics. Haematological characteristics were, Red blood cells count, White blood cells count, Hemoglobin; Hematocrit; Mean corpuscular Volume; Mean corpuscular hemoglobin; Mean Corpuscular Hemoglobin Concentration; Platelets and plaquetocrit, evaluated using an automatic blood analyzer.

Weight and volume of organs

After dissection of the rabbits, the kidney and liver were collected and weighed.

Indicators of oxidative stress

Activities of superoxide dismutase, total peroxidases, catalase and concentration of malondialdehyde in ovary were measured using the methods proposed by Misra and Fridovich [18], Moron., *et al.* [19], Aebi [20] and Botsoglou., *et al*. [21], respectively. Total ovarian proteins (TOP) were dosed using Chronolab kit (Barcelona, Spain).

Data analysis

Data were submitted to one-way analysis of variance (ANOVA) to test the effects of dose of Lambda-cyhalothrin on parameters studied. The test of Duncan was used to separate means when the difference was significant. The results were expressed as mean ± standard deviation and the significance limit was set at 5%. The software used for the analysis was SPSS 20.0.

Results

Oxidative stress markers in pregnant does exposed to lambda cyhalothrin

The effects of lambda cyhalothrin on oxidative stress markers in pregnant does are shown in table 2. CAT and SOD activities as well as POD concentration and MDA levels registered a dose-dependent significant ($p < 0.05$) increase in ovaries of lambda cyhalothrin-exposed does when compared with the control group. Contrary to these, a significant decrease was noted in total ovarian protein levels in the pesticide-treated groups in comparison with that given distilled water.

Oxidative stress markers	Doses of lambda cyhalothrin (mg/kg bw)			P
	0 (n = 5)	4.16 (n = 5)	8.32 (n = 5) (n = 0)	
SOD (U/min/g of ovarian proteins)	0.22 ± 0.07^b	0.42 ± 0.08^a	0.45 ± 0.10^a	0.002
CAT (uM/min/g of ovarian proteins)	0.53 ± 0.09^b	0.86 ± 0.04^a	0.90 ± 0.09^a	0.000
TPO (mM/min/g of ovarian proteins)	40.39 ± 10.03^b	61.07 ± 18.46^a	65.36 ± 13.68^a	0.040
MDA (uM/g of ovary)	2.41 ± 0.45^b	6.83 ± 1.81^a	8.70 ± 2.12^a	0.000
TOP (g/dl)	3.07 ± 0.39^a	2.09 ± 0.09^b	2.37 ± 0.14^b	0.000

***Table 2**: Effects of lambda cyhalothrin on oxidative stress markers in pregnant does.*
a, b: Values affected with the same letter in the same line are not significantly different ($p > 0.05$).
n: Number of animals per group. CAT: Catalase; MDA: Malondialdehyde; SOD: Superoxide Dismutase; TPO: Total Peroxidase; TOP: Total Ovarian Proteins.

Haematological characteristics in pregnant does exposed to lambda cyhalothrin

Table 3 shows the effects of lambda cyhalothrin on hematological characteristics in pregnant rabbit does. It was observed that independently of doses, values were comparable ($p > 0.05$) among groups except in monocytes and granulocytes where a significant ($p < 0.05$) increase was recorded in females treated with lambda cyhalothrin as opposed to control.

Hematological characteristics	Doses of lambda cyhalothrin (mg/kg bw)			P
	0 (n = 5)	4.16 (n = 5)	8.32 (n = 5)	
WBC (10^3/µl)	7.92 ± 1.81	9.75 ± 1.57	9.80 ± 0.89	0.219
Lymph (10^3/µl)	3.75 ± 0.85	3.05 ± 0.61	3.10 ± 0.78	0.396
Mono (10^3/µl)	0.45 ± 0.13^b	0.70 ± 0.22^a	0.73 ± 0.23^a	0.045
Granul (10^3/µl)	3.73 ± 0.45^b	6.00 ± 1.33^a	5.97 ± 0.80^a	0.016
RBC (10^6/µl)	5.23 ± 0.40	4.72 ± 0.43	4.84 ± 0.83	0.431
Hgb (g/dl)	11.83 ± 0.88	10.63 ± 0.84	9.33 ± 1.19	0.198
HCT (%)	34.25 ± 2.53	31.58 ± 2.32	31.20 ± 5.73	0.474
MCV (%)	65.58 ± 3.42	66.55 ± 2.26	64.50 ± 4.33	0.729
MCH (PG)	22.65 ± 1.48	22.53 ± 0.43	21.93 ± 1.49	0.722
MCHC (g/dl)	34.53 ± 0.67	33.63 ± 0.62	34.03 ± 0.35	0.154
PLT (10^3/µl)	323.75 ± 28.00	337.00 ± 42.68	308.33 ± 10.26	0.523
PCT (%)	0.25 ± 0.04	0.26 ± 0.06	0.22 ± 0.02	0.530

