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Quercetin Protects Against Deltamethrin-Induced Hepatotoxicity in Rats: Histomorphometric and Stereological Evidence of Reduced Oxidative Stress, Inflammation, and Apoptosis

La Quercetina Protege Contra la Hepatotoxicidad Inducida por Deltametrina en Ratas: Evidencia Histomorfométrica y Estereológica de la Reducción del Estrés Oxidativo, la Inflamación y Apoptosis

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SUMMARY: Deltamethrin (DLM), a widely used pyrethroid insecticide, induces hepatotoxicity through oxidative stress, inflammation, and apoptosis. This study investigated the protective effects of quercetin against DLM-induced liver injury in rats. Twenty male Wistar rats were randomly assigned to four groups: Sham, Que (50 mg/kg quercetin), DLM (5 mg/kg deltamethrin), and DLM-Que. Treatments were administered orally once daily for 5 weeks. Serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were measured to assess liver function. Oxidative stress markers (GSH, SOD, CAT, and MDA), inflammatory (IL-1β, TNF-α, and NF-κB) and apoptosis-related (caspase-3, bax, and bcl-2) gene expression were evaluated in liver tissue. Histopathological and stereological analyses were also performed. DLM administration caused marked hepatic injury, characterized by histopathological alterations, elevated ALT, AST, and MDA levels, reduced antioxidant enzyme activities, increased expression of inflammatory and pro-apoptotic genes, and decreased bcl-2 expression. Quercetin significantly attenuated these changes by restoring antioxidant status, suppressing inflammatory responses, and modulating apoptosis-related gene expression. Histological findings were supported by stereological data, showing significant improvements in hepatocyte density, sinusoidal length, and liver volume in the DLM-Que group compared with the DLM group. These findings demonstrate that quercetin protects against DLM-induced hepatotoxicity through regulation of oxidative stress, inflammation, and apoptosis and may represent a promising therapeutic strategy against pesticide-induced liver injury.

KEY WORDS: Quercetin; Deltamethrin; Hepatotoxicity; Oxidative stress; Apoptosis.

INTRODUCTION

The liver is a crucial organ that performs a broad spectrum of physiological functions including metabolism, detoxification, biosynthesis of critical biomolecules and immune regulation (Arias *et al*., 2020). The liver is especially vulnerable to toxic insults because it plays a key role in biotransformation of both xenobiotics and environmental toxicants (Hinton *et al*., 2017). Synthetic pyrethroids are one of the many pollutants found in the environment, and, in particular, deltamethrin has been used in agriculture and home gardens and poses a risk to human health because of its toxicity to nontarget organisms (Lu *et al*., 2019; Han *et al*., 2020).

Deltamethrin (DLM) is a type II synthetic pyrethroid that is widely used as an insecticide (Rehman *et al*., 2014). Although it is a highly effective insecticide, and relatively less toxic to mammals than other insecticides, there are increasing reports of various toxicological effects associated with chronic or excessive exposure to DLM including nephrotoxicity and hepatotoxicity (Rjeibi *et al*., 2016; Khalatbary *et al*., 2016, 2017). Liver is one of the most crucial locations for metabolism of DLM and is vulnerable to DLM effects. DLM has been shown to cause oxidative stress through the production of reactive oxygen species (ROS) causing lipid peroxidation, protein carbonylation and DNA damage (Lu *et al*., 2019). In addition, oxidative stress induced by deltamethrin can lead to a chain reaction of inflammatory response and apoptotic signaling pathways, which ultimately results in liver dysfunction and hepatocellular injury (Arora *et al*., 2016).

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The discovery of natural compounds with antioxidant, anti-inflammatory and anti-apoptotic properties that can reduce the harmful effects of different environmental factors has been the focus of a large number of studies (Geronikaki & Gavalas, 2006). A natural occurring flavonoid, rich in fruits, vegetables and grains, quercetin has been found to be a powerful bioactive compound with established hepatoprotective effects (Kelly, 2011; Miltonprabu *et al*., 2017). The protective action of quercetin is mediated by several mechanisms, such as its antioxidant activity, by scavenging free radicals and enhancing endogenous antioxidant defense systems, by inhibiting pro-inflammatory cytokines (e.g., tumor necrosis factor a [TNF-α], IL-1β, and IL-6), and by suppression of apoptosis-related proteins (Domitrovic *et al*., 2012; Costa *et al*., 2021).

The current study is designed for the evaluation of hepatoprotective activity of quercetin against DLM induced liver toxicity in experimental model. This study specifically addresses the evaluation of quercetin's modulation of oxidative stress, inflammatory responses and apoptotic pathways induced by DLM exposure. By assessing biochemical markers, histopathological changes, and molecular signaling pathways, this research seeks to provide a mechanistic understanding of the protective effects of quercetin and support its potential use as a natural therapeutic agent in pesticide-induced liver injury.

MATERIAL AND METHOD

Ethics approval

The experimental protocol was approved by Animal Research Ethics Committee. All authors state that all animal experiments conform to the ARRIVE guidelines 2.0 (Animal Research: Reporting of in vivo Experiments) and should be performed in compliance with the U.K. Animals (Scientific Procedures) Act, 1986 and associated guidelines, EU Directive 2010/63/EU for animal experiments, or the National Institutes of Health guide for the care and use of Laboratory animals (NIH Publications No. 8023, revised 1978).

Animal Model and Housing Conditions

Twenty adult male Wistar rats (weight 230–250 g) were obtained and acclimatized under standard laboratory conditions (temperature 24–26 °C, 12/12 h light/dark cycle, and constant humidity) with free access to food and water. The local Ethics Committee approved all procedures, and they were carried out following institutional and international guidelines for the care of animals.

