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Lauric acid attenuates oxidative stress and liver injury in a letrozole-induced mouse model of polycystic ovary syndrome

Elnaz Harooni[1], Akram Ahangarpour[2]*, Vahid Radmehr[3]*, Razieh Kazemzadeh[1] & Seyed Sobhan Bahreiny[4]

[1]Student Research Committee, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, 613571-5794 Iran

[2] Persian Gulf Physiology Research Center, Medical Basic Sciences Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, 613571-5794, Iran

[3] Diabetes Research Center, Health Research Institute, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, 613571-5794 Iran

[4] Department of Physiology, Faculty of Medicine, Tehran University of Medical Sciences, Poorsina Ave, Tehran, 1416634793 Iran

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Polycystic ovary syndrome (PCOS) is a common disorder that affects women of reproductive age. It is associated with various health complications, including liver dysfunction. Lauric acid (LA), a medium-chain fatty acid abundant in coconut oil, possesses antioxidant and metabolic properties. However, research on LA's protective effects against letrozole (LETZ)-induced liver damage is limited. This study aimed to evaluate the beneficial effects of LA on LETZ-induced hepatotoxicity in adult PCOS mice. The experiment involved four groups: 1) control, 2) LA (150 mg/kg), 3) LETZ (6 mg/kg), and 4) LETZ + LA. After 15 days of LA treatment, plasma levels of liver enzymes, hepatic malondialdehyde (MDA), and antioxidant enzyme levels were measured. TNF-α and HNF-4α mRNA expressions, and histopathological assessment were evaluated. LETZ-treated mice exhibited elevated liver enzymes and MDA levels, diminished antioxidant enzyme content, increased TNF-α, reduced HNF4α expression, and altered liver tissue histology. LA attenuated these alterations by significantly reducing liver enzymes and MDA levels, increasing antioxidant activity, reducing TNF-α and increasing HNF4α expressions, and improving liver histology. LA treatment exhibited hepatoprotective effects in LETZ-induced PCOS mice by modulating oxidative stress and HNF-4α expression. These findings suggest potential therapeutic applications of LA in managing PCOS-associated liver complications.

Keywords: Lauric acid, liver, oxidative stress, mice, polycystic ovary syndrome

Introduction

Polycystic ovary syndrome (PCOS) is a prevalent disorder affecting 5-20% of women of reproductive age. This disorder is characterized by excessive androgen production, irregular ovulation, and endocrine and metabolic problems[1]. Although extensive research has been conducted, the mechanisms underlying PCOS remain unclear. However, PCOS is associated with multiple health complications, including insulin resistance, inflammation, and liver dysfunction[2]. Brown et al. first documented a case of non-alcoholic fatty liver disease (NAFLD) in a woman with PCOS[3]. Research suggests that endogenous increases in testosterone levels are associated with PCOS and NAFLD[4, 5].

Oxidative stress (OS) is associated with PCOS in the liver. OS leads to the development of liver abnormalities, characterized by elevated liver enzyme levels[6]. OS in the liver results in high levels of hepatic biomarkers, such as alanine transaminase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP)[7]. Hepatocyte nuclear factor 4 alpha (HNF4-α) is a key regulator of hepatocyte gene transcription, making it vital for liver function and regulating various liver metabolic pathway[8]. Several studies have demonstrated that HNF4-α is widely targeted by cytokines during inflammatory conditions. It has been suggested that cytokines such as tumor necrosis factor-alpha (TNF-α) negatively impact HNF4-α transcription on target genes and subsequently cause liver damage[9].

Coconut oil is considered a healthy oil and has various benefits, including anti-toxic and protective effects[10]. Lauric acid (LA), a medium-chain fatty acid with 12 carbon atoms, is derived mainly from coconut oil (45-53%)[11].LA is also found in various foods, including fruits, seeds, and milk, and accounts for approximately half of the fatty acid content in palm kernel oil[12]. Animal studies have shown that LA

*Correspondence:
E-mail: vahid.radmehr2@gmail.com;
akramahangarpour@gmail.com

reduces oxidative stress and liver inflammation[7, 13]. Recent studies have also emphasized the potential of LA in metabolic disorders, such as obesity and insulin resistance[13, 14]. There is no direct research on the ameliorating effects of LA in PCOS models; however, there is evidence that LA can influence reproductive parameters, such as the estrous cycle[14]. Given the evidence of liver damage in patients with PCOS and the key role of hyperandrogenism, this study aimed to investigate the impact of LA, a beneficial fatty acid in a letrozole (LETZ)-induced PCOS mouse model.

