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ORIGINAL ARTICLE

PROTECTIVE EFFECTS OF *MELISSA OFFICINALIS* EXTRACT AGAINST LEAD-INDUCED TOXICITY IN HEPATIC, RENAL AND TESTICULAR TISSUES OF MALE RATS

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ABSTRACT

Background: Lead exposure poses significant health risks by affecting various organ systems and causing oxidative stress. *Melissa officinalis* is recognized for its antioxidant properties and potential protective effects. This study aimed to evaluate the protective effects of *Melissa officinalis* extract on hepatic, renal, and testicular tissues in male rats exposed to lead toxicity.

Materials & Methods: This quasi-experimental study was conducted at Isra University (IU) Hyderabad from October 2024 to March 2025. Forty healthy male Albino Wistar rats, weighing 180-200 grams, were divided into four groups: Group A (control) received saline; Group B received saline and 20 mg/kg lead acetate; Group C was treated with 20 mg/kg *Melissa officinalis* extract, followed by 20 mg/kg lead acetate; Group D received 100 mg/kg *Melissa officinalis* extract, then the same lead dose. Biochemical parameters, including ALT, AST, ALP, urea, creatinine, and testosterone levels, were analyzed, along with sperm characteristics and histological examinations of liver and kidney tissues.

Results: Forty healthy male Albino Wistar rats, weighing 180-200 grams, were divided into four groups: Group A was a control group, while others were experimental. Group B showed significantly increased ALT (155.22 U/L), AST (114.52 U/L), and ALP (148.32 U/L) levels while decreasing testosterone (1.0 ng/ml). *Melissa officinalis* treatment improved these parameters, especially in Group D, with ALT (59.96 U/L), AST (49.79 U/L), and ALP (61.72 U/L) showing marked reductions. Sperm count and motility were significantly higher in Groups C and D, with Group D exhibiting only 12.4% abnormal morphology. Histological analyses revealed reduced liver degeneration and improved kidney architecture.

Conclusion: *Melissa officinalis* extract significantly protects against lead-induced hepatic, renal, and reproductive toxicity in rats, suggesting its therapeutic potential.

KEY WORDS: Antioxidants; Lead Poisoning; *Melissa officinalis*; Oxidative stress; Reproductive Health; Testosterone.

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INTRODUCTION

Lead is a major environmental contaminant widely used in chemical manufacturing, posing significant health risks. In many countries, lead exposure remains a major concern, with sources including food, beverages, and soil.[1] The severity of lead toxicity depends on the duration and level of exposure, affecting multiple organ systems, including the liver, kidneys, reproductive system, hematological system, and central nervous system.[2] Lead accumulation in tissues induces oxidative stress by impairing antioxidant defenses and increasing reactive oxygen species (ROS) production. Additionally, it disrupts cellular energy metabolism, damages mitochondria and DNA, and triggers apoptosis.[2] Lead poisoning manifests as

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interstitial fibrosis, proximal tubular nephropathy, and glomerular sclerosis. Chronic exposure is associated with enzymuria, altered proteinuria, impaired organic anion and glucose transport, and reduced glomerular filtration rate.[3] In the male reproductive system, lead disrupts spermatogenesis, reducing sperm count, viability, and seminiferous tubule diameter, leading to reversible infertility.[4] Some studies suggest lead affects the hypothalamic-pituitary axis, altering levels of luteinizing hormone, follicle-stimulating hormone, and testosterone, while others highlight its direct impact on testicular function.[5] Human sperm, rich in unsaturated fatty acids, is highly susceptible to ROS-induced peroxidative damage.

Lead toxicity also affects liver histology and function, causing hydropic degeneration, necrosis, cellular swelling, and glycogen depletion in animal models.[6] In humans, lead exposure is linked to an increased risk of non-alcoholic fatty liver disease (NAFLD) and elevated liver enzymes, including aspartate transaminase, alkaline phosphatase, and alanine transaminase.[7]

Melissa officinalis (lemon balm), a medicinal herb from the Lamiaceae family, is native to West Asia and the East Mediterranean.[8] It is rich in antioxidants and contains bioactive compounds such as terpenes, flavonoids, rosmarinic acid, and caffeic acid.[9] Traditionally, it has been used to treat wounds, amenorrhea, bronchitis, asthma, indigestion, nausea, anxiety, insomnia, epilepsy, and depression. Research suggests *Melissa officinalis* possesses anti-inflammatory and antioxidant properties, mitigating liver enzyme elevation, renal dysfunction, and testicular damage caused by toxins.[10] This study aimed to evaluate the protective effects of *Melissa officinalis* extract on hepatic, renal, and testicular tissues in male rats exposed to lead toxicity.

