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Histopathological and ultrastructural alterations reveal the hepatotoxicity of lead against Moringin: Sub-chronic-chemotherapeutic trial

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ABSTRACT

Background: Several researchers in the past have described lead acetate (LA), Pb, as a toxic heavy metal compound that can significantly affect the organs and the body systems, thereby influencing their functions.

Aim: This article aimed to look at the negative effects of LA toxicity on rabbit liver samples, detect many histological abnormalities, and then examine the hepatoprotective properties of glucomoringin. Since ancient times, *Moringa oleifera* has been a rich source of antioxidants. Here, we orally gavaged Moringin extracted from *M. oleifera* seeds to the experimental animals to reduce toxicity.

Methods: In this study, 30 rabbits were randomly categorized into three groups, with every group containing 10 rabbits (i.e., $n = 10$). The animals in Group A (control) were administered distilled water, while those in Groups B and C were given a 2% oral LA solution. However, during the complete study duration, the animals in Group C were administered Moringin (100 mg/kg/rabbit).

Results: The findings in this study indicated that oral LA administration caused significant pathological changes in the livers of the experimental animals which included degeneration, fibrosis, necrosis, inflammation, significant reduction in the plasma catalase and superoxide dismutase activities, and increased plasma malondialdehyde activities. It was hypothesized that the administration of Moringin would mitigate the histopathological changes in the liver tissues. The results indicated that the extract displayed a hepatoprotective effect and considerably reduced the harmful effects of LA on the functions and hepatic tissue.

Conclusion: Finally, Moringin is highly efficacious in abating oxidative stress and cellular damage in rabbits.

Keywords: Adverse effects, Antioxidant, Hepatopathy, Lead acetate, Moringin.

Introduction

Lead is widely recognized as a significant environmental contaminant due to its extensive application in various manufacturing sectors (Poli *et al.*, 2022). Both industrialized nations and developing economies face substantial risks from environmental and occupational exposure to harmful pollutants (Medjedded *et al.*, 2024). Even trace amounts of toxic heavy metals such as lead pose serious threats to human and animal well-being (Mesalam *et al.*, 2023). Exposure to lead manifests through numerous health issues, including anaemia, weight loss (Kahalerras *et al.*, 2022), kidney damage, infertility, liver toxicity, cardiovascular problems, reproductive dysfunction, and several other disorders (Gurer-Orhan *et al.*, 2004). It exacerbates oxidative degradation in liver cells by promoting lipid peroxidation of membranes (Adeyomoye *et al.*, 2022),

a damaging sequence driven by oxygen-derived free radicals (Jomova *et al.*, 2024). The toxic effects of lead are primarily linked to elevated oxidative stress levels in soft tissues and blood caused by lead exposure (Lakka *et al.*, 2023). Cellular damage arises when the equilibrium between oxidants and antioxidants becomes disturbed (Abdelhamid *et al.*, 2020). Research has shown that lead not only heightens lipid peroxide levels but also alters the antioxidant defence mechanisms in hepatic tissue (Rauf *et al.*, 2024).

Additionally, reactive oxygen species (ROS) have been identified as key contributors to the intensification of lead-induced toxicity in biological systems. In the past few years, many researchers have expressed their interest in determining the significance of oxidants and antioxidants in the field of medicine, biology, and nutrition research (Jomova *et al.*, 2023). Studies

