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Lavender (*Lavandula stoechas*) essential oils attenuate Lambda-Cyhalothrin induced liver damage in Rabbit

[Los aceites esenciales de lavanda (*Lavandula stoechas*) atenúan el daño hepático 4inducido por Lambda-Cyhalothrin en conejos]

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Abstract: The health consequences of pesticide exposure are a frequent concern for population, and essential oils are used in phytotherapy. This study was carried out to determine the detoxifying effect of *Lavandula stoechas* essential oil (LS.EO) against the insecticide Lambda-Cyhalothrin (LCT) in the rabbit *Cuniculus lepus*. Which they were divided into a control group, a group treated with (LCT) (100mg/Kg/BW), and the last group with the combination of (100 mg/Kg/BW LCT+500 mg/Kg/BW.LS.EO). LCT and LS.EO were administered orally via diet for one month. Serum biomarkers were assessed. Results showed a highly significant increase in CRP levels in both treated groups compared with control. Blood glucose, TC, and HDL levels showed no significant differences. On the other hand, the two groups treated with LCT and LCT+LS.EO showed a very significant increase in LDL and TG levels compared to control. However, the combined treatment reduced toxicity (LCT) by recording significant changes in most of the biochemical markers studied.

Keywords: Detoxification; Lambda-Cyhalothrin; *Lavandula stoechas* oil; Rabbit; Biochemical markers.

Resumen: Las consecuencias para la salud de la exposición a pesticidas son una preocupación frecuente para la población, y los aceites esenciales se utilizan en fitoterapia. Este estudio se llevó a cabo para determinar el efecto desintoxicante del aceite esencial de *Lavandula stoechas* (LS.EO) contra el insecticida Lambda-Cyhalothrin (LCT) en el conejo Cuniculus Lepus. Los conejos se dividieron en un grupo de control, un grupo tratado con LCT (100 mg/Kg/PV), y el último grupo con la combinación de (100 mg/Kg/PV LCT + 500 mg/Kg/PV LS.EO). Se administraron LCT y LS.EO por vía oral a través de la dieta durante un mes. Se evaluaron biomarcadores séricos. Los resultados mostraron un aumento altamente significativo en los niveles de CRP en ambos grupos tratados en comparación con el control. Los niveles de glucosa en sangre, colesterol total (TC) y lipoproteínas de alta densidad (HDL) no mostraron diferencias significativas. Por otro lado, los dos grupos tratados con LCT y LCT + LS.EO mostraron un aumento muy significativo en los niveles de lipoproteínas de baja densidad (LDL) y triglicéridos (TG) en comparación con el control. Sin embargo, el tratamiento combinado redujo la toxicidad del LCT al registrar cambios significativos en la mayoría de los marcadores bioquímicos estudiados.

Palabras clave: Desintoxicación; Lambda-Cyhalothrin; Aceite de Lavandula stoechas; Conejo; Marcadores bioquímicos

INTRODUCTION

Since the start of the Industrial Revolution, pollution has increased considerably and is considered one of the world's biggest problems. It comes from multiple and significant sources: industrial activity, roads, aviation, increased energy consumption, incineration of municipal waste, etc (Sharma *et al*., 2019). Consequently, the deterioration of air, water, and soil quality, as well as its impact on climate and human health, has become a major problem as the situation worsens. Large cities suffer most from global emissions, the adverse effects of which can be felt across the planet for a long time to come (Sabarwal *et al*., 2018). In parallel with rapid development and population growth, efforts must be made to guarantee large quantities of food, which depends on the development of science, particularly pesticides. The systematic and repeated use of plant protection products has led to the emergence of resistance in target organisms and the emergence of endocrine and nervous system disorders in animals (Medithi *et al*., 2021). In Algeria, the use of pesticides in agriculture is becoming more and more common with the increase in cultivated areas (Zamoum *et al*., 2023). 80 types of active ingredients are registered, and these products are put on the market every year and are necessary, even indispensable, tools for farmers to ensure the profitability of a large part of their production (Mokhnane *et al*., 2023). These molecules generally present a risk to the environment due to their ecotoxicity, bioaccumulation potential and endocrine effects. As such, pesticides pose a real public health problem, affecting entire populations. To cleanse the body of these molecules, man has used various means, the most recent being the use of medicinal plants, which are present in the environment and represent a reservoir offering the advantage of a diversity of chemical structure and wide distribution (Al-Farsi *et al*., 2005). Although Algeria covers an area of 2381741 km^2, it has a very diverse floral heritage, particularly in aromatic plants. Two major mountain ranges, the Terran Atlas in the north and the Saharan Atlas in the south, divide the country into three types of environments: relief, morphology, and climate, creating significant biodiversity (Bouzabata, 2015). Around the Mediterranean basin, the use of aromatic plants played a major role in both daily life and rituals in Egyptian, Hebrew, Greek, and Roman civilizations (Ali *et al*., 2019). Essential oils are value-added products that can be used in a various field, including pharmaceuticals, cosmetics, and the food industry. These complex blends can contain hundreds (sometimes more) of ingredients. As it evolves, each plant has its own way of accumulating, storing, and using essential oils. Two of the most common forms are on the surface, in the form of "epidermal glandular hairs", as in the *Lamiaceae* family. Phytotherapy is certainly the best approach to health medicine for both preventive and curative purposes (Rekioua, 2023). To investigate the extent of local plant use in Souk Ahras state, we identified one type of medicinal and aromatic plant *Lavandula stoechas*. The present study aimed to determine the protective effect of *Lavandula* essential oil on several biochemical parameters in local *Cuniculus Lepus* rabbits poisoned by the insecticide Lambda-Cyhalothrin, marketed under the name "Karateka®".