***Table 3**: Effects of lambda-cyhalothrin on hematological characteristics in pregnant does*
a, b: Values affected with the same letter in the same line are not significantly different ($p > 0.05$).
n: Number of animals per group. RBC: Red Blood Cell Count; WBC: White Blood Cell Count; Lymph: Lymphocytes; Mono: Monocytes; Granul: Granulocytes; Hgb: Hemoglobin; HCT: Hematocrit; MCV: Mean Corpuscular Volume; MCH: Mean Corpuscular Hemoglobin; MCHC: Mean Corpuscular Hemoglobin Concentration; PLT: Platelets; PCT: Plaquetocrit.

Hepato-toxicity of lambda cyhalothrin in pregnant does

The effects of lambda cyhalothrin on hepato-toxicity indicators in pregnant does summarized in table 4. It appears from this table that there is a dose-dependent significant ($p < 0.05$) increase in liver weight and ALAT levels, with a significant ($p < 0.05$) decline in liver volume and total proteins values; in lambda cyhalothrin-exposed animals with respect to control group. Meanwhile, ASAT, albumin and globulin levels were comparable ($p > 0.05$) among all groups.

Liver toxicity indicators	Doses of lambda cyhalothrin (mg/kg bw)			P
	0 (n = 5)	4.16 (n = 5)	8.32 (n = 5)	
Weight (g/100 g bw)	2.13 ± 0.20^{b}	2.52 ± 0.17^{a}	2.79 ± 0.05^{a}	0.002
Volume (ml)	104.75 ± 19.16^{a}	78.25 ± 10.75^{b}	90.00 ± 11.00^{ab}	0.048
ALAT (UI)	45.33 ± 8.91^{b}	53.90 ± 6.93^{ab}	60.38 ± 11.70^{a}	0.045
ASAT (UI)	36.08 ± 4.72	38.30 ± 6.54	39.90 ± 3.75	0.516
Total Proteins (g/dl)	4.70 ± 0.23^{a}	4.34 ± 0.30^{ab}	4.20 ± 0.43^{b}	0.048
Albumin (g/dl)	2.68 ± 0.34	2.50 ± 0.28	2.52 ± 0.17	0.541
Globulins (g/dl)	2.02 ± 0.41	1.84 ± 0.23	1.69 ± 0.36	0.344

***Table 4**: Effects of lambda cyhalothrin on hepato-toxicity indicators in pregnant does*

a, b: Values affected with the same letter in the same line are not significantly different ($p > 0.05$).

n: Number of animals per group. ASAT: Aspartate Aminotransferase; ALAT: Alanine Aminotransferase.

Nephrotoxicity of lambda-cyhalothrin in pregnant does

Lambda-cyhalothrin administration produced various effects on pregnant doe kidney (Table 5). Kidney weight, creatinine and urea levels significantly ($p < 0.05$) increased with the highest values observed in the lower dose (4.16 mg/kg bw) of lambda-cyhalothrin with respect to the distilled water-receiving group. Nevertheless, a non-significant ($p > 0.05$) difference was noted in kidney volume.

