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Evaluating the Hepatoprotective Potential of Ginger Ethanolic Extract Against Lambda-Cyhalothrin-Induced Toxicity in Male Rats

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A B S T R A C T

Ginger (*Zingiber officinale* Rosc.) is a traditional plant that is widely used as a spice or folk medicine. Lambda-cyhalothrin (LCT) is a synthetic pyrethroid that is widely used to control insecticide. The present study aimed to evaluate the potential protective effect of ginger ethanolic extract (GEE) on liver toxicity experimentally induced by LCT in albino rats. The experiment involved thirty adult male rats (Rattus norvegicus), randomly allocated to one of three groups (n=10/group: control group, administered distilled water orally for 12 weeks; LCT-treated group, received 5.43 mg/kg BW (1/15 LD_{50} dose calculated in this study as 81.5 mg/kg BW) orally, for 12 weeks; LCT-GEE-treated group, received the same dose of LCT along with GEE at 100 mg/kg BW orally. Body weights were recorded at the start, and at 4, 8, and 12 weeks into the treatment. Upon completion of the study, blood samples were collected for liver enzymes alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) assessment. Additionally, liver samples were collected for histopathological examination. The LCT-treated group exhibited a significant decrease in BW at 4, 8, and 12 weeks compared to the control and LCT-GEE-treated groups. The LCT-treated rats showed increased levels of liver enzymes ALP, AST, and ALT. Histological evaluation revealed signs of liver necrosis, mononuclear cell infiltration, and congestion in LCT-treated rats. These pathological changes were less pronounced in the LCT-GEE-treated group, indicating a mitigating effect. The study demonstrates the detrimental effects of LCT on the health of male rats, particularly regarding BW and liver health. Alongside, it highlights *Zingiber officinale*'s potential in reducing these adverse effects, suggesting its efficacy in environments with LCT exposure.

Keywords: Lambda-cyhalothrin, *Zingiber officinale*, liver, rat

INTRODUCTION

Pesticides, encompassing insecticides, rodenticides, herbicides, fungicides, and fumigants, play a crucial role in agricultural yield by controlling pests that significantly reduce the value of crops (1). Despite their beneficial effects in enhancing food production and preservation, the use of pesticides raises significant health concerns (2, 3). Pesticide residues are considered a major risk factor in public health, with some pesticides possessing the potential to be toxic to non-target species including humans (4).

Among pesticides, pyrethroid insecticides, known for their lipophilic nature and composed of an alcohol and an acid moiety, have been extensively used in agriculture, household pest management, and veterinary formulations (5,6). Lambda-cyhalothrin (LCT, α-cyano-3-phenoxybenzyl-3-(2-chloro-3,3,3-trifluoro-1 propenyl)-2,2-dimethylcyclopropane carboxylate), a synthetic type II pyrethroid insecticide, is widely employed against a broad spectrum of arthropods. Nonetheless, several studies have demonstrated its potential to induce genotoxicity, mutagenicity, embryotoxicity, hepatotoxicity, and

nephrotoxicity in rodents (7-10), underlying the need for effective mitigation strategies (11).

Ginger (*Zingiber officinale* Roscoe), a widely used culinary and medicinal herb, has been extensively studied for its protective effects against pesticide-induced toxicities. Numerous studies have highlighted the potential of ginger and its bioactive compounds, such as gingerols, in mitigating the dangerous effects of pesticides on various organs, including the liver, kidneys, and brain, attributing its protective effects to potent antioxidant enzymes, free radical scavenging, and anti-inflammatory properties (12-28). Additionally, studies have further reinforced the role of ginger in enhancing the body's defense mechanisms, pointing to a decrease in oxidative stress markers and an increase in the activities of detoxifying enzymes when ginger is administered alongside a range of toxins, including ethanol, carbon tetrachloride (CCl_4), bromobenzene, acetaminophen, and lead suggesting its broader application in countering liver damage (29-36).