MATERIAL AND METHODS

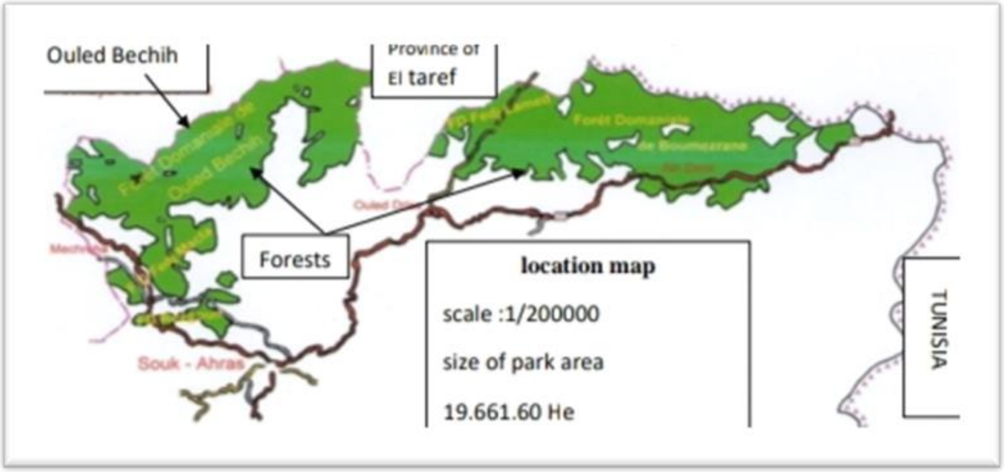
Presentation of the harvesting area

The town of El Machrouha is located to the north of the wilaya in the Souk Ahras region. It is considered a tourist destination, and its healthy, clean climate makes it a place for healing and treating respiratory illnesses. It is located at an important crossroads, where two roads intersect. One is the route Nationale 16 (Annaba - Tébessa), and the other is the railroad line that links the town of Annaba, its wilaya, and the town of Ouenza. The town of Machrouha lies in the extreme north of the Souk Aras wilaya and is bordered to the north by the towns of Bouchegouf (Guelma) and Bouhadjar (El Tarf), as well as the towns of Souk Aras and Hnancha. To the south is the town of Ouled Driss, and to the west is the town of Oued Cheham (Guelma) (Saighi, 2023).

Floristic wealth

El Machrouha region is characterized by many plants and trees that are typical of the Mediterranean climate. It has the densest forests of cork oak and saw oak. This commune's forest heritage offers ecological niches at all levels (Saighi, 2023).

Figure No. 1



Ouled Bechih State Forest location map

Harvesting the plant

Lavender is harvested at flowering time, between March and May. The aerial parts of *L. stoechas* were collected in March 2024 in the Ouled Bchih region of the Elmachroura mountains, Souk Ahras, Algeria, and identified by Dr. Ketfi Louisa, botanist at the botany laboratory of the Faculty of Natural and Life Sciences at Mohammed Cherif Messaadia University. They were then deposited in the botany laboratory herbarium. The aerial parts were dried at room temperature (20 - 25°C) for 14 days.