Experimental Design and Treatment Groups

After a week of acclimatization, 20 adult male Wistar rats were randomly distributed into four experimental groups of 5 rats each. Randomization was done by using simple random number table: each animal was assigned with an identification number, and the grouping of animals was done by random number. The randomization was done by a researcher not involved in subsequent experimental procedures, sample collection or data analysis (allocation concealment); to minimize selection bias. All treatments were given by oral gavage once a day for five weeks. (I) Sham group received only dimethyl sulfoxide (DMSO; Merck, Germany), which served as the vehicle control. (II) Quercetin (50 mg/kg/day; Sigma-Aldrich, USA) group was administered. (III) DLM group, received deltamethrin (5 mg/kg/day; Sigma-Aldrich, USA), diluted in DMSO. (IV) DLM-Que group, received both treatments for 5 weeks.

The dose and duration of DLM administration was chosen according to the similar previous studies (Ben Slima *et al*., 2013; Khalatbary *et al*., 2017). In addition, this dose of quercetin (50 mg/kg/day) was selected due to previous studies showing antioxidant and anti-inflammatory protective effects of quercetin at this concentration in liver related conditions (Kumar Mishra *et al*., 2013; El Faras & Elsawaf, 2017; Uylas *et al*., 2018; Zhang *et al*., 2021; Firouzeh *et al*., 2024), and our preliminary pilot evaluations that established its efficacy and tolerability in our experimental conditions.

To minimize circadian variability, all substances were freshly prepared prior to each administration and administered at the same time each day (10:00 AM). Treatment period was 35 days, on the 36th day samples were taken following anaesthetic and analysed. Doses, routes and duration of exposure selected were intended to approximate sub-chronic exposures yet were within the limits of ethical approval and physiologic relevance.

To minimize experimental bias, the following procedures were applied: (I) the groups for the experimental animals were allocated at random as described above; (II) all the sample labeling and coding were carried out by a researcher not engaged in the data collection; (III) investigators involved in stereological, molecular (qRT-PCR), and biochemical (enzyme activity and oxidative stress) assays were blinded to group identity while the data were acquired and analyzed.

Histomorphometry and Stereological Measurements

Liver samples were obtained and then fixed in 10 %

neutral buffered formalin (Merck, Germany) for a minimum of 72 h. Increasing concentrations of ethanol (50–100 %) were used to dehydrate the samples before clearing them in xylene and embedding them in paraffin at 60–70 °C in a Leica automated embedder (Leica Biosystems, Germany). For preparation of serial sections, a rotary microtome (Leica RM2235, Germany) was used to cut 5 µm-thick sections. Eight random sections of each liver were stained with hematoxylin and eosin (H&E; Merck, Germany) for stereological analysis. The images were taken with an Olympus BX53 microscope (Olympus Corp., Japan) and processed using ImageJ software (National Institutes of Health, USA). Total liver volume and numerical density of hepatocytes were used for quantitative evaluations. Furthermore, sinusoidal vessel density was determined. We used unbiased methods that were based on the principles of point counting and field sampling to ensure accuracy and reproducibility (Fig. 1) (Howard & Reed, 2004; Alshehri *et al*., 2025).

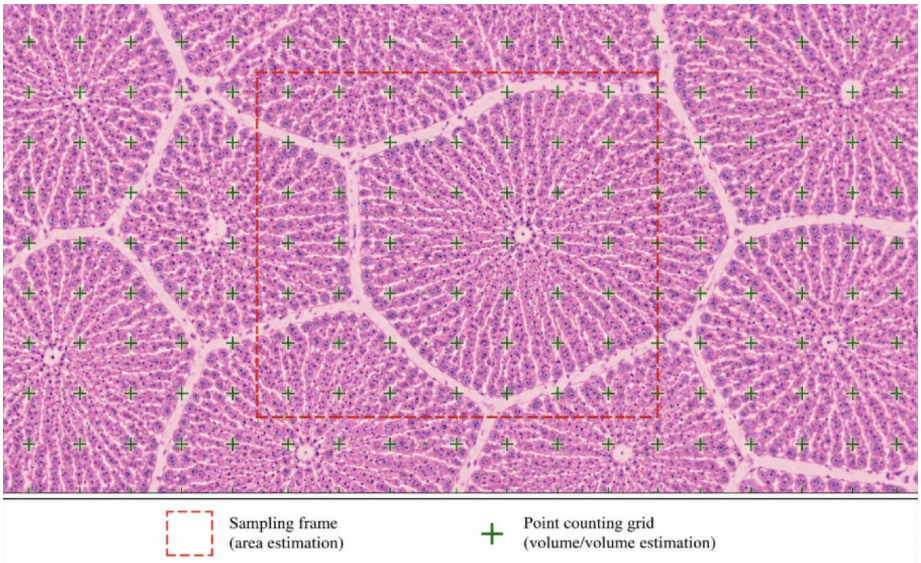


Fig. 1. Schematic Representation of the Stereological Methods Applied to Liver Tissue. Representative H&E-stained liver section (¥10). A point grid and an unbiased counting frame were superimposed on the image for estimation of hepatocyte number and sinusoidal length. This figure is a schematic illustration provided to demonstrate the stereological procedures used in the study.

Molecular Assessment

Total RNA was isolated from liver tissues using the RNeasy Mini Kit (Qiagen, Germany) to assess the expression of mRNA inflammatory (IL-1β, TNF-α and NF-κb) and apoptosis (caspase-3, bax and bcl-2) genes. The iScript™ cDNA Synthesis Kit (Bio-Rad, USA) was used for complementary DNA (cDNA) synthesis. Genespecific primers (Table I) were used in quantitative real-time PCR. The internal control was GAPDH and gene expression was determined by 2^-DDCt method. Three biological replicates were used for each analysis.

Table I. Primer sequences used for gene expression analysis using quantitative real time-PCR.