While the defensive potential effect of ginger against various toxins has been established, research investigating its efficacy against LCT-induced hepatotoxicity remains scarce. This study, therefore, aims to estimate the potential protective effects of ginger ethanolic extract in mitigating LCT-induced liver toxicity in male rats.

MATERIALS AND METHODS

Ethical Approval

Ethical approval for the study was obtained from the local Animal Care and Use Committee, College of Veterinary Medicine, University of Baghdad (Approval Number: P.G/1915, dated September 19, 2023.

Plant Material and Extraction

Fresh ginger (*Zingiber officinale*) commercially purchased a reference sample was authenticated by the Iraqi National Herbarium, Directorate of Seed Testing and Certification belong to the Iraqi Ministry of Agriculture with a certified Number of 5223 on 8th November 2023.

For 24 h at room temperature, 50 g of plant material was steeped in 200 mL of 100% ethanol (Fancy, India). The resultant extract was then run through Whatman No. 1 filter paper. The filter residue was removed twice using the same method. The resulting filtrates were mixed, and a rotary evaporator operating at 40°C was used to rotary evaporate them. The yield was maintained at -20°C until 500 mg of extract and 25 mL of cold water were used as stock solutions (37) with 0.5 mL of this solution being used for every 100 g/BW.

LCT Dose Calculation

The LD_{50} was calculated using the Up-and-Down method (38). The sequential dosing and administered, k= value from the appendix, and d = difference between dose levels. In this test, single doses were sequentially administered to each animal at intervals of 24 h. Animals that died within 24 h after showing clinical signs of poisoning were observed. According to a predetermined dose progression factor (10 mg/kg BW), the dose was decreased after each death and increased after each survival.

In the determination of the experimental dose of LCT, a $1/15^{th}$ LD_{50} dose (5.43 mg/kg BW) was chosen to reflect sub-lethal, environmentally relevant exposure levels. Importantly, this response outcomes were recorded, facilitating the calculation of the oral LD_{50}. The dose of LCT LD_{50} was determined using the following equation: LD_{50} = xf + kd, where xf = last dose. The study utilized a commercial lambda cyhalothrin product as opposed to a purified laboratory-grade chemical. This decision was made to better simulate real-world scenarios, as animal owners typically utilize commercially available products for pest control, including tick treatment. Such products often contain a mixture of active ingredients and adjuvant, which can influence the toxicity profile and metabolic fate of the pesticide in vivo. Thus, the selected dosage not only represents a sub-toxic threshold but also aligns with the concentrations that animals might realistically encounter, thereby enhancing the translational value of the research findings.

Animals and Experimental Design

A total of 30 healthy adult male albino rats (Rattus norvegicus), aged about three months and weighing 250-300 g, were utilized in this experiment. The rats were bred and maintained at the animal house, College of Veterinary Medicine, University of Baghdad. Prior to the initiation of the experiment, the rats were acclimated for 4 weeks in standard cages (20×30×50 cm) with 5 animals per cage under controlled environmental conditions of 22 (±3) °C, 50(±5)% relative humidity, and a 14/10-h light/dark cycle. Standard feed pellets and water were available ad libitum throughout the experimental period.

The rats were randomly allocated into three treatment groups of ten animals. The control group was administered distilled water orally for 12 weeks to establish baseline responses. The LCT-treated group was exposed orally to a sub-lethal dose of 1/15 of LD_{50} (5.43 mg/kg BW) 0.5 mL to 100 gm/BW Lambda-cyhalothrin (TORNADO 2.5 EC, VAPCON, Jordan). The LCT-GEE group was treated with the same dose of LCT for 12 weeks, 100 mg/kg BW of ginger ethanolic extract orally.

Blood Sample Collection

For the last part of the study, about 4 mL blood samples from all animals (n=10 group) were collected under chloroform inhalation anesthesia (Merck, Germany) via cardiac puncture using 5 mL disposable syringes. The blood samples were collected in plain gel tubes, left at room temperature for 2 h to be clotted, and centrifuged at 3500 rpm for 5 min. The sera were aliquoted into gel tubes (BD Vacutainer, UK) and kept frozen at -20°C until used for biochemical analysis.