Materials and methods

Animal maintenance

This study involved 40 mature female NMRI mice (7-8 weeks old) weighing 20 - 30 g. The mice were kept under conditions with 12 h light-12 h dark periods, the room temperature 20 ± 4 °C, and had unrestricted access to food and water. All animal experimental procedures were performed in compliance with the Experimental Animal Guidelines of Jundishapur University of Medical Sciences in Ahvaz, Iran, and received approval (IR.AJUMS.AEC.1403.016) in accordance with the Guide for the Care and Use of Laboratory Animals. One week before the start of the experiment, the animals were brought to the laboratory for acclimatization.

Chemicals and reagents

LA, Tween-20, and carboxymethyl cellulose (CMC) were purchased from Sigma-Aldrich. LA was dissolved in Tween 20 /normal saline and administered via oral gavage. LETZ tablets (2.5 mg) were obtained under the brand name Letrax (Abu Raihan Pharmaceutical Co. Iran) and dissolved in 1% CMC.

Induction of the PCOS Model and grouping

The PCOS induction was achieved through daily oral administration of LETZ at a dose of 6 mg/kg for 21 days. The model was confirmed by elevating blood testosterone levels and ovarian cystic follicles and observing cycle disruption in animals. According to the Rotterdam criteria, PCOS is defined as having two of the three criteria[15]. The animals were divided into four groups (n=10) as follows:

Group 1: control vehicle, CMC was administered orally for 21 days + LA vehicle for the last 15 days.

Group 2: CMC was administered orally for 21 days + LA (150 mg/kg) was given for the last 15 days.

Group 3: LETZ was administered orally for 21 days + LA vehicle was given for the last 15 days.

Group 4: LETZ was administered orally for 21 days + LA (150 mg/kg) was given for the last 15 days.

The experimental design and treatment timeline are presented in (Fig. 1).

Sample collection and biochemical analysis

Following anesthesia, blood was collected and transferred to an EDTA-containing tube and centrifuged for 10 min at 3000 rpm. The plasma was stored at -20 °C for subsequent tests. The livers were isolated, rinsed with normal saline, and sectioned. A portion of the liver tissue was snap-frozen in liquid nitrogen vapor and stored at -80°C. Another portion was fixed in 10% formalin for histological analyses. Commercial kits (Pars Azmoon Co. Tehran, Iran) were used to measure ALP, ALT, and AST levels in the plasma samples of mice.

Assessment of oxidative stress markers

The liver tissue sample (100 mg) was homogenized with phosphate-buffered saline (PBS) and centrifuged at 4°C (4000–6000 rpm). The supernatants were collected, and malondialdehyde (MDA) concentration, total antioxidant capacity (TAC), catalase (CAT), superoxide dismutase (SOD), reduced glutathione (GSH), and glutathione peroxidase (Gpx) were measured using commercial kits (Zell Bio

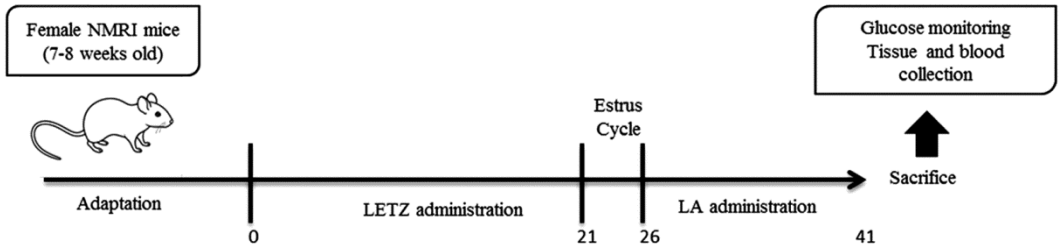

Fig. 1 — Experimental timeline illustrating LETZ administration, LA treatment phase, and sample collection. The diagram outlines the sequence and duration of all the procedures performed in this study. LA: Lauric acid, LETZ: letrozole.