Gene	Sequence (5 ' > 3 ')	Length (bp)	Accession no
IL-1β	**F:** TCTGAAGCAGCTCTGGCAAC **R:** TCAGTCTCAAGAACAGGTCA	119	XM_032902343.1
TNF- α	**F:** GCTCCCTCTCATCAGTTCCA **R:** GCTCGGTGGTTTGCTACGAC	102	XM_032888689.1
NF-kβ	**F:** GCCAGACACAGATGATCGCC **R:** GTTTCGGGTAGGCACAGCAA	112	NP_001102792.1
Caspase-3	**F:** GGAGCTTGGAACGCGAAGAA **R:** ACACAAGCCCATTTCAGGGT	169	NM_012922.2
Bax	**F:** ACACCTGAGCTGACCTTGGA **R:** AGTTCATCGCCAATTCGCCT	115	NM_017059.2
Bcl-2	**F:** CTGGTGGACAACATCGCTCT **R:** GCATGCTGGGGCCATATAGT	115	NM_016993.1
GAPDH	**F:** AGTGCCAGCCTCGTCTCATA **R:** GATGGTGATGGGTTTCCCGT	248	NM_017008.4

Biochemical and Oxidative Stress Analysis

Cardiac puncture was used to collect blood and let it clot for 30 min at room temperature. AST and ALT levels were determined by enzymatic reagent kits following the manufacturer's instructions after centrifugation of the serum at 3000 rpm, 4 °C, for 10 min. A small sample of liver tissue was taken and homogenized in phosphate-buffered saline for the oxidative stress markers. The levels of reduced glutathione (GSH) and superoxide dismutase (SOD) were assessed spectrophotometrically using trichloroacetic acid (Sigma-Aldrich, USA) and pyrogallol (Sigma-Aldrich, USA) at 420 nm and 412 nm, respectively (Ellman, 1959; Sun *et al*., 1988). The levels of catalase (CAT) were measured by adding hydrogen peroxide to a phosphate buffer and measuring the absorbance at 245 nm (Aebi, 1974). The level of malondialdehyde (MDA) was measured by thiobarbituric acid (Sigma-Aldrich, USA) and absorbance was read at 520 nm (Mihara & Uchiyama, 1978).

Statistical Analysis

The analyses were done with SPSS v23 (IBM, USA), and data are presented as mean ± SD. Differences between groups were compared by one-way ANOVA and Tukey's post hoc test. The p value < 0.05 was used as the criterion of statistical significance.

RESULTS

Quercetin mitigates DLM-induced histopathological alterations and restores liver microarchitecture

The liver showed significant structural changes after DLM exposure on H&E staining. The hepatic lobular architecture in the DLM group was severely distorted with disarrayed hepatic cords, constriction of sinusoid spaces and irregular central vein morphology. Cytoplasmic vacuolization and pyknotic nuclei were often seen in the hepatocytes, suggesting early necrotic changes and cell damage. Liver sections in the sham group on the other hand showed normal lobular architecture with hepatic cords radiating away from the center of the lobule, normal hepatocyte morphology, and well-defined sinusoids. Likewise, the hepatic plates and sinusoid distribution in the quercetin group remained near normal. The partial recovery of hepatic organization by co-administration of DLM with quercetin is also interesting, evidenced by the improvement in hepatocyte morphology, more even sinusoidal arrangement, and the reduction of degenerative changes in the liver when compared to the DLM group (Fig. 2A). These observations were confirmed by stereological analyses. DLM group liver volume was significantly reduced in comparison to the sham and Que groups (P=0.0032 and P=0.0002, respectively), while co-treatment with quercetin (DLM-Que group) partially reversed the liver volume (P=0.0316 vs. DLM) (Fig. 2B).

The same pattern was observed with hepatocytes, with a significant decrease in the DLM group, and the sham and Que groups experienced higher densities (P=0.0004 and P=0.0003, respectively). To our surprise, the DLM+Que group showed a significant improvement over DLM (P=0.035) (Fig. 2C).

The number of sinusoidal vessels was significantly reduced in the total length of sinusoidal vessels of the livers in the DLM group (P=0.001 and P=0.0005, respectively) in comparison with the sham group. This reduction was significantly reversed in the DLM-Que group in comparison with DLM group (P=0.0011) (Fig. 2D).

Quercetin attenuated inflammation after DLM-induced hepatotoxicity

The expression levels of pro-inflammatory genes IL-1β, TNF-α and NF-κb were significantly induced after DLM exposure. As anticipated, both sham and Que groups expressed significantly less in all genes compared to DLM group (all P<0.0001). The sham and Que groups also had a significantly lower expression of the genes for IL-1β (P=0.003 and P=0.0035, respectively) and TNF-α (P=0.0181 and P=0.0221, respectively) compared to the DLM-Que group and similarly showed a significantly lower expression of the gene for NF-κb (P=0.0045 and P=0.003, respectively). In particular, quercetin significantly reduced these inflammatory markers, IL-1β, TNF-α, and NF-κb, in the DLM-Que group, in comparison to DLM alone (P=0.0003, P=0.0002, and P=0.0003, respectively) indicating a potent modulatory effect of quercetin on hepatic inflammation (Fig. 3A, B).

Quercetin attenuated apoptosis after DLM-induced hepatotoxicity

The DLM group had a significant increase in Bax and caspase-3 transcripts (both, P<0.0001) in the analysis of apoptotic markers, when compared with the sham and Que group respectively. The DLM-Que group had significantly higher gene expression levels of caspase-3 and bax than both the sham and Que groups (P=0.0098 and P=0.0103, respectively, for the DLM-Que group compared to sham; P=0.0012 and P=0.0012, respectively, for the DLM-Que group compared to Que). Importantly, the expression of these was significantly reduced by quercetin co-administration compared with DLM alone (P=0.0004 and P=0.0009, respectively) (Fig. 4A, B).