MATERIAL AND METHODS

This Quasi experimental study was conducted in Isra University Hyderabad from October 2024 to March 2025 after getting approved from the Isra University Ethical Review Board. *Melissa officinalis* was sourced from Organica Pakistan. The extract was prepared following Eivani et al.'s method.[10] In summary, 150 grams of *Melissa officinalis* leaves were dried, finely ground, and soaked in 600 mL of 96% ethanol for 24 hours. After filtration, the remaining plant material underwent a second extraction using 70% ethanol for another 24 hours. Both filtrates were then combined and reduced to one-third of their volume with a rotary evaporator set at 50°C and 70 rpm. The resulting concentrate was oven-dried at 45°C, converted into powder form, and suspended in distilled water for oral administration via gavage.

A total of 40 Albino Wistar rats, each weighing between 180 and 200 grams, were procured from Sindh Agriculture University, Tandojam. The number of animals was determined using conventional power analysis techniques applicable to animal research.[11, 12] The rats were housed under controlled laboratory conditions, maintained at 23°C with a 12-hour light/dark cycle, and provided with unlimited access to food and water. Following a 15-day acclimatization period, the animals were randomly allocated into five experimental groups, with eight rats in each group, and subjected to treatment for five consecutive days.

Group A (control) received 1 mL/kg saline via gavage and an intraperitoneal saline injection 30 minutes later. Group B was given saline orally, followed by 20 mg/kg lead acetate intraperitoneally. Group C received 20 mg/kg *Melissa officinalis* extract by gavage, then 20 mg/kg lead acetate. Group D was treated with 100 mg/kg *Melissa officinalis* extract followed by the same dose of lead acetate after 30 minutes.

Twenty-four hours following the last dose, rats were sacrificed by cervical dislocation, and a heart puncture was used to draw blood. After centrifuging the samples for 20 minutes at 3000 rpm, the serum was kept for analysis at -20°C. Commercial kits from Biossay Technology were used to assess the levels of testosterone, urea, creatinine, ALT, ALP, AST, glutathione peroxidase (GPx), and C reactive protein (CRP) in accordance with the manufacturer's instructions. Using normal methods, sperm samples were taken from the cauda epididymis at the conclusion of the experiment and examined for motility, morphology, and count.[13,14] A light microscope was used to evaluate the morphological alterations for that purpose liver and kidney tissues were excised, fixed in 10% formalin, and processed for histological examination using hematoxylin and eosin (H&E) staining.[15,16] The collected was analyzed in SPSS ver. 22. The mean ± standard deviation (SD) of the data was displayed for quantitative variable. For analyzing the comparision between the variables, one-way analysis of variance (ANOVA) followed by post-hoc Tukey's analysis was used. The significance level of $p \leq 0.05$ was considered as significant.

RESULTS

Forty healthy male Albino Wistar rats, weighing 180-200 grams, were divided into four groups: Group A (control) received saline; Group B received saline and 20 mg/kg lead acetate; Group C was treated with 20 mg/kg *Melissa officinalis* extract, followed by 20 mg/kg lead acetate; Group D received 100 mg/kg *Melissa officinalis* extract, then the same lead dose. Group B received saline and 20 mg/kg lead acetate; Group C was treated with 20 mg/kg *Melissa officinalis* extract, followed by 20 mg/kg lead acetate; Group D received 100 mg/kg *Melissa officinalis* extract, then the same lead dose. The biochemical parameters of the experimental groups are presented in Table 1. Significant differences ($p < 0.001$) were observed in the levels of alanine transaminase (ALT),

aspartate transaminase (AST), alkaline phosphatase (ALP), urea, creatinine, and testosterone among the groups. Compared to the control group (Group A), the lead-exposed group (Group B) exhibited significantly elevated levels of ALT, AST, ALP, urea, and creatinine, indicating potential renal and hepatic dysfunction. In contrast, testosterone levels in Group B were considerably lower. Treatment with *Melissa officinalis* extract at both low (Group C) and high dosages (Group D) partially reversed these biochemical alterations, with Group D showing a more pronounced protective effect. Testosterone levels in Group D were significantly higher than in Group B, while ALT, AST, and ALP levels were notably lower, suggesting that *Melissa officinalis* may help mitigate lead-induced toxicity.