GmbH, Germany), according to the manufacturer's instructions. The Bradford protein assay was used to determine the protein concentrations of the samples.

Quantitative real-time PCR (qPCR) analysis

TNF-α and HNF-4α gene expression levels in the liver were determined using qPCR. According to the manufacturer's protocol, total mRNA was extracted from 50 mg of liver tissue using a total RNA extraction kit (Parstous, Iran). After RNA extraction, the optical absorbance of 5 µL of RNA solution was measured using a NanoDrop device (Pishroh Pehosh Spectrometer, Iran) at 260 nm to evaluate the total RNA content. Then, cDNA was generated using an EasyTM cDNA synthesis Kit (Parstous, Iran). RT-qPCR was performed in 12.5 µL reactions using a 2X SYBR Green Real-Time PCR Kit and a Lava 96 Real-time PCR Detection System (DaAnGene Co. Ltd.). The results were evaluated using the ΔΔCt comparative method and Lava96 3.2 software. GAPDH was used for normalization. (Table 1) lists the specific primers used in this study.

Histopathological analysis

The liver and ovarian tissue samples were initially preserved in a 10% formalin solution, subjected to dehydration with increasing concentrations of alcohol, and finally embedded in paraffin. Sections (4–6 µm thick) were prepared and subjected to hematoxylin and eosin (H & E) staining. The sections were examined for histological alterations using an Olympus CX41 light microscope.

Statistical analysis

Statistical analysis was performed using one-way analysis of variance (ANOVA) or t-test, followed by Tukey's post hoc multiple comparison tests. The Kruskal-Wallis test was used for nonparametric data. Results are presented as mean ± standard deviation (SD), and $P< 0.05$ was considered statistically significant. Statistical analyses and figure drawing were performed using Prism software. Before analysis, the normality of the data was checked using the Shapiro-Wilk test.

Results

Validation of PCOS induction

(Table 2) shows increased levels of testosterone (P=0.03) and plasma glucose (P=0.010) in LETZ-induced mice compared to those in the control group. (Fig. 2a) shows the results of the estrous cycle assessment in LETZ-induced mice, which presented disruption of the cycle in seven out of ten mice. In (Fig 2b), ovarian histology in the LETZ group showed multiple cysts, while the tissue of the normal group showed a large number of healthy and corpus luteum without cysts.

Table 1 — Forward and reverse sequences of primers used for quantitative real-time PCR analysis of TNF-α and HNF-4 gene expression.

	Forward (5'-3')	Reverse (5'-3')
GAPDH	CATCACTGCC ACCCAGAAGACTG	ATGCCAGTGA GCTTCCCGTTCAG
TNF-α	TTCTCATTC CTGCTTGTGGC	ACTTGGTGG TTTGTGAGTGTG
HNF-4	GGCATGAAG AAGGAAGCTGT	ATTGATCCCA GAGATGGGAGAG

Table 2 — Changes in testosterone and glucose levels of LETZ-induced mice

	Testosterone (ng/ml)	Glucose (mg/dl)
Control	0.082± 0.045	110.8 ± 15.22
LETZ	0.177 ± 0.063*	145.7 ± 22.24 *

Plasma testosterone and glucose levels in experimental groups. Statistical comparison was performed using an unpaired t-test. * indicates a significant difference compared with the control group. LETZ: letrozole

Effects of LA on liver lipid peroxidation and antioxidant activity

As shown in (Fig. 3a), the levels of MDA, a marker of lipid peroxidation, significantly increased in the liver tissue of the LETZ-induced mice compared to the control and LA groups (P<0.001). However, compared with LETZ treatment, LA treatment for 15 days significantly decreased the MDA level (P=0.006).