Figure No. 2

A. *L. stoechas* in its natural state **B.** Dried plant *L. stoechas*

Extraction of Lavandula stoechas essential oils by hydro-distillation

The plant is air-dried, away from light, to preserve the integrity of the molecules and prevent alteration and reproduction by microorganisms. Next, 100 g of dried plant aerial part is placed in a double 1000 mL flask saturated with 530 mL distilled water and boiled for 3 hours, occasionally adding distilled water to prevent the mixture from drying out. The essential oil-filled vapors passing through the condenser are condensed and collected in a clean bottle. (Sarah *et al*., 2017).

Extraction yield

Essential oil yield is defined as the ratio between the mass of essential oil obtained and the mass of plant material (Hassiotis, 2010; Sarah *et al*., 2017):

$$E.O\ yield\ (\%) = [E.O\ mass\ (g) / plant\ mass\ (g)] \times 100$$

Chemical

The product used was a synthetic insecticide belonging to the pyrethroid family. Its active ingredient is lambda-cyhalothrin (LCT). The product's commercial name is KARATEKA®, and it was obtained from the local market.

Animals' rearing

Male *Cuniculus* rabbits were obtained from Pasteur Institute (Algiers), weighing 600 ± 50 g. Animals were maintained in the Animal House of the Biology Department under controlled conditions, in which they were subjected to standard experimental conditions of light, humidity, and temperature. The 'NLFB', food for Leporids" from Blida, Algeria, supplied a standard diet.

Animals' treatment

27 male rabbits were distributed equally into 3 groups. The control group received a standard diet, while the second group received 100 mg/kg/d lambda-cyhalothrin (LCT). The last group was treated with a combination of 100 mg lambda-cyhalothrin (LCT) and 500 mg *Lavandula stoechas* extracts (LS.EO). All administrations were carried out daily in the morning in the diet for one month. The Animal Science Ethics Committee of the University Mohamed Cherif Messadia authorized Animal treatments in Souk Ahras, Algeria, before starting the experiment.

Biochemical assays

At the end of the treatment, the blood was collected, then the serum was centrifuged. Blood samples were collected in dry tubes and centrifuged at 3000 rpm for 10 minutes to obtain serum. The following C-reactive protein (CRP), glucose and lipid profile tests: triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and hepatic parameters: aspartate aminotransferase (AST), alanine aminotransferase (ALT), Alkaline Phosphatase (ALP) were measured using biochemistry (ARCHITECT ci4100) supplied with commercial kits (Spinreact, Spain).

Statistical analysis

Statistical analysis was carried out using R software. Results are presented in the form (mean ± standard deviation), with comparisons between groups made by analysis of variance (one-way ANOVA). The significance of the difference between the control and treated batches was verified using the Tukey test.

RESULTS

Essential oil yield

Table No. 1 shows that the yield of essential oil extracted from the aerial part of *Lavandula stoechas*, with a value of 0.34% recorded.

Table No. 1
***Lavandula soechas* essential oil yield**

Species	***Lavandula stoechas***
Yield (%)	0, 34

Serum biochemical markers

Serum biochemical markers are seen in Table No. 2. The C-reactive protein (CRP) concentration observed in Table 2 shows a significant increase in the LCT group compared with the control. As regards lipid balance, the results shown in Table No. 2 reveal a non-significant difference in glucose, total cholesterol, and HDL levels in the treated group compared with the control, while circulating LDL and triglyceride concentrations showed a highly significant increase in the LCT group compared with the control. According to the results shown in Table No. 2, a highly significant increase was recorded in the enzymatic activity of ALAT, ASAT, and PAL in the LCT-treated group compared with the control group. Meanwhile, treatment supplemented with *L. stoechas* essential oil improved the target biochemical parameters of this study.

Table No. 2
Variation in the levels of some biochemical parameters in rabbits in the different experimental batches (X ± SD) compared with the control

Markers	Control	LC T	LCT + LS.EO	Observation
C-reactive protein (CRP) (mg/L)	2,14 ± 0,28	21,41 ± 3,48	16,21 ± 4,14	a**, b**
Glucose(U/L)	1,26 ± 0,16	1,34 ± 0,37	1,24 ± 0,43	a=NS, b=NS
Total Cholesterol (g/L)	1,03 ± 0,40	1,16 ± 0,32	1,11 ± 0,51	a=NS, b=NS
High-density lipoproteins HDL (g/L)	0,31 ± 0,07	0,27 ± 0,03	0,23 ± 0,03	a=NS, b=NS
Low-density lipoproteins LDL (g/L)	0,48 ± 0,10	1,45 ± 0,34	0,56 ± 0,17	a**, b=NS
Triglycerides(g/L)	0,89 ± 0,16	1,61 ± 0,54	1,57 ± 0,36	a**, b=NS
Aspartate aminotransferase (ASAT U/L)	37,58 ± 1,32	88,72 ± 8,72	54,30 ± 6,57	a***, b*
Alanine aminotransferase (ALAT U/L)	55,68 ± 6,33	112,88 ± 15,05	91,65 ± 14,34	a***, b**
Alkalin Phosphatase (ALPU/L)	70,06 ± 4,29	99,51 ± 13,6	96,57 ± 11,72	a**, b**