Biochemical Analysis

Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were determined using

commercially available kits (BioSystems, Spain). For ALT, 100 µL of blood serum was combined with 1000 µL of reagent 1 and let to sit for 5 minutes. Following the addition of 250 µL of reagent 2, the absorbance was determined at λ=340 nm. According to the manufacturer's methodology and published ALT methodologies, the observed absorbance was ALT (39). For AST, 100 µL of blood serum were combined with 1000 µl of reagent 1 and let to sit for 5 min. Following the addition of 250 µl of reagent 2, the absorbance was determined at λ=340 nm. The manufacturer's procedure and AST-reported techniques were followed when measuring the absorbance (40).

The serum ALP activity was measured using a commercially available kit (ALKALINE PHOSPHATASE (ALP)-DEA, BioSystems, Spain), following the manufacturer's protocol. The assay is a kinetic colorimetric based on the ability of ALP to catalyze the hydrolysis of 4-nitrophenyl phosphate to form 4-nitrophenol and inorganic phosphate in the presence of diethanolamine. In the reaction mixture containing diethanolamine buffer and 4-nitrophenyl phosphate substrate, ALP present in the serum samples hydrolyzes 4-nitrophenyl phosphate. The reaction is monitored kinetically by measuring the increase in absorbance at 405 nm due to the formation of 4-nitrophenol over time. The rate of increase in absorbance is directly proportional to the ALP concentration in the sample. The ALP activity was then expressed in units per liter (U/L), where one unit is defined as the amount of enzyme that catalyzes the formation of 1 micromole of 4-nitrophenol per minute under the specified conditions of the test (41).

Histopathological Examination

After blood collection, rats were euthanized using overdose anesthesia and liver tissues were collected and fixed in 10% phosphate-buffered formalin for 48 h. Following fixation, samples were sectioned to 5 µm thickness and placed in plastic cassettes. Dehydration and clearing of the tissues were automated using a Histo-Line Laboratories ATP1000 tissue processor (Italy). Subsequently, the dehydrated tissues were embedded in paraffin wax via a Histo-Line Laboratories HESTION TEC2900 embedding system, with temperature regulation managed by a TEC2900 Thermal Console (Histo-Line Laboratories, Italy). Tissue blocks were then sectioned at 4-5 µm thickness using a Histo-Line Laboratories MRS3500 rotary microtome (Italy). The sections were floated in a water bath (37°C) and temperature-controlled hot plate, both regulated by the TEC2900 Thermal Console, before mounting on glass slides. Staining was performed using Hematoxylin and Eosin (H&E, Dakocytomation, Denmark). The stained tissue sections were examined under a light microscope (Olympus, Japan) at 40× and 10× magnifications for detailed histological assessment **(42)**.

Statistical Analysis

A program was used to determine the effects of various circumstances on the research parameters. The Least Significant Difference (LSD) test (Analysis of Variance, ANOVA) was used to statistically compare between means. A *P*-value of < 0.05 was considered as statistically significant (43).

RESULTS

The acute toxicity study found that the oral LD_{50} of LCT as estimated by the Up and Down method were 81.5 mg/kg BW in male rats for 24 h (Table 1).

Table 1. Oral LD_{50} of Lambda-cyhalothrin (LCT) in adult male rats as calculated by Up and Down method

Initial dose mg/kg BW	Final dose mg/kg BW	Number of animals	Result after 24 h	LD_{50} mg/kg BW
119	89	8	XXXXOXOX	81.5

LD_{50}=xf+kd, LD50=89+(-0.741)×10, LD_{50}=81.5 mg/kg BW. xf=last dose administrated, k= value from appendix (-0.741), d= difference between dose levels (10). O=Survival animal, X=Dead animal

Body Weight

Table 2 illustrates the impact of ginger ethanolic extract on BW changes in male rats exposed to LCT-induced liver toxicity. Initially, there were no statistically significant differences in BW among the control group, the LCT-treated group, and the LCT-GEE group at baseline (Day 0). However, notable distinctions emerged over time. By the 4th week of treatment, a significant (*P*<0.05) reduction in BW was observed in the LCT-treated group compared to both control and LCT-GEE groups. This trend of significant weight decrease persisted at the 8th and 12th weeks of treatment, indicating the adverse effects of LCT on BW, which were mitigated by the co-administration of ginger.