As shown in (Fig 3 b-f), the activities of the antioxidant enzymes TAC, SOD, CAT, GSH, and GPx were markedly lower in the LETZ group compared to the control and LA groups (P< 0.001). LA treatment resulted in significant improvements in TAC (P=0.009), CAT (P=0.002), GSH (P<0.001), Gpx (P=0.001), and SOD (P=0.02) levels compared with those in to LETZ-induced mice.

Effects of LA on hepatic enzyme markers

LETZ administration had a detrimental effect on hepatic function, as indicated by significantly elevated ALT (P<0.0001), AST, and ALP (P<0.001) levels compared to the control and LA groups. LA treatment significantly lowered ALP, AST (P<0.001), and ALT (P<0.0001) levels, restoring them close to control values. No significant difference was observed between the LA and control groups (Fig. 4).

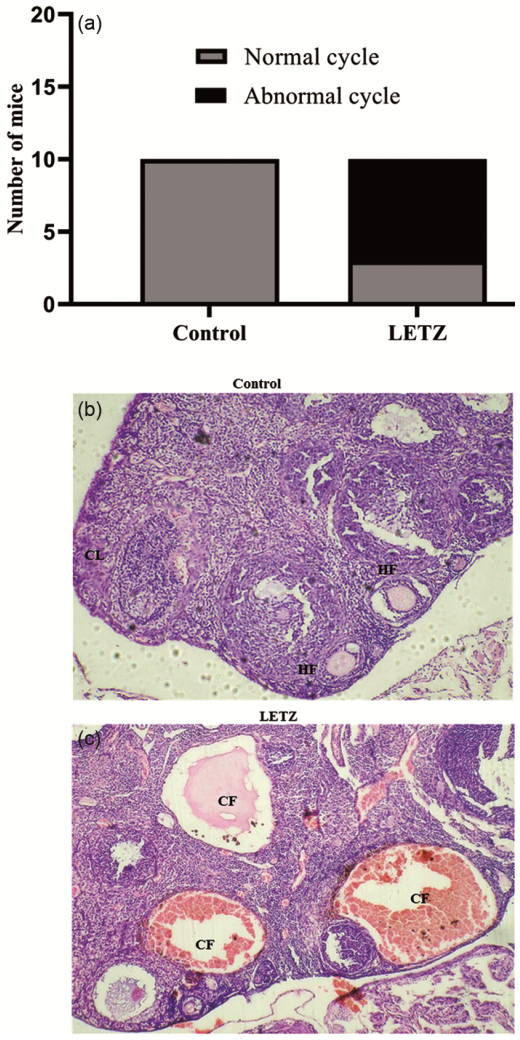

Fig. 2 — (a) Number of mice exhibiting normal and abnormal estrous cycles in each group. (b) Representative ovarian histology images showing healthy follicular (HF) and corpus luteum (CL) in the control group and cystic follicles (CF) in LETZ-induced mice. LETZ: letrozole. 4× magnification.

The effects of LA TNF-α and HNF4α mRNA expression in the liver tissue

LETZ administration had a pro-inflammatory effect on hepatocytes. RT-qPCR analysis revealed significantly increased TNF-α expression in the LETZ group compared to that in the control and LA groups (P<0.001) (Fig. 5a).

Conversely, LETZ administration significantly diminished (P<0.001) HNF4α mRNA expression in hepatocytes (Fig 5b). However, LA administration significantly reversed the elevated TNF-α levels (P=0.03) and reduced HNF4α expression in the LETZ group (P=0.02). Interestingly, compared with the control, LA alone elevated HNF4α expression (P=0.04) and mitigated TNF-α expression (P=0.03).

Effects of LA on liver histopathology

As shown in (Fig. 6a), normal liver histology was observed in the control and LA groups. LETZ-induced liver damage in the animals resulted in significant inflammation (Fig 6b) and marked infiltration of neutrophils compared to the control group (P=0.0009). In addition, wide areas of congestion (Fig 6c) were observed in the LETZ group (P<0.001). Compared with LETZ-affected mice, LA treatment for 15 days reduced congestion and inflammation in the liver tissue (P=0.02 and P=0.037, respectively).