LCT: 100 mg/kg/d of lambda-cyhalothrin; LCT+LS.EO: 100 mg/kg/d of lambda-cyhalothrin + 500 mg *Lavandula stoechas* essential oil. NS: No significant *p*<0.05; *: Significant *p*<0.01; **: Highly significant, *p*<0.001; *: Very highly significant *p*<0.0001. a=Control x LCT; b=Control x LCT+LS.EO**

DISCUSSION

Essential oil yield

The yield of essential oil obtained by Clevenger's method is 0.34%. The low yield of essential oil maybe due to the nature of the plant itself and its environment (species, harvesting period, temperature, humidity, climate, soil type). This result corroborates with those of Benabdelkader (2012), who showed that the yield of essential oils extracted by hydrodistillation from 11 populations of *Lavandula stoechas* from three Algerian wilayas (Ain Defla, Médéa, Chlef and two regions at virtually the same location in the wilaya of Bouira (Lakhedaria, Taguedit)), presented EO contents of (0.36%; 0.34%; 0.52%; 0.6%; 0.52%). On the other hand, the yield for the wilaya of Bouira was 1.30% and 137% (Ben Abdelkader *et al*., 2011).

Chemical contaminants, especially pesticides, cause several diseases (Buscail *et al*., 2015; Nicolopoulou-Stamati *et al*., 2016). The liver is a major organ whose primary tasks are the decomposition of exogenous molecules and the reinforcement of the immune system (Bürgisser *et al*., 2021). It is also an indicator of pesticide toxicity (Magdy *et al*., 2016).

CRP is a protein synthesized by the liver. When inflammation occurs, the liver releases more CRP protein into the bloodstream (Calvino *et al*., 2014). The results obtained in our study reveal a highly significant increase in CRP levels in the LCT and LCT+LS.EO treated groups compared with the control. These results are consistent with the work of (Pandey *et al*., 2019), who showed that chronic exposure of 37 male rats to Roundup (0, 5, 10, 25, 50, 100, and 250 mg/kg (bw) induced a significant increase in CRP, which suggest the development of inflammation in lipid and liver organs. The same observation was recorded by (Waring *et al*., 2013; Woolbright & Jaeschke, 2018).

In the present experiment, adding *Lavandula stoechas* essential oil extract decreased glucose concentrations compared with the control and treated groups. This decrease is probably due to the protective effect of essential oils against the toxicity of lambda-cyhalothrin. These results align with other published work on lambda-cyahlothrin toxicity in 24 rabbits (Basir *et al*., 2011). In contrast to our results, the work of Shakoori *et al*. (1993) and Boumezrag *et al*. (2021), reported hyperglycemic concentrations in rabbits intoxicated with LCT. According to these researchers, the hyperglycemia observed may be due to the formation of glucose from a non-carbohydrate source carbohydrate source by increasing the activity of enzymes involved in gluconeogenesis (Afshar *et al*., 2008). on the other hand, some insecticides increase glucose release from the liver into the blood by activating glycogenolysis.

According to the results, an increase in lipid markers was recorded in the LCT-treated group, probably due to adipose tissue degradation affecting energy and lipid metabolism (Chen *et al*., 2018). we note that the combination of *Lavandula stoechas* essential oil and lambda-cyhalothrin (LCT) normalized the levels of these parameters. The hypercholesterolemia observed in this study may be due to the pesticide's inhibitory effect on hepatic cyt-p-450 enzymes (Yousef *et al*., 2003). it has also been confirmed that pesticides cause changes in hepatic cell membrane permeability and that their accumulation in the liver disrupts lipid metabolism, thereby increasing plasma cholesterol levels (Shakoori *et al*., 1990). In the assessment of cardiovascular disease, individual lipoprotein concentration is considered one of the best indicators (Kroliczewska *et al*., 2018; Makhlouf *et al*., 2020). Long exposure to low or high doses of insecticide can disrupt the biochemical profile and cause functional changes in certain target organs (Fetoui *et al*., 2010; Khaldoun *et al*., 2017).