Kidney toxicity indicators	Doses of Lambda cyhalothrin (mg/kg bw)			P
	0 (n = 5)	4.16 (n = 5)	8.32 (n = 5)	
Weight (g/100 g bw)	0.45 ± 0.02^{b}	0.53 ± 0.04^{a}	0.47 ± 0.02^{ab}	0.007
Volume (ml)	14.95 ± 2.88	17.00 ± 1.78	15.67 ± 2.08	0.482
Creatinine (mg/dl)	0.78 ± 0.09^{b}	1.10 ± 0.19^{a}	0.98 ± 0.13^{a}	0.012
Urea (mg/dl)	18.06 ± 4.67^{b}	25.51 ± 6.34^{a}	23.33 ± 1.40^{ab}	0.045

***Table 5**: Effects of lambda-cyhalothrin on kidney toxicity indicators in pregnant does.*

a, b: Values affected with the same letter in the same line are not significantly different ($p > 0.05$).

n: Number of animals per group.

Discussion

Excessive application of pesticides is usually followed by serious problems of pollution and health hazard. Pyrethroids (PYRs) are increasingly used as pesticides and can generate some toxic effects in the liver, kidneys, and other organs of various types of experimental animals by producing free radicals (FR) that destroy all cell components [9]. Many studies have reported that the induction of oxidative stress (OS) and disturbance of the total antioxidant (AO) defence were the possible mechanisms of PYR type II toxicity in animals [22].

Pyrethroid insecticide like lambda-cyhalothrin at particular doses and conditions has been demonstrated to accumulate in biological membranes bringing about oxidative damage due to its lipophilic nature. It has been proposed that some consequences directly related to pesticide toxicity might be because of alterations in membrane fluidity, in lipid contents and inhibition of activities of enzyme [23].

An attractive way to explain the toxicity of many xenobiotics (e.g. pesticides) is free radicals (FR) and some of these free FR interact with various tissue components, leading to malfunction [24]. Oxidative damage caused by excessive generation of reactive oxygen species (ROS) has been linked with defective organs malfunction and the inhibition of enzymes involved in FR removal result in the accumulation of hydrogen peroxide (H_2O_2), which promote lipid peroxidation and modulation of DNA, alter gene expression and cell death [25]. Superoxide dismutase (SOD), catalase (CAT) and Glutathione peroxidase (GPx) are known to play an important role in scavenging ROS. SOD catalyzes the destruction of the superoxide radicals to H_2O_2, while CAT together with GPx decreases the H_2O_2 into H_2O and O_2 to prevent oxidative stress (OS) and in maintaining cell balance.

In the case of oxidative stress, SOD will behave in two different manners. Initially, the body will respond to moderate OS by over-expressing and raising its activity; therefore the increment of SOD activity in the current study might be linked to the fact that lambda-cyhalothrin generated moderate free radicals leading to an increase in SOD. If the stress persists and generates excess ROS, the SOD will be damaged and its activity will decline.

The increment in total peroxidase (TPO) and CAT in rabbits administered LCT could equally be in response to raised oxidative stress. When a condition of OS strongly sets in, the defense capacities against ROS becomes insufficient [25], in turn ROS also alter the antioxidant (AO) defense mechanisms, decreases the intracellular concentration of glutathione, lipid peroxidation and modify the activity of AO enzymes e.g., SOD, CAT and POD.

In this study, the increase in SOD and CAT activities is not in line with previous findings showing that rats exposed to pyrethroid had reduced AO defense systems in different tissues [26,27]. It has been proposed that this comes from reactive species (RS) attack on the enzyme proteins causing site-specific amino acid alterations [28]. Thus, it is conceivable that the increased generation of RS caused by LCT in the present work may have contributed to the increment of these antioxidant activities.

The alterations in these biomarkers of oxidative stress (OS) have been shown to be an indicator of the ability of tissue to manage OS [24].

One of the molecular mechanisms involved in pesticide-induced toxicity has been suggested to be lipid peroxidation [23]. The level of Malondialdehyde (MDA) in LCT exposed animals was significantly higher than that in control, indirectly suggesting a rise in oxygen free radicals generation in rabbits. Metabolites of oxygen which are highly reactive, particularly hydroxyl radicals, act on unsaturated fatty acids of phospholipid components of membranes to generate MDA which is a product of lipid peroxidation. Earlier studies show that insecticides in both *in vivo* and *in vitro* tests modify the activities of enzyme linked to defense mechanisms of antioxidants [26].