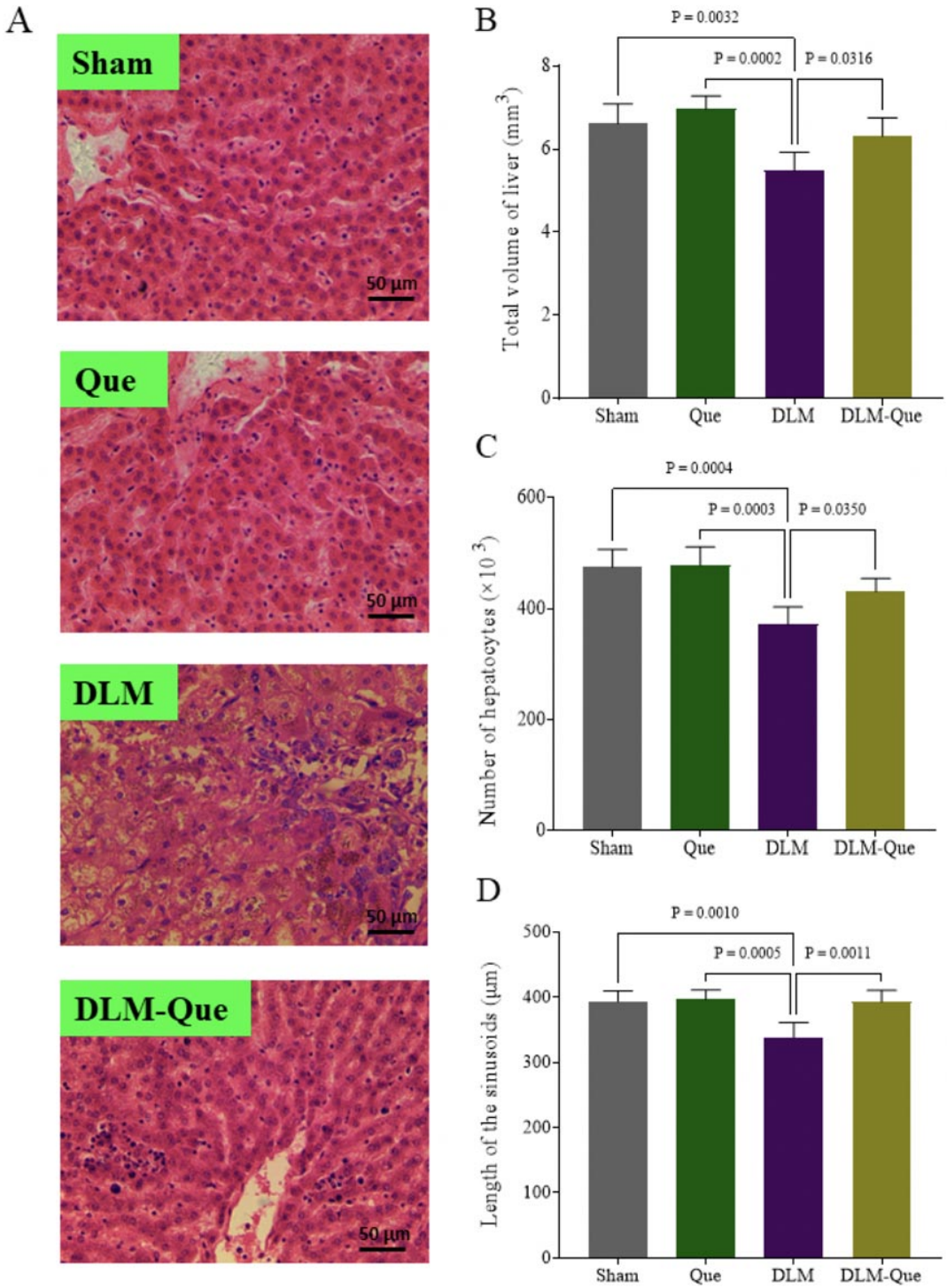


Fig. 2. The effects of quercetin on liver histology and stereological characteristics after DLM-induced hepatotoxic effect. Representative tissue sections of liver stained with H&E from experimental groups. The hepatic lobular architecture in the sham group is normal, with radiating hepatic cords, normal hepatocyte morphology, and normal sinusoidal distribution. The histological appearance of the Que group is similar to the sham group. The DLM group is, on the other hand, structurally disorganized, with disruption of hepatic cords, narrow sinusoidal spaces and hepatocyte degeneration and cytoplasmic vacuolization. The combination of quercetin and DLM partially reversed the liver architecture, as there was improvement in hepatocyte morphology and more organized sinusoidal structures than seen in the DLM group (A). The quantitative stereological analysis is shown as (B) total liver volume, (C) numerical density of hepatocytes, and (D) sinusoidal vessel length. All data are reported as the mean ± SD (n=5).