Discussion

Women with PCOS are prone to liver damage, which is a metabolic manifestation of the syndrome[16]. Our study demonstrated the efficacy of LA in mitigating LETZ-induced liver damage. In the current study, LETZ was administered to induce a PCOS model in female mice. LETZ is a nonsteroidal aromatase inhibitor that mimics PCOS in rodents by inducing hyperandrogenism[17]. As previously mentioned, elevated testosterone levels increase the probability of NAFLD in patients with PCOS; however, the precise relationship between hyperandrogenism and NAFLD in patients with PCOS is complex and not fully understood[18]. In our study, hepatotoxicity induced by 21 days of LETZ administration was evident, as demonstrated by increased plasma levels of liver biomarkers and histological analyses. PCOS is associated with OS and inflammation, which are important factors in its pathogenesis. Antioxidant enzymes, such as CAT, SOD, and GPx, play important roles in the pathogenesis of PCOS and the female reproductive system and are reduced due to OS in women with PCOS[19]. Increased lipid peroxidation in hepatocyte membranes during OS leads to elevated MDA levels, which have also been previously reported in the LETZ-induced PCOS model[20, 21]. In this study, high levels of MDA were detected in the liver tissue, indicating increased lipid peroxidation and OS in hepatocytes. Similarly, Butt *et al*. confirmed that LETZ-induced OS increased MDA and decreased SOD and CAT levels[22]. Furthermore, during OS, the antioxidant defense system is weakened due to reduced antioxidant enzyme levels in hepatocytes. Our findings showed that the levels of antioxidants, such as TAC, CAT, SOD, GPx, and GSH, were significantly reduced in LETZ-administered mice, which was reversed by LA treatment.