Likewise, these results are in agreement with earlier reports [29]. Moreover, the liver and kidney are the organs most susceptible to pesticide damage and can be used as an indicator for xenobiotics toxicity. A variety of bioindicators are measured in toxicity studies to evaluate a great range of physiological and metabolic functions that affect the identification of target organs and the assessment of lesions of tissue. A group of some biochemical characteristics give better information for pattern recognition, e.g. albumin, globulin, aspartate aminotransferase (ASAT) and alanine aminotransferase (ALAT) for hepatotoxicity, creatinine and urea as nephrotoxicity [30]. The most important indicators of liver destruction are the sending out of intracellular enzymes like ALAT and ASAT to the exterior of the cell. As soon as lambda-cyhalothrin gets into the biological system, it is converted into its metabolites, which can bind to cellular macromolecules and react with free amino groups of proteins. Thus, the macromolecules may lose their physiological functions or trigger hepatocytes to generate more toxic metabolites [31]. Hence, cellular membrane destruction results initially to a more prominent increment in ALAT activity, where severely destroyed hepatocyte ASAT is also increased.

In this work LCT brought about a significant dose-dependent increase of the activity of aspartate aminotransferase, demonstrating a liver malfunction in rabbits. These results coincide with those recorded in other studies [29,32].

Lambda-cyhalothrin hinders the incorporation of amino acids into proteins leading to modifications in creatinine and urea levels that are the main nitrogen-containing metabolic products of metabolism of protein [33]. Increased urea level is known have a correlation with an elevated protein catabolism in mammals and /or conversion of ammonia to urea because of raised synthesis of arginase enzyme involved in urea generation [34]. The significant increment in the creatinine and urea values with lambda-cyhalothrin exposure showed a declined ability of the kidney to filter by-products and eliminate them in the urine. These observations were similar to the results of [35,36], who reported that lambda-cyhalothrin administration resulted in a significant elevation in creatinine and urea levels in animals.

The essential organic macromolecules for cellular structure and function (proteins), are expected to react first with pesticide after the entry of pesticide into cells of the body. Pesticides possess the ability to modify very rapidly the buffering system of the intracellular environment. Pesticides disrupt metabolism of protein resulting may be to a disarrangement of the cell's functional and structural status [37]. In this work, LCT had a significant reducing influence on total ovarian protein levels which might be because of the disruption of protein synthesis and necrosis of hepatocyte cells. Decrement in total protein might be because of destruction in liver caused by LCT as reported earlier that hepatotoxicity leads to declined serum protein in rat [38]. Decrease in total protein has been observed already in other pesticide-treated models of animal [39].

Assessment of the weight of organs of detoxification is of great value for testing the toxicity of substances. Liver plays an essential role in the metabolism and detoxification [40]. Alterations in kidney weight may demonstrate nephrotoxicity, tubular hypertrophy or chronic progressive nephropathy.

Increased weight of liver recorded in this study might be because of elevated circulation due to raised requirements for the detoxifying compounds that are toxic [41]. These results are in accordance to those reported by Vemo., *et al* [42].

Blood acts as a pathological indicator of the status of animals exposed to toxins and other conditions and/or agents. Associates of white blood cells (WBC) such as monocytes, granulocytes, and lymphocytes, fight against pathogens and tend to be elevated in case of infection. The rise in WBC may be a demonstration of stimulation of defense and immune system of the body [46]. This might lead to an elevation in release of WBC from bone marrow storage pool into the blood. Therefore, the increase in monocytes and granulocytes in the current work could be explained by the fact that LCT might have been recognized as a toxicant.

Conclusion

From these results it can be concluded that, lambda cyhalothrin generates significant adverse consequences in the various biochemical characteristics; oxidative stress markers, liver and kidney functions, as well as haematological modifications in female rabbits. Thus, high doses of lambda cyhalothrin in tissues may induce the production of reactive oxygen species, which are associated with haematological, renal and liver toxicity in rabbit does.

Conflict of Interest

The authors declare no conflict of interest.

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