Table 2 summarizes the effects of lead exposure and *Melissa officinalis* treatment on sperm parameters, including sperm count, motility, and morphology. Lead exposure (Group B) resulted in a significant reduction in sperm count and motility compared to the control group (Group A) ($p < 0.001$). Sperm morphology was also adversely affected, with a marked increase in abnormal sperm forms in Group B. In contrast, the administration of *Melissa officinalis* showed a dose-dependent improvement in these parameters.

The results indicate a significant reduction in sperm count and motility in lead-exposed rats compared to controls ($p < 0.001$). Morphological abnormalities were markedly increased in Group B, with 26.2% of sperm showing abnormal morphology compared to 7.7% in the control group. In Group C, 18.4% of sperm exhibited abnormalities, whereas Group D showed a further improvement, with only 15.7% abnormal morphology. The primary abnormalities observed included tail defects, followed by head abnormalities.

Table 3 shows that lead exposure significantly increased serum CRP levels and reduced GPx levels, indicating inflammation and oxidative stress in Group B ($p < 0.001$). Treatment with *Melissa officinalis*, particularly at 100 mg/kg (Group D), notably lowered CRP and restored GPx levels close to control values, suggesting dose-dependent protective effects.

The liver photomicrographs of the several experimental groups (H&E × 400) are displayed in **Figure 1**. Hepatocytes in the control group were distributed in cords extending from the central vein, indicating normal hepatic architecture, according to histological analysis of liver tissues. Rats exposed to lead, on the other hand, showed signs of intranuclear inclusion bodies, bile duct hyperplasia, nuclear apoptosis, and severe vacuolar degeneration. Treatment with *Melissa officinalis* in Group C resulted in reduced vacuolar degeneration and mild granular changes in hepatocytes. Group D showed further improvement, with hepatic cords appearing more organized and fewer degenerative changes observed.

Table 1. Biochemical Markers of Liver and Kidney Function and Serum Testosterone Levels Across Experimental Groups

Group	Group A	Group B	Group C	Group D	p-value
ALT (U/L)	39.37 ± 2.5^{bcd}	155.22 ± 5.8^{acd}	109.71 ± 3.7^{abd}	59.96 ± 3.1^{abc}	**0.000***
AST (U/L)	37.43 ± 3.1^{bcd}	114.52 ± 2.6^{acd}	73.48 ± 7.5^{abd}	49.79 ± 4.5^{abc}	**0.000***
ALP (U/L)	42.28 ± 2.7^{bcd}	148.32 ± 4.7^{acd}	97.59 ± 4.9^{abd}	61.72 ± 3.9^{abc}	**0.000***
Urea (mg/dL)	23.51 ± 2.84^{bcd}	58.26 ± 3.46^{acd}	39.44 ± 1.21^{abd}	31.08 ± 2.18^{abc}	**0.000***
Creatinine (mg/dL)	0.46 ± 0.11^{bcd}	1.31 ± 0.42^{acd}	0.94 ± 0.25^{abd}	0.54 ± 0.13^{abc}	**0.000***
Testosterone (ng/ml)	2.2 ± 0.2^{bcd}	1.0 ± 0.15^{acd}	1.3 ± 0.2^{abd}	1.7 ± 0.26^{abc}	**0.000***

Table 2. Comparison of Sperm Parameters Among Experimental Groups

Group	Group A	Group B	Group C	Group D	p-value
Sperm Count ($x10^6$/ml)	4.11 ± 0.67^{bcd}	2.39 ± 0.38^{acd}	2.88 ± 0.54^{abd}	3.12 ± 0.36^{abc}	**0.000***
Sperm Motility (%)	81.2 ± 1.3^{bcd}	67.8 ± 3.5^{acd}	70.6 ± 2.8^{abd}	74.8 ± 2.4^{abc}	**0.000***
Sperm Morphology (%)	7.7 ± 1.2^{bcd}	26.2 ± 3.7^{acd}	17.1 ± 2.2^{abd}	12.4 ± 0.9^{abc}	**0.000***