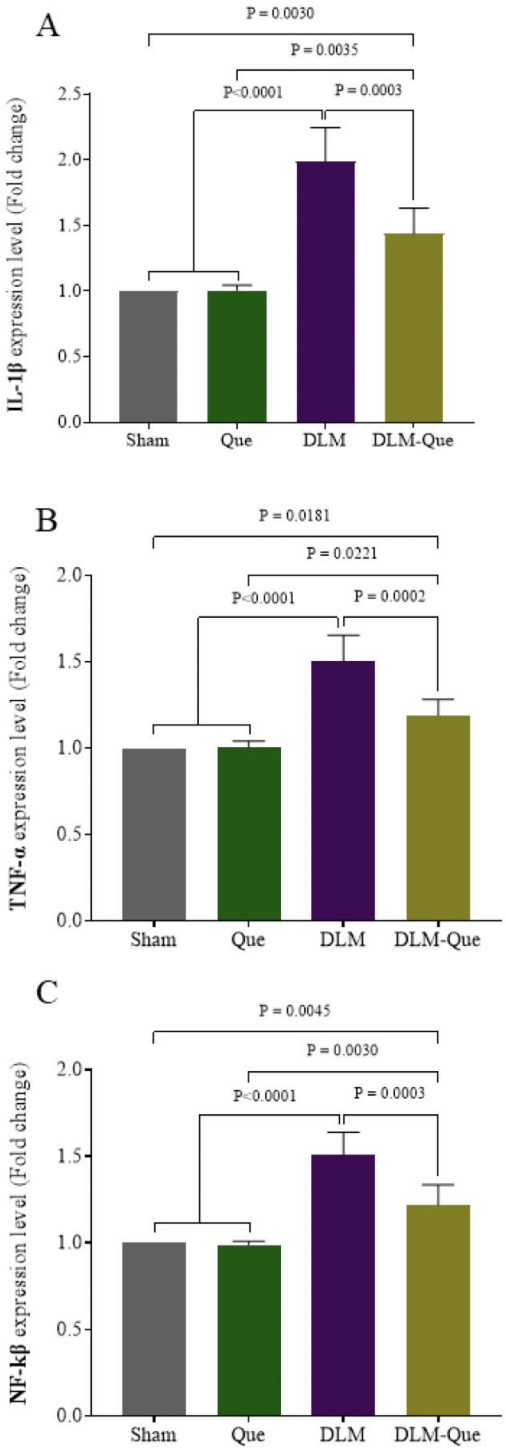


Fig. 3. Quercetin effects on the expression of inflammatory genes in the liver of rats with DLM-induced hepatotoxicity. Liver tissue was analysed by qRT-PCR to determine relative levels of mRNA for IL-1b, TNF-a, and NF-kb (A, B, and C). The levels of gene expression were normalized to the GAPDH expression and compared by the 2^-DDCt method. Data are presented as mean ± SD (n = 5).

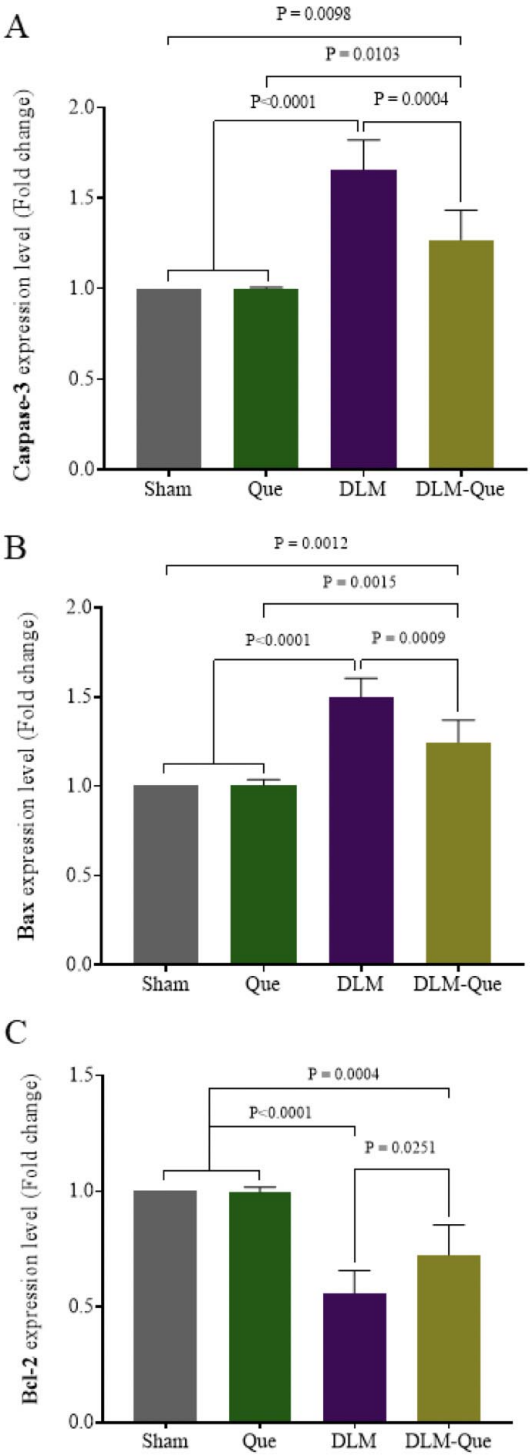


Fig. 4. The effect of quercetin on the expression of genes related to apoptosis in a rat liver under hepatotoxicity conditions induced by DLM. The relative mRNA expression of caspase-3, bax and bcl-2 was determined in liver tissue by qRT-PCR (A–C). The level of expression was normalized against GAPDH and calculated as 2^-DDCt. Data are shown as mean ± SD (n = 5).

The anti-apoptotic gene bcl-2, on the other hand, had the opposite trend. DLM treatment significantly reduced its expression while the expression in sham and Que groups were preserved (both, P<0.0001). Furthermore, the expression level of both sham and Que groups were also significantly higher than the DLM-Que group (both P=0.0004). The expression of bcl-2 was reduced in DLM group, but co-treatment with quercetin partially restored the expression of bcl-2 (P=0.0251) (Fig. 4C) suggesting that quercetin may restore the pro- and anti-apoptotic balance.