Table 2. Effect of ginger ethanolic extract (GEE) on body weight (g) of male rats subjected to Lambda-cyhalothrin (LCT)-induced liver toxicity

Time	Control	LCT	LCT-GEE
Zero day	190.33±0.33 [a]	190.00±0.57 [a]	190.67±0.67 [a]
4 Week	215.67±2.40 [a]	183.33±0.33 [c]	208.00±0.57 [b]
8 Week	255.33±2.33 [a]	171.00±0.57 [c]	233.67±0.88 [b]
12 Week	298.67±0.88 [a]	160.33±0.88 [c]	262.00±1.53 [b]

Values are means±SEM, n=10. Means with different lowercase letters in the same row are significantly different (*P*≤0.05)

Liver Enzymes

By the 12th week, there was a significant increase (*P*<0.05) in the serum levels of hepatic enzymes (AST, ALT) in the LCT-treated group compared to the control group, indicating liver damage (Table 3).

Table 3. Effect of ginger ethanolic extract (GEE) on serum liver enzymes ALP, AST, and ALT of male rats subjected to Lambda-cyhalothrin (LCT)-induced liver toxicity

Group	ALT (µg/dL)	AST (µg/dL)	ALP (U/L)
Control	35.50±0.95 [c]	160.90±1.64 [c]	390.9±23.11 [b]
LCT	50.20±1.17 [a]	285.70±1.68 [a]	586.0±1.810 [a]
LCT-GEE	40.60±0.67 [b]	186.60±1.54 [b]	412.1±2.050 [b]

Values are means ± SEM, n=10. Means with different lowercase letters in the same column are significantly different (P≤0.05

This increase was significantly (*P*<0.05) higher in the LCT-treated group than in both the LCT-GEE and control groups. ALP levels were also significantly (*P*<0.05) elevated in the LCT-treated group, underscoring pronounced liver

stress and damage. This elevation was significantly reduced in the LCT-GEE group, suggesting the protective effect of ginger

Histopathology

Histopathological examination of the liver in rats treated with LCT for 12 weeks revealed significant pathological alterations, including increased activity of Kupffer cells, marked portal vein dilation, congestion, and mild periductal mononuclear cell (MNC) infiltration (Figure 1 A). Furthermore, moderate to severe focal hepatic necrosis was observed in the portal region, along with hepatic cord atrophy and additional MNC infiltration (Figure 1 B). In contrast, the liver sections from rats in the LCT-GEE group displayed only mild periductal MNC infiltration, with no significant alterations in the hepatic cords, indicating a protective effect of ginger against LCT-induced liver damage (Figure 1 C). In Figure (1 D) demonstrating no significant changes in hepatic cords.