The present results show that lambda-cyhalothrin treatment induces liver toxicity, which is characterized by a significant increase in the enzymatic activity of ASAT, ALAT, and PAL in rabbits. These results are in line with several works that indicate that LCT e induces elevated serum AST and ALP levels in rats and rabbits (Basir *et al*., 2011; Abdul-Hamid *et al*., 2020; Ali *et al*., 2022; Omar *et al*., 2022; Settar *et al*., 2023). ALT is considered a more accurate and sensitive indication of hepatocellular injuries than AST in the animal laboratory, and ALP has been suggested for assessing hepatobiliary lesions (Ramaiah, 2007). However, the increase in these indicators is a sign of liver damage, which is explained by the leakage of enzymes from the tissue into the blood due to altered membrane permeability (Martínez *et al*., 2018). In many organs, cellular damage is determined by the presence of certain cytoplasmic enzymes in the blood, and this is the case after lambda-cyhalothrin accumulation in hepatocytes. Similarly, Boumezrag *et al*. (2021), suggest an increase in (AST) activity in both treated groups, which may be due to increased cell membrane permeability. The same result was observed in the work of Shakoori *et al.* (1990), who recorded an increase in ALT activity in rabbits treated with oral LCT after 15 days. However, several studies (Morgan & Osman, 2007; Fetoui *et al*., 2009; Çavuşoğlu *et al*., 2011) have noted increased serum activities of alanine aminotransaminase (ALT) and aspartate aminotransaminase (AST) in pyrethroid-treated animals, and it has been suggested that biliary insufficiency may indicate an increase in alkaline phosphatase (Moss & Butterworth, 1974).

Lavender essential oil is a mixture of volatile organic compounds. Its composition is mainly related to climatic and geographical conditions and genetic differences (Pascual *et al*., 1983; Nogueira & Romano, 2002). *L. stoechas* essential oils are characterized by their powerful scavenging capacity due to the presence of phenolic compounds (Matos *et al*., 2009). The work of (Ahmad *et al*., 2011) showed that xenobiotic-treated rats became hyperglycemic due to the destruction of pancreatic β-cells (Szkudelski, 2002) and changes in biochemical biomarkers and liver function (Milagro & Martinez, 2000). On the other hand, insulin deficiency renders lipoprotein lipase deactivated, resulting in hypertriglyceridemia. Pushparaj *et al.* (2001), have shown that *L. stoechas* essential oils can act as an anti-hyperglycemic agent by increasing the action of plasma insulin. However, the work of (Barazandeh, 2002) suggests that treatment with *L. stoechas* essential oil restored circulating concentrations of ALAT and ASAT, the same results recorded in the work of Amer *et al*. (2022), illustrating the hepatoprotective effects of lavender against xenobiotic-induced toxicity. Treatment with *L. stoechas* essential oils restored the activity of these enzymes, which may be due to the reduction in oxidative stress. Similar studies have shown the richness of phenolic compounds in lavender extracts and essential oils of *L. stoechas* (Matosa *et al*., 2009). These molecules are the main source of this plant's antioxidant capacity, scavenging free radicals such as hydroxyl (OH), which react with all biological substances, the most sensitive of which are polyunsaturated fatty acids, leading to lipid peroxidation (Kumazawa *et al*., 2002). Lavender essential oils reduce the toxic effect of lambda-cyhalothrin, mainly thanks to their antioxidant characteristics, and they play a major role as hepatoprotective products. In the combined group, the addition of the essential oil of *Lavandula stoechas* considerably reduced the concentrations of ALAT, ASAT, and PAL enzyme activities, where the antioxidants present in this plant can stabilize hepatocellular membranes and protect molecules against the toxic effects of lambda-cyhalothrin.

CONCLUSION

Chronic exposure to lambda-cyhalothrin adversely affects the liver of male rabbits by modifying the biomarkers studied. This oil reduced and corrected the toxic effect of the insecticide and reversed the alteration of biomarkers, bringing them back to near-normal levels. In light of the results obtained in this study, new information has been added concerning the biochemical alterations caused by lambda-cyhalothrin. It is important to continue the work using different doses of the insecticide over different time intervals to assess dose-effect and dose-response relationships, as well as carrying out scientific work targeting the anti-inflammatory, antioxidant, antimicrobial, insecticidal, larvicidal, hepatoprotective, nephroprotective, antidiabetic and anticancer effects of the plant's essential oils.

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