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have shown that the continuous production of pro-oxidants like the free oxygen radicals is essential for the sustenance of aerobic life. ROS signalling molecules, including nitric oxide, hydroxyl radical, and superoxide anion (O_2^-), are highly reactive free radicals due to their unpaired electron. These radicals occur in the body as a consequence of various metabolic activities but are usually restricted within specific cellular compartments. Conversely, certain endogenous antioxidants—for instance, glutathione peroxidase (GPx), glutathione (GSH), vitamins C and E, and superoxide dismutase (pSOD)—are scavengers of radicals that are free, helping to neutralize excess ROS production (Abdollahi *et al.*, 2014). A previous research revealed that free radicals caused by pathological mechanisms following lead exposure, suggesting that supplementing antioxidants might offer an effective alternative to conventional chelation therapies (Amadi *et al.*, 2019). An uncommon glucosinolate extracted from *Moringa oleifera* seeds, known as the hydrolysis derivative of glucomoringin (GMG) or Moringin (GMG-ITC), comprises various bioactive compounds such as reducing sugars, alkaloids, tannins, sterols, terpenoids, anthraquinones, flavonoids, and saponins (Abd Karim *et al.*, 2023). The seeds are particularly abundant in rhamnose sugars and unique compounds such as glucosinolates and isothiocyanates, with their beneficial effects largely attributed to phytochemicals such as flavonoids and isothiocyanates. Additional bioactive components include glucosinolates, phenolic acids, niazirin, terpenes, niazinin, quercetin, gossypetin, sitosterol, and ascorbic acid (Patil *et al.*, 2022). Beyond *M. oleifera*, extracts from *Garcinia hombroniana* bark and essential oils obtained from *Tarchoanthus camphoratus* leaves and stems also displayed potent antioxidant properties (El Kamari *et al.*, 2023). Research demonstrated that *M. oleifera* L extracts effectively suppressed lipid peroxidation by maintaining key antioxidant enzyme activities, including pSOD, catalase (pCAT), and GPx, in the plasma of treated animals. Another study assessed the influence of *Juniperus phoenicea* extracts on liver antioxidant enzymes in oxonate-administered rats (Gdoura *et al.*, 2013; Vo *et al.*, 2024). However, to our knowledge, no prior investigation has examined the efficacy of Moringin derived from *M. oleifera* seeds in alleviating lead-induced oxidative injury in hepatic tissue homogenates. Hence, in this study, we explored whether orally administering the extract to rabbits could mitigate liver damage, such as hepatocyte degeneration, necrosis, and fibrosis, triggered by lead acetate (LA) exposure.

Research aims

Inspect pathological mechanisms behind LA toxicity, utilizing rabbits as the experimental model. Gain deeper insights into the harmful impact of LA exposure across different toxic dosage levels. Lay the groundwork for future studies focused on LA toxicity and the adverse

effects of trace elements in both humans and animals. Evaluate the protective potential of Moringin's antioxidant activity against LA-induced hepatic injury.

Materials and Methods

Setup of the experiment

Thirty rabbits of both sexes, aged between 6 and 12 months, with body weights ranging from 1,200 to 1,750 gm, were looked after in line with the World Health Organization's (WHO) guidelines for breeding and caring for laboratory animals. More specifically, they were given a basic diet and plenty of fresh drinking water. They lived in stainless-steel cages maintained at a temperature of $21^\circ\text{C} \pm 2^\circ\text{C}$, a constant humidity level ranging from 40% to 70%, 12 hours of light, and 12 hours of darkness.

Grouping

The 30 animals were separated randomly into three groups, with the control Group (A) receiving distilled water, the 2% LA Group (B) receiving 2% LA solution, and the LA+Moringin Group (C) receiving 2% LA+Moringin (100 mg/kg/rabbit) solution.

Animal blood and tissue sampling

All rabbits enrolled in this experiment were euthanized 3 months after the final treatment session. Blood samples were drawn via cardiac puncture several hours before euthanasia to facilitate subsequent biochemical evaluations. These blood samples that were collected from each animal were separated into 2 parts, wherein one part of the sample was kept in a plain bottle, whereas the second part of the sample was added to a bottle containing ethyl di-amine tetra acetic acid. Also extracted the hepatic tissues from each animal and fixed the tissues in the 10% (v/v) saline formalin solution. The preserved liver tissues were sectioned, mounted onto glass slides, and subjected to haematoxylin and eosin (H&E) staining to carry out further histopathological examinations. Here, the procedures outlined in earlier research for sample preparation and plasma extraction are used to determine the activity of plasma enzymes. Such as pSOD, pCAT, and malondialdehyde (pMDA).