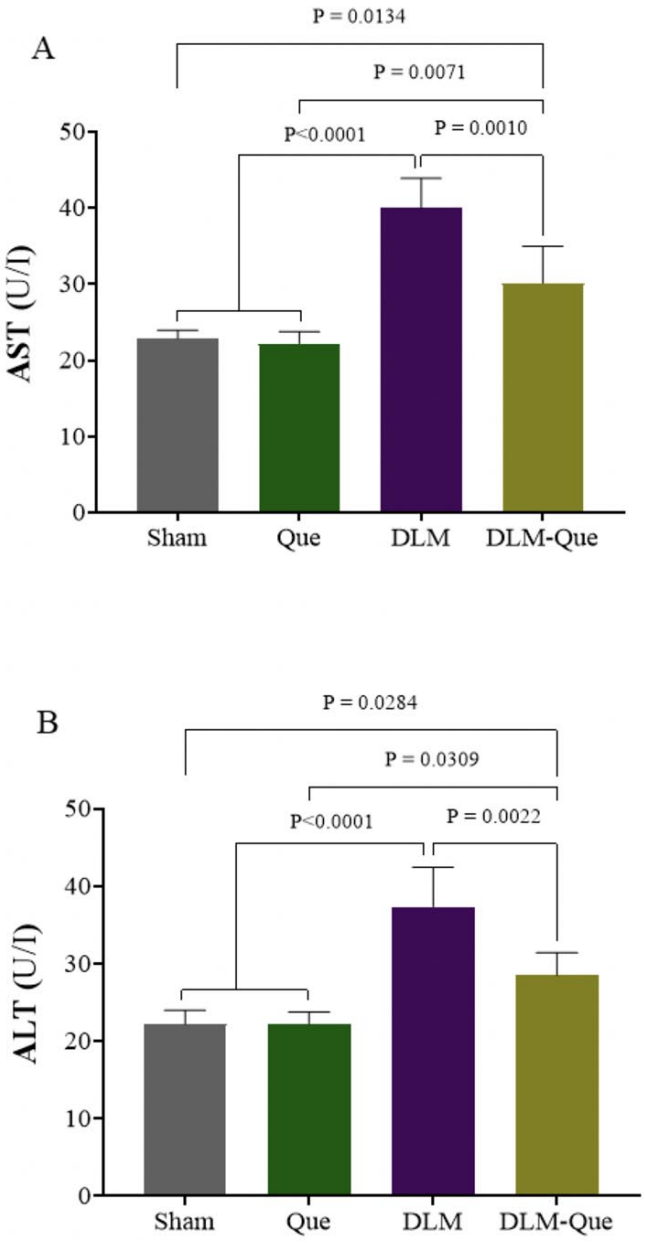


Fig. 5. Changes in AST and ALT activities in blood serum of hepatotoxic rats induced by DLM treatment. The effect of quercetin on the AST and ALT levels of DLM induced hepatotoxicity in rats. To determine the hepatic function after treatment, (A) AST and (B) ALT were measured in the blood. Data are presented as mean ± SD (n = 5).

Quercetin attenuated DLM-induced liver dysfunction

Biochemical analysis of liver enzyme activity showed that DLM treatment had significantly increased AST and ALT serum levels when compared with the sham and Que groups (both, P<0.0001). Importantly, animals in DLM-Que had a significant reduction in both enzymes as compared to the DLM group (P=0.001 and P=0.0022, respectively) indicating partial functional recovery of the liver. However, although the levels of both enzymes were lower in the DLM-Que group than in the DLM group, the levels of AST (P=0.0134 and P=0.0071) and ALT (P=0.0284 and P=0.0309) enzymes were still higher than in the sham and Que groups, respectively. (Fig. 5A, B).

Quercetin attenuated oxidative stress after DLM-induced hepatotoxicity

GSH, SOD and CAT levels were increased in the Que and sham groups compared to the DLM group (all, P<0.0001) for assessment of antioxidant biomarkers. The two control groups had higher GSH (P=0.0075 and P=0.0049, respectively), SOD (P=0.0302 and P=0.0035, respectively) and CAT (P=0.016 and P=0.0051, respectively) levels compared to the DLM-Que group. In groups that received deltamethrin, there was a significant increase in GSH, SOD and CAT levels in the DLM-Que group as compared to the DLM group (P=0.0002, P=0.0029 and P=0.0029, respectively) (Fig. 6A–C).

The MDA concentrations were however significantly lower in the sham and Que groups than in the DLM group (P=0.0019 and P=0.0003, respectively). Importantly, the antioxidant enzyme activities were significantly restored in DLM-Que group when compared with DLM alone (P=0.0241) (Fig. 6D) indicating strong antioxidative activity of quercetin.

DISCUSSION

The main objective of this work was to explore the hepatoprotective property of quercetin against the liver toxicity induced by chronic DLM. The prime results establish that DLM causes severe liver injury involving oxidative stress, inflammation and apoptosis, whereas quercetin through its antioxidant and anti-inflammatory properties significantly reduces the liver injury and partially restores liver function and architecture.