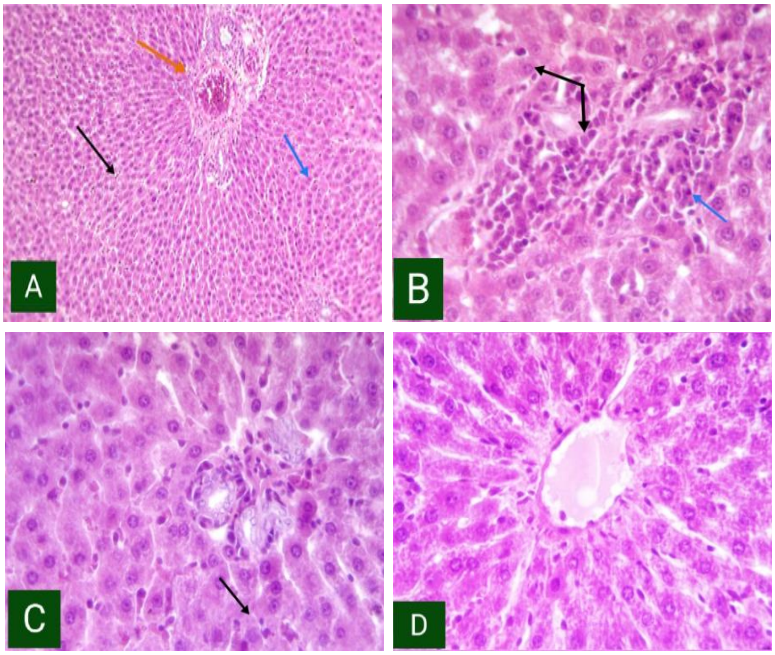

Figure 1. Histological sections of liver in adult male rats at (H&E, 40×): **(A)** Lambda-cyhalothrin (LCT) treatment indicating Kupffer cell prominence (blue arrow), portal vein dilation and congestion (orange arrow), and mild periductal mononuclear cells (MNCs) infiltration (black arrow); **(B)** LCT treatment showing moderate to severe focal hepatic necrosis (black arrow), hepatic cords atrophy (blue arrow); **(C)** Lambda-cyhalothrin+ginger treatment demonstrating mild periductal MNCs infiltration (black arrow); **(D)** demonstrating no significant changes in hepatic cords

DISCUSSION

This study demonstrates significant BW loss in male rats exposed to LCT over periods of 4, 8, and 12 weeks. The observed reduction in body weight can be attributed to the toxic effects of LCT, which likely impaired food conversion efficiency and reduced nutrient intake. This correlation is supported by prior research indicating LCT-induced weight loss across different species, including rats and rabbits. The mechanism behind this phenomenon may involve LCT's interference with metabolic processes, leading to diminished energy production and accumulation (44).

Ginger's protective role against LCT-induced weight loss can be partly explained by its rich composition of proteins, small peptides, flavonoids, phenols, and other phytochemicals. These components are believed to activate central serotonin signaling pathways, which are crucial for regulating satiety. Thus, ginger might mitigate weight loss by enhancing nutrient absorption and improving overall metabolic health, consistent with its historical use in herbal medicine to support digestive health (45).

Regarding liver enzyme elevation (ALT and AST), our findings corroborate the established understanding that LCT exposure results in significant liver damage, as evidenced by increased enzyme levels. This damage is indicative of hepatocellular injury, where enzyme leakage occurs due to compromised cellular integrity (46). The administration of *Zingiber officinale* extract led to a reduction in these enzyme levels, suggesting its hepatoprotective effects. This observation is in line with existing literature that attributes ginger's liver-protective effects to its potent antioxidant properties, offering therapeutic benefits by enhancing the liver's detoxifying capabilities (47).

Histopathological analysis revealed marked leukocytic infiltration and mononuclear cell (MNC) infiltration in the liver following LCT treatment, indicating hepatic necrosis. This is consistent with studies on other pyrethroids, such as

fenvalerate and deltamethrin, which have been shown to disrupt antioxidant defense mechanisms and increase lipid peroxidation, contributing to oxidative stress and subsequent tissue damage in the liver, kidney, and testis (48,49). Furthermore, the liver histopathology in LCT-exposed animals mirrors findings in previous research on the effects of cypermethrin, another pyrethroid, highlighting severe perihepatitis, necrosis, and congestion, underscoring the hepatotoxic potential of pyrethroids (50, 51).

The therapeutic effects of ginger in this context may be attributed to its diverse pharmacological actions, as well as anti-platelet, antioxidant, anti-inflammatory, and anti-hepatotoxic activities. These properties prevent the aggregation of MNCs and mitigate inflammation and oxidative stress, thereby offering protection against LCT-induced liver damage (52).