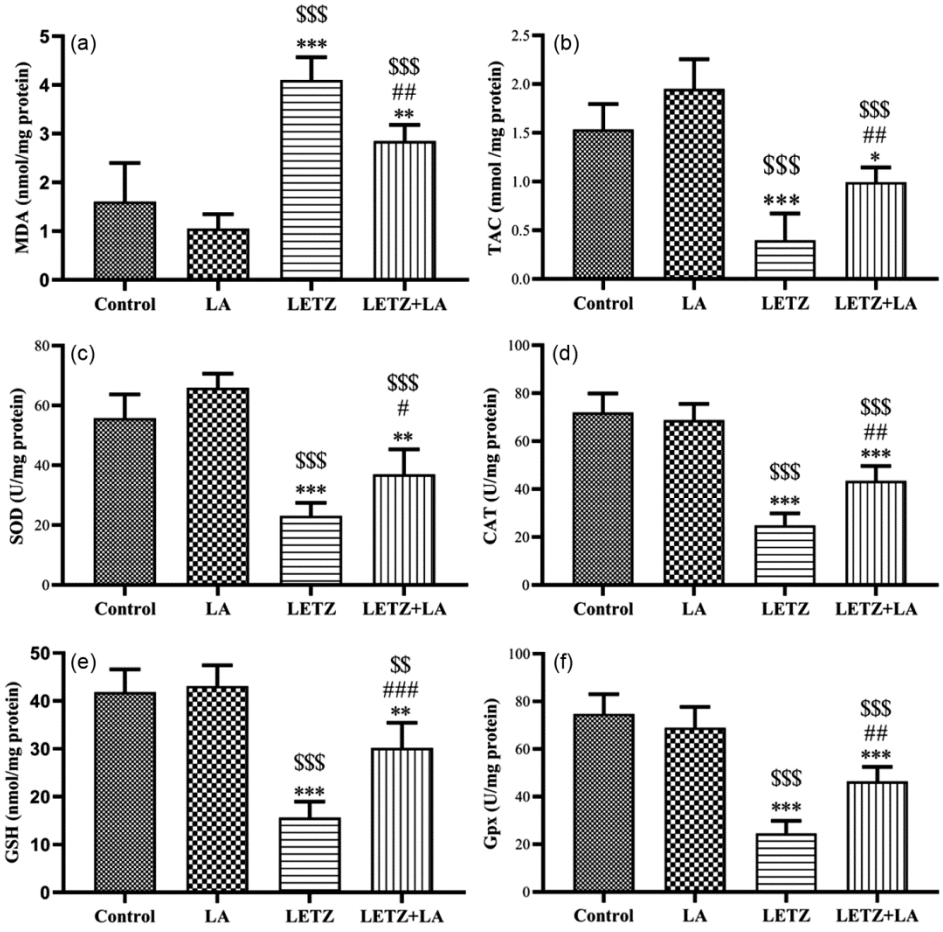

Fig. 3 — Oxidative stress was suppressed by LA administration (150 mg/kg) via a: MDA concentration diminished and b-f: Antioxidant enzyme levels increased in LETZ (6 mg/kg)-induced liver damage. Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD post hoc test. The data are expressed as the mean ± SD. * significant difference with the Control group; # significant difference with the LETZ group; $ significant difference with the LA group. LA: Lauric acid, LETZ: letrozole, MDA: malondialdehyde, TAC: total antioxidant capacity, SOD: superoxide dismutase, CAT: catalase, GSH: reduced glutathione, Gpx: glutathione peroxidase.

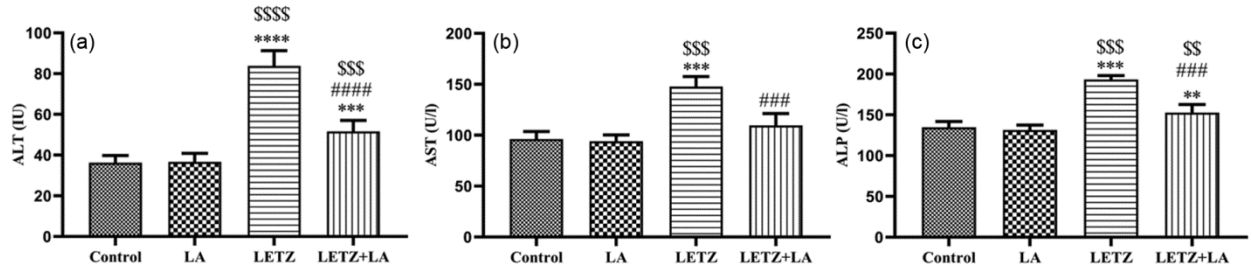

Fig. 4 — LA administration (150 mg/kg) decreased plasma ALT, AST, and ALP levels in LETZ (6 mg/kg)-induced liver damage. Statistical analysis was performed using one-way ANOVA followed by a Tukey's HSD post hoc test. The data are expressed as the mean ± SD. * significant difference with the Control group; # significant difference with the LETZ group; $ significant difference with the LA group. LA: Lauric acid, LETZ: letrozole, ALT: alanine transaminase, AST: aspartate aminotransferase, and Alp: alkaline phosphatase.

LA possesses antioxidant properties and restores the activity of endogenous antioxidants. Specifically, LA enhances the activities of SOD, GSH, and CAT in hepatocytes[13]. Additional research corroborates these findings, indicating that exogenous components alter antioxidant content and that LA can relieve liver damage through its hepatoprotective properties[7,23]. The current study demonstrated that LA prevents the reduction in antioxidant levels by inhibiting lipid peroxidation. LA suppressed OS by inhibiting lipid