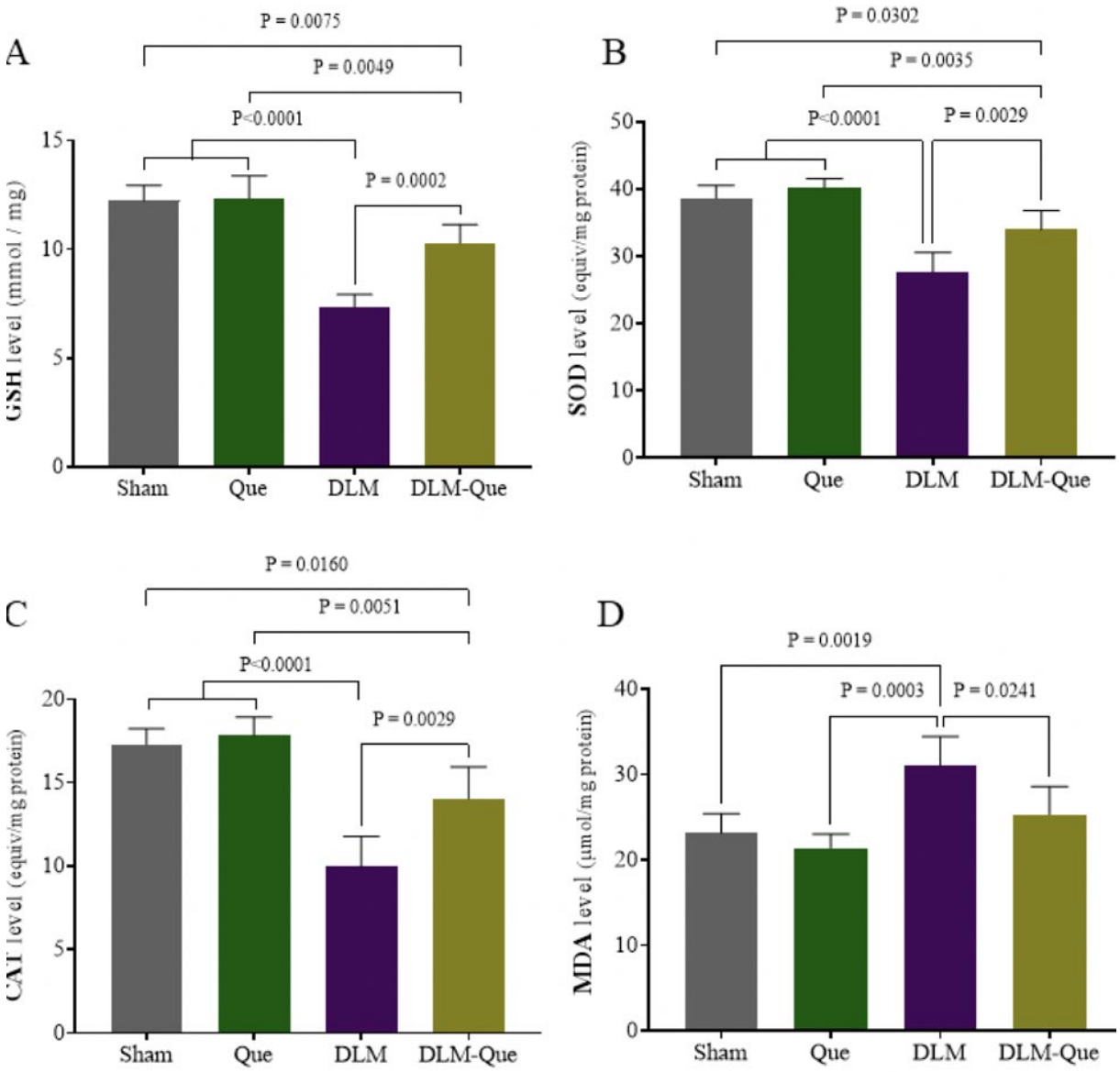


Fig. 6. Dietary supplementation with quercetin alters the oxidative-stress markers in a DLM-induced hepatotoxicity in rats. The antioxidant biomarker levels in liver homogenates were analyzed biochemically and were found as (A) GSH, (B) SOD and (C) CAT and oxidative stress marker (D) MDA. Data are presented as mean ± SD (n = 5).

Inflammation is a vital biological mechanism to remove harmful stimuli and does become injurious and contributes to disease progression when it becomes excessive or chronic, particularly in the liver (Campana *et al*., 2021). Toxic insults can lead to the upregulation of pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF-α) and interleukin (IL-1β), which play a critical role in hepatic inflammation, which can contribute to additional cell damage (Liu *et al*., 2011). We found in our study that exposure to DLM resulted in a significant increase in the expression of IL-1β, TNF-α and NF-kb in liver, what reflected an activated inflammatory state which is likely to worsen liver injury. This upregulation is consistent with previous published data which has reported the hepatotoxicity effect of pyrethroids is associated with an inflammatory response (Khalatbary *et al*., 2017; Küçükler *et al*., 2021; Alzahrani *et al*., 2025). Most importantly, these pro-inflammatory cytokines were significantly reduced by quercetin co-treatment, indicating the anti-inflammatory activity of quercetin could modulate hepatic inflammatory response. This effect could be due to quercetin's inhibitory effects on NF-κB signaling, a process which is known to regulate the production of inflammatory cytokines (Cho *et al*., 2003; Min *et al*., 2007; Chen *et al*., 2020).

Apoptosis is an important process in maintaining tissue homeostasis by the removal of damaged or dysfunctional cells. But, when the apoptosis in the liver is excessive, hepatocytes are lost and liver dysfunction and disease can occur (Neuman, 2001). The proteins that regulate apoptosis are divided into pro- and anti-apoptotic proteins, among which caspase-3 and bax are pro-apoptotic proteins while bcl-2 is an anti-apoptotic protein that regulate the fate of cells (Sharma *et al*., 2011). The results show that DLM strongly induced the levels of caspase-3 and bax expression and down regulated that of bcl-2, suggesting that DLM activated the intrinsic mitochondrial apoptotic pathway. The change to apoptosis may be responsible for the damage to hepatocellular cells seen. Co-administration of quercetin reversed these changes, reducing pro-apoptotic gene expression and restoring bcl-2 levels, thus helping to maintain cellular viability. This protective effect is in line with previous results that have shown quercetin can maintain mitochondrial integrity and prevent apoptosis in models of oxidative stress (Wang *et al*., 2017; Zhu *et al*., 2017).

Excessive ROS production and/or inadequate antioxidant capacity leads to oxidative stress (Liu *et al*., 2010). In this study, chronic exposure to DLM caused significantly altered the oxidative balance in the liver. There was significant loss of important antioxidant defenses. At the same time, there was a marked rise in MDA, a marker of lipid peroxidation, and is considered a good indicator of oxidative damage to the cell membranes. The results show that DLM produces excess production of ROS resulting in oxidative damage to the liver, which accounts for the hepatotoxicity observed. In liver tissue, MDA accumulation was significantly decreased and antioxidant enzyme activities were restored by quercetin administration. It implies that quercetin has the potential to boost the body's antioxidant system and to absorb free radicals, which in turn inhibits lipid peroxidation and cell damage. The hepatoprotective activities of quercetin in this study are well supported by its established antioxidant activity. Quercetin, due to its anti-oxidative properties, is able to maintain hepatocyte functions and integrity and thus, decrease subsequent inflammatory and apoptotic responses triggered by ROS (Dias *et al*., 2005; Amália *et al*., 2007; Liu *et al*., 2010).

ALT and AST are considered to be sensitive markers of hepatocellular damage, since their increased serum levels reflect hepatocellular membrane damage and leakage of intracellular constituents. Various models of chemical induced liver toxicity have been shown to have elevated ALT and AST levels (Lala *et al*., 2023). As a result of this study, it was concluded that the DLM exposure induced significant increase in both ALT and AST level, which further confirms the damage to hepatocyte cells. These enzymes were significantly reduced upon quercetin treatment suggesting an improvement in the integrity of the membrane and liver function. This biochemical enhancement aligns with the anti-inflammatory and antioxidant properties of quercetin that diminish the oxidative damage and cell damage, which results in the prevention of enzyme leakage.

Histopathological examination allows a direct visualization of tissue level changes, which indicate molecular and biochemical disturbances (Alshehri *et al*., 2025). Signs of structural damage and impaired microcirculation were observed in the liver tissue of DLM-treated rats, such as disorganization of hepatic cords, reduction in sinusoidal spaces, decrease in the number of hepatocytes, and shortening of sinusoidal vessels. These changes are associated with oxidative stress, inflammation and apoptosis observed in our study. Quercetin partially ameliorated the microarchitecture in the liver, namely the liver volume, hepatocyte density and the length of sinusoidal vessels. This indicates that quercetin preserves the integrity of the structures, probably through its anti-damaging properties and the preservation of vascular functions.