Table 3. Comparison of Sperm Parameters Among Experimental Groups

Group	Group A	Group B	Group C	Group D	p-value
Serum CRP (mg/dl)	0.13 ± 0.12^{bcd}	0.86 ± 0.16^{acd}	0.66 ± 0.15^{abd}	0.48 ± 0.08^{abc}	**0.000***
Serum GPX (ng/dl)	1.48 ± 0.21^{bc}	0.79 ± 0.34^{acd}	1.13 ± 0.31^{abd}	$1.45 \pm 0.0.29^{bc}$	**0.000***

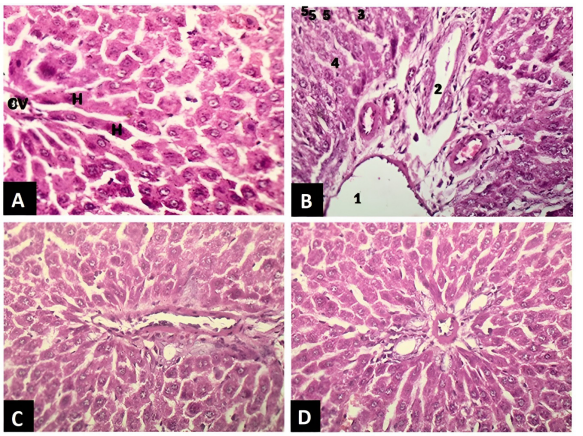

Figure 1. Histological sections of liver tissue from different experimental groups stained with H&E (×400). (A) Control group showing normal hepatic architecture with hepatocyte cords radiating from the central vein (CV). (B) Lead-exposed group exhibiting marked pathological changes including portal vein dilation (1), disrupted hepatic cords, bile duct hyperplasia and dilation (2), intranuclear inclusion bodies (3), extensive vacuolar degeneration (4), and varying degrees of nuclear degeneration (5). (C) Group C (20 mg/kg Melissa officinalis) showing mild granular changes and occasional intranuclear inclusions. (D) Group D (100 mg/kg Melissa officinalis) displaying largely preserved liver structure with minimal granular degeneration.

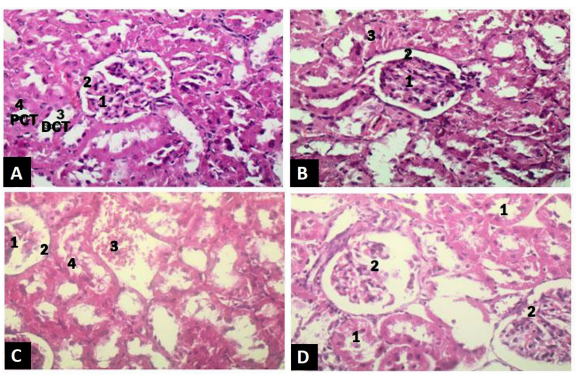

Figure 2. Histological examination of kidney cortex in experimental groups stained with H&E (×400). (A) Control group exhibits normal renal architecture, including intact glomeruli (1), Bowman's capsules (2), and well-preserved proximal (PCT) (3) and distal convoluted tubules (DCT) (4). (B) Lead acetate group reveals atrophic glomeruli (1), dilation of the subcapsular space (2), and extensive tubular damage with coagulative necrosis (3). (C) Group C (20 mg/kg Melissa officinalis) displays glomerular disruption (1), subcapsular space dilation (2), intertubular hemorrhage (3), and signs of tubular necrosis (4). (D) Group D (100 mg/kg Melissa officinalis) shows only mild glomerular and tubular damage with limited hemorrhagic changes.

Figure 2 shows the Photomicrographs of kidneys of different experimental groups (H&E × 400). Kidney histology demonstrated that the control group had normal glomeruli with intact Bowman's capsules and renal tubules. Lead exposure caused glomerular atrophy, dilation of the subcapsular space, and coagulative necrosis of renal tubules. In Group C, renal damage was still evident but less severe, with intertubular hemorrhage and moderate necrosis. Group D exhibited mild destruction of renal tubules and glomeruli, with signs of tissue recovery.