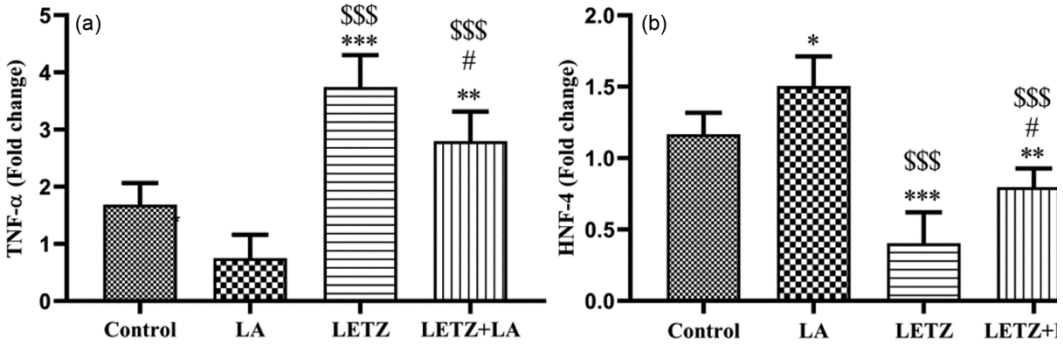

Fig. 5 — LA administration (150 mg/kg) modulated a: TNF-α, and b: HNF4α mRNA expression, LETZ (6 mg/kg)-induced liver damage. Statistical analysis was performed using one-way ANOVA followed by Tukey's HSD post hoc test. The data are expressed as mean ± SD. * significant difference with the Control group; # significant difference with the LETZ group; $ significant difference with the LA group. LA: Lauric acid, LETZ: letrozole, TNF-α: tumor necrosis factor, HNF4α: Hepatocyte nuclear factor 4 alpha.

peroxidation and restoring endogenous antioxidants in hepatic tissues.

The immune system and OS are interconnected. The initial immune response to OS inevitably leads to the production of inflammatory mediators such as TNF-α[24]. In response, the excessive production of inflammatory factors increases ROS production and consequently exacerbates OS. TNF-α plays a crucial role in mediating inflammatory responses and has been linked to hepatic inflammation in a rat PCOS model induced by LETZ, as discussed by Olaniyi *et al*[25]. In another study, LETZ administration increased TNF-α levels and altered liver function in a PCOS rat model[26]. Our results showed that LA has an anti-inflammatory effect on liver cells due to TNF-α expression in LA-treated PCOS mice. Furthermore, our findings are consistent with other studies in which LA was shown to reduce the levels of inflammatory cytokines, including TNF-α, in liver disorders[7,23]. Furthermore, our histopathological evaluations also support these findings.

HNF4α plays a central role in the metabolic regulatory pathways of hepatocytes, including fatty acid and carbohydrate metabolism. Therefore, HNF4α downregulation leads to liver dysfunction[23]. As previously mentioned, under inflammatory conditions, HNF4α expression is affected by cytokines, particularly TNF-α. The study by Xing *et al*. supports this claim, as they showed that PCOS-IR mice exhibit reduced HNF-α expression [9,27]. LA accumulation activates the nuclear receptor HNF4α-p38 MAPK signaling pathway[28]. LA protects hepatocytes against liver inflammation and influences the TNF-α signaling pathway[13]. In our study, LA treatment significantly improved the decreased expression of HNF4α observed in LETZ-induced liver damage. There is not much evidence on how LA affects inflammatory factors; however, it seems likely that LA regulates inflammatory factor levels through its effect on gene expression. Notably, LA administration to healthy mice also decreased the expression of TNF-α and increased the expression of HNF4α in the liver, indicating the beneficial effect of this fatty acid on liver function under normal conditions. In the present study, the beneficial effects of LA on liver damage were observed through biochemical and histological evaluations.

Elevated hepatic enzyme levels in plasma can indicate liver injury. During oxidative damage, hepatocytes release ALT, AST, and ALP into the circulation, indicating liver damage. Among these enzymes, ALT is considered the most accurate indicator of hepatocyte injury. A study by Minato *et al.* on Japanese women revealed that increased liver enzyme levels are common in PCOS[29]. In our study, the LETZ-administered group showed significantly higher levels of ALT, AST, and ALP than the control group. Similar studies have reported that LETZ-induced OS increases the activity and quantity of liver enzymes in hepatocytes[30,31]. However, a conflicting report suggested that LETZ induced liver inflammation without causing OS[32]. In this study, LA treatment mitigated these alterations and significantly improved plasma liver enzyme levels, indicating improved liver function. Histological image analysis revealed neutrophil infiltration in the liver tissue, and extensive areas of congestion with red blood cells. These findings indicate that LETZ exerts an inflammatory effect on hepatocytes. Treatment with LA reduced congestion and improved liver histology, which is likely a result of the improvement in the oxidative status of liver