In conclusion, this study provides compelling evidence of the detrimental effects of LCT on male rats, particularly in terms of BW reduction and liver damage. Concurrently, it highlights the potential protective role of ethanolic extract of *Zingiber officinale* in mitigating these effects, suggesting its beneficial use as an antioxidant in contexts of LCT exposure.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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تقييم إمكانات الحماية الكبدية لمستخلص الزنجبيل الإيثانولي ضد السمية التي يسببها لامدا-سيهالوثرين في ذكور الجرذان

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الخلاصة

الزنجبيل هو نبات تقليدي يستخدم على نطاق واسع كتوابل أو في الطب شعبي بينما الامبيدا سيهالوثرين هو بيريثرويد اصطناعي يستخدم على نطاق واسع للسيطرة كمبيدات حشرية. هدفت الدراسة الحالية إلى تقييم التأثير الوقائي المحتمل لمستخلص الزنجبيل الإيثانول على سمية الكبد المستحثة تجريبيا بواسطة لامبيدا سيهالوثرين في الجرذان البيضاء. شملت التجربة ثلاثين من ذكور الجرذان البالغة ، تم توزيعها عشوائيا على واحدة من ثلاث مجموعات (ن = ١٠ / مجموعة): قسمت لقفصين كل مجموعة مجموعة السيطرة ، اعطيت الماء المقطر عن طريق الفم لمدة ١٢ أسبوعا.المجموعة المعالجة بلامبيدا سيهالوثرين ، تلقت ٥،٤٣ مغ/كغ من وزن الجسم (١٥/١ جرعة المميتة الوسطية محسوبة في هذه الدراسة على أنها ٨١،٥ مغ/كغ من وزن الجسم) عن طريق الفم، لمدة ١٢ أسبوعا؛ بينما تلقت المجموعة المعالجة بلامبيدا سيهالوثرين و مستخلص كحولي للزنجبيل نفس الجرعة من لابيدا سيهالوثرين مع مستخلص الكحولي للزنجبيل (١٠٠ ملغم / كغم من وزن الجسم) عن طريق الفم. تم تسجيل أوزان الجسم في البداية ، وبعد ٤ و ٨ و ١٢ أسبوعا من العلاج. عند الانتهاء من التجربة ، تم جمع عينات الدم لتقييم إنزيمات الكبد ألانين أمينوترانسفيراز (ALT) ، والأسبارتات أمينوترانسفيراز (AST) ، والفوسفاتيز القلوي (ALP). فضلا عن ذلك ، تم جمع عينات الكبد للفحص النسيجي المرضي. أظهرت المجموعة المعالجة بالامبيدا سيهالوثرين انخفاضا كبيرا في وزن الحيوان في ٤ و ٨ و ١٢ أسبوعا مقارنة بمجموعة السيطرة ومجاميع المعالجة بالامبيدا سيهالوثرين ومستخلص الكحولي للزنجبيل. أظهرت الجرذان المعالجة بالامبيدا سيهالوثرين مستويات متزايدة من إنزيمات الكبد ALP و AST و ALT. وكشف التقييم النسيجي عن علامات نخر للكبد وارتشاح الخلايا أحادية النواة والاحتقان في الجردان المعالجة بالامبيدا سيهالوثرين وكانت هذه التغيرات المرضية أقل وضوحا في المجموعة المعالجة بالامبيدا سيهالوثرين ومستخلص الكحولي للزنجبيل ، مما يشير إلى وجود تأثير مخفف لتاثر بالامبيدا سيهالوثرين على الكبد اوضحت الدراسة الآثار الضارة للامبيدا سيهالوثرين على صحة ذكور الجردان ، وخاصة فيما يتعلق بوزن الجسم والكبد. إلى جانب ذلك ، فإنه يسلط الضوء على إمكانات زنجبيل في الحد من هذه الآثار الضارة ، مما يشير إلى فعاليته كمضاد للأكسدة في البيئات التي تتعرض فيها لمبيد لامبيدا سيهالوثرين.

الكلمات المفاحية: لامبيدا سيهالوثرين، زنجبيل، الكبد، الجرذان