DISCUSSION

This study evaluated the impact of *Melissa officinalis* hydroalcoholic extract on serum testosterone, renal function indicators, and hepatic enzyme levels in rats subjected to lead toxicity. Findings revealed that treatment with *Melissa officinalis* at a dose of 100 mg/kg markedly lowered kidney function markers and liver enzyme levels when compared to the lead-exposed group. Furthermore, serum testosterone levels were notably higher in the Melissa extract treatment groups (100 mg/kg) than in the lead-only group. Consistent with previous research, the administration of 20mg/kg of lead acetate intraperitoneally for five consecutive days resulted in elevated liver enzyme levels along with an increase in renal function markers.[10] The toxic effects of lead on liver and kidney tissues may account for these biochemical alterations. Previous studies have shown that subtoxic concentrations of lead acetate induce structural changes in hepatocytes, sinusoids, and portal triads.[10] Moreover, prolonged lead exposure has been reported to cause degenerative changes in the proximal tubules of the kidney cortex.[17] Additionally, in alignment with previous research, testosterone levels in the blood dropped significantly following lead exposure.[18] Lead acetate has also been shown to suppress steroidogenesis in Leydig cells by inhibiting key enzymes such as 3β-hydroxysteroid dehydrogenase and P450scc, along with downregulating the expression of the StAR protein.[10,19]

The findings of this study suggest that *Melissa officinalis* plays a protective role in liver and kidney function, as rats treated with Melissa extract showed improved hepatic enzyme profiles and levels of renal function markers after lead exposure. This aligns with prior research indicating that Melissa extract effectively reduces hepatotoxicity and nephrotoxicity.[10] In this study, *Melissa officinalis* also enhanced plasma testosterone levels as well as sperm count, motility, and morphology in lead-exposed rats, suggesting a protective effect on the testes. Since testosterone is crucial for spermatogenesis, it can be inferred that Melissa extract mitigates lead-induced testicular damage which is consistent with previous research.[10] Similarly, ethanol exposure has been reported to reduce sperm count and suppresses gonadotropins

and testosterone levels, whereas Melissa extract supplementation restores these parameters.[20]

The protective effects of *Melissa officinalis* are largely attributed to its potent antioxidant and anti-inflammatory properties.[10,21] In this study *Melissa officinalis* administration was followed by a rise in serum GPx levels and a decline in serum CRP levels which is consistent with the findings of Draginic et al.[21] According to Sipos et al., the aqueous extract of Melissa exhibits antioxidant activity equivalent to 30% ascorbic acid, a potent antioxidant known for scavenging free radicals and protecting cellular components from oxidative stress.[22,23] Additionally, the antioxidant properties of *Melissa officinalis* are also attributed to its phenolic compounds and flavonoids, which are potent antioxidants and help reduce oxidative stress.[21,24] By neutralizing reactive oxygen species, these compounds help protect liver, kidney, and testicular tissues from damage.

Overall, the findings of this study support the potential therapeutic role of *Melissa officinalis* in mitigating lead-induced toxicity by improving liver and kidney function and preserving testosterone levels. Further research is needed to explore the underlying cellular mechanisms and to establish optimal dosing regimens for its protective effects.

Despite these findings, several limitations must be acknowledged. The study focused only on liver, kidney, and reproductive toxicity, without evaluating potential effects on other organ systems such as the nervous and cardiovascular systems. Lastly, only two doses (20 mg/kg and 100 mg/kg) were tested, leaving uncertainty about whether intermediate or higher doses might offer greater protection. Future research should address these gaps to better understand the full therapeutic potential of *Melissa officinalis*.

CONCLUSION

Melissa officinalis extract significantly protects against lead-induced hepatic, renal, and reproductive toxicity in rats, suggesting its therapeutic potential.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.

AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

Conception or Design:	TFM, KAM
Acquisition, Analysis or Interpretation of Data:	TFM, KAM, SK, FN, AAM, AAT
Manuscript Writing & Approval:	TFM, KAM, SK, FN, AAM, AAT

All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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