In conclusion, the histological recovery supports the results of the biochemical and molecular markers observed, with a significant role played by quercetin as a hepatoprotective agent. The dosages of deltamethrin and quercetin used in the present study were optimized for the experimental rodent models, but when dosed accordingly for body surface area, they fall within the ranges commonly used in experimental sub-chronic environmental exposure and therapeutic dosage studies on humans. This dose of DLM (5 mg/kg/day) is roughly equivalent to 0.8 mg/kg/day in humans and is above typical environmental exposure levels, but is nevertheless useful to model cumulative effects under a controlled dose exposure experiment. The dosage of quercetin (50 mg/kg/day) is also comparable with the human dose (8 mg/kg/day) that is attainable by dietary supplementation or by pharmacologic formulations. The conversions, normalized to body surface area as described by Reagan-Shaw *et al*. (2008), offer a basis for clinical translatability, and indicate that this hepatoprotective effect seen in this model may have relevance to human exposure scenarios.

Though quite robust in the current results, some limitations should be noted. The relatively small sample size in each group (n = 5), may reduce statistical power and result in non-reproducible outcomes. The number of animals used was limited to the smallest number required according to ethical guidelines and consistent with a number of studies previously published with similar designs; however future

studies with larger numbers of animals are warranted to validate and extend these findings. Secondly, only a vehicle (DMSO) control was added. The use of low concentrations of DMSO does not seem to have a significant effect on oxidative stress or liver function, but the addition of extra samples with solvent control or dose response experiments could provide further support for the protective effect of quercetin. Third, only short-term (5-week) exposure was assessed and the long-term hepatoprotective effects and recovery following quercetin treatment were not evaluated; long-term follow-up studies are needed to determine the persistence and reversibility of the effects of quercetin. Fourth, the study examined male rats only, and sex differences were not included in the study; future investigations should include female rats to understand differences in response. Fifth, mechanistic evaluation was limited to a few inflammatory and apoptotic genes and, in some instances, no protein-level validation (western blot or ELISA) was done, which may limit mechanistic conclusions. Sixth, oxidative stress was evaluated by classical biomarkers (MDA, GSH, SOD, CAT) and not by direct measurements of ROS; addition of ROS-sensitive assays would further support the interpretation of the mechanisms. Last, one-way ANOVA with Tukey's post hoc test was used initially for analyses and data was assumed to be normally distributed. There are some limitations to this assumption as a result of the small sample size. The same general pattern was seen with subsequent nonparametric reanalysis (Kruskal–Wallis with Dunn's multiple comparisons and Bonferroni correction), though some comparisons were not as significant as seen with the parametric analysis, suggesting that the study might not have been powered enough to show subtle effects. More research is needed with larger samples to validate the present findings. Lastly, although the doses of each compound were chosen according to literature and pilot experiments, they have an approximate relevance to human exposure and should be interpreted with caution.

CONCLUSION

In general, our study reveals that DLM causes considerable toxicity in the liver by causing oxidative stress, inflammatory response, and apoptosis, which results in liver impairment and dysfunction. Quercetin effectively reduces these effects by regulating inflammatory responses, regulating apoptotic signals, restoring antioxidant defenses and maintaining the architecture of tissues. All these findings could pave the way for the use of quercetin as a therapeutic agent for prevention and treatment of liver damage caused by pesticides.

Conflict of interest. The authors declare that there are no conflicts of interest associated with this study.

JU, H. & CHEN, W. La quercetina protege contra la hepatotoxicidad inducida por deltametrina en ratas: Evidencia histomorfométrica y estereológica de la reducción del estrés oxidativo, la inflamación y apoptosis. *Int. J. Morphol., 44(4)*:1320-1330, 2026.

RESUMEN: La deltametrina (DLM), un insecticida piretroide ampliamente utilizado, induce hepatotoxicidad a través del estrés oxidativo, la inflamación y la apoptosis. Este estudio investigó los efectos protectores de la quercetina contra el daño hepático inducido por DLM en ratas. Veinte ratas macho Wistar fueron asignadas aleatoriamente a cuatro grupos: Sham, Que (quercetina 50 mg/kg), DLM (deltametrina 5 mg/kg) y DLM-Que. Los tratamientos se administraron por vía oral una vez al día durante 5 semanas. Se midieron los niveles séricos de alanina aminotransferasa (ALT) y aspartato aminotransferasa (AST) para evaluar la función hepática. En el tejido hepático se evaluaron los marcadores de estrés oxidativo (GSH, SOD, CAT y MDA) y la expresión génica de marcadores inflamatorios (IL-1β, TNF-α y NF-κB) y relacionados con la apoptosis (caspasa-3, bax y bcl-2). También se realizaron análisis histopatológicos y estereológicos. La administración de DLM provocó un daño hepático marcado, caracterizado por alteraciones histopatológicas, niveles elevados de ALT, AST y MDA, reducción de la actividad de enzimas antioxidantes, aumento de la expresión de genes inflamatorios y proapoptóticos, y disminución de la expresión de bcl-2. La quercetina atenuó significativamente estos cambios al restaurar el estado antioxidante, suprimir las respuestas inflamatorias y modular la expresión génica relacionada con la apoptosis. Los hallazgos histológicos fueron respaldados por datos estereológicos, que mostraron mejoras significativas en la densidad de hepatocitos, la longitud sinusoidal y el volumen hepático en el grupo DLM-Que en comparación con el grupo DLM. Estos hallazgos demuestran que la quercetina protege contra la hepatotoxicidad inducida por DLM mediante la regulación del estrés oxidativo, la inflamación y la apoptosis, y podría representar una estrategia terapéutica prometedora contra el daño hepático inducido por pesticidas.

PALABRAS CLAVE: Quercetina; Deltametrina; Hepatotoxicidad; Estrés oxidativo; Apoptosis.

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