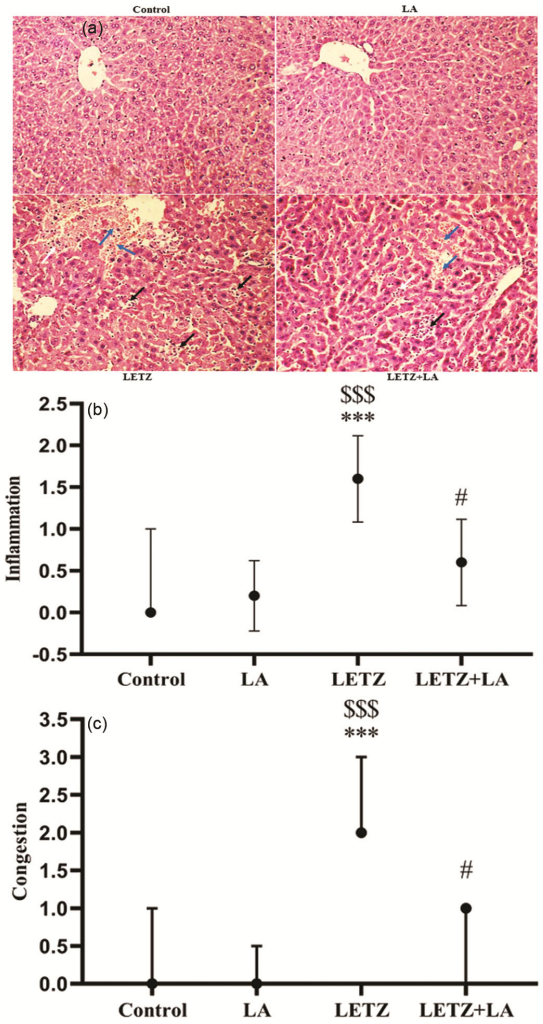

Fig. 6 — LA administration (150 mg/kg) improved liver histopathology by mitigating congestion (blue arrows) and inflammation (black arrows) at ×100 magnification. The data are expressed as median ± IQR (Interquartile range). *significant difference with the Control group; # significant difference with the LETZ group; $ significant difference with the LA group. LA: Lauric acid, LETZ: letrozole.

tissue, as proven in this study by biochemical analyses.

Given that PCOS is a multifactorial syndrome affecting many organs, LA may exert protective or modulating effects beyond the liver. Although our study focused on hepatic complications, the known antioxidant and anti-inflammatory properties of LA suggest potential benefits for other tissues affected by PCOS, including the ovaries, adipose tissue, and pancreas, as well as for metabolic and endocrine parameters.

This study provides a more comprehensive understanding of the therapeutic potential of LA in the management of multi-organ complications associated with PCOS. However, further research is required to confirm these findings. Furthermore, the hepatoprotective and antioxidant properties observed in this study highlight the potential of LA as a candidate for managing PCOS-related liver complications.

Conclusion

Our investigation showed that LA exhibited significant beneficial effects on LETZ-induced liver damage in PCOS mice. These effects are achieved through several mechanisms, including the inhibition of OS, enhancement of the antioxidant system, amelioration of liver enzyme biomarkers, and increased HNF4α expression. Furthermore, our study demonstrated that LA reduced TNF-α expression and suppressed inflammation, as verified by histological analysis. Moreover, LA can modulate OS and inflammatory pathways. Restoration of HNF4α also suggests that LA may support hepatic metabolic homeostasis. These findings strengthen the evidence that LA offers hepatoprotective properties in the LETZ-induced PCOS mouse model.

Ethical statements

All experimental procedures involving animals were approved by the Institutional Animal Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Approval No. IR.AJUMS. AEC.1403.016). All protocols followed the guidelines of the Committee for Control and Supervision of Experiments on Animals (CPCSEA) and the National Institutes of Health (NIH).

Acknowledgment

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Conflict of interest

There is no conflict of interest.

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