Animal tissue preparation and microscopic examination

Specimens of hepatic tissue were extracted from the animals immediately after sacrificing all the animals, 3 months after treatment. Thereafter, these tissues were sliced into sections and fixed with the help of a 10% (v/v) saline formalin solution. After fixing, these samples were processed and embedded in liquid paraffin. The paraffinized tissue blocks were sliced using a rotatory microtome into 5 μm -thick slices, deparaffinized, and stained using H&E stains. Finally, these samples were examined using an Olympus® light microscope to determine the LA treatment-induced histopathologic changes (Hayat and Giaquinta, 1970).

Data collection method and statistical analyses

After collecting the liver tissue samples from the animals in every group, the samples were homogenized, and the cell-free supernatant was used to determine the

Table 1. Alterations in the antioxidant biomarkers and lipid peroxidation/enzymes (mean $\pm$ SE) of all the groups.

Group (n = 10)	pSOD	pCAT	pMDA
(A) Control	1.966 $\pm$ 0.05	0.388 $\pm$ 0.03	0.25 $\pm$ 0.04
(B) 2% LA(Pb)	1.131 $\pm$ 0.05*	0.2451 $\pm$ 0.02*	4.1 $\pm$ 0.06*
(C) 2% LA(Pb)+ Moringin [100 mg/kg/rabbit/daily]	1.791 $\pm$ 0.06*	0.3697 $\pm$ 0.01	2.2 $\pm$ 0.06*

*Statistically significant at $p < 0.05$; data are mean $\pm$ SE (compared with Group A and Group C).

*Bold values statistically significant at $p < 0.05$.

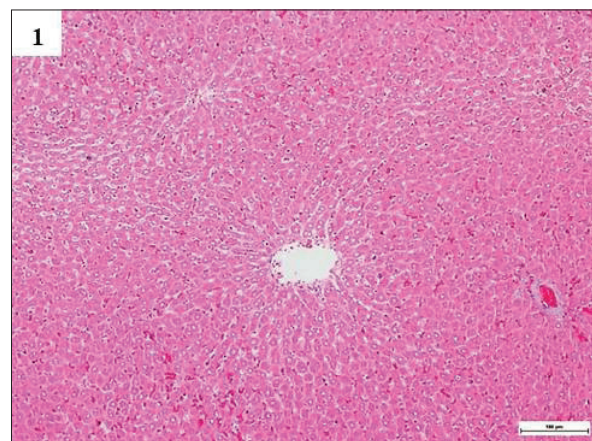


Fig. 1. Photomicrographs of H&E-stained livers in the sub-chronic trial at 10 $\times$ magnification. The livers in Group A were normal, having sinusoidal capillaries and hepatocytes positioned regularly around the central vein.

activities of enzymes such as pSOD, pCAT, and pMDA based on the processes described in the past (Ahmed *et al.*, 2000). Here, the researchers carried out statistical analysis and presented the values as mean $\pm$ SE. The mean value differences were compared using the IBM® SPSS® 22.0 software and the one-way ANOVA test. The $p < 0.05$ was regarded as a statistically significant value.

Results

Therapeutic efficacy of Moringin and lead acetate (LA)-induced oxidative stress on liver enzymes and biomarkers

The findings in this study are described as mean $\pm$ SEM. Values showing $p < 0.05^*$ were deemed to be significant. After conducting the enzymatic analysis of the liver tissue samples, the animals in Group B showed a significant decrease ($p < 0.05$) in their pSOD and pCAT enzyme activities in comparison to Group A. However, the liver tissue extracts of the Group C animals did not present any significant variation ($p > 0.05$) in their pCAT and pSOD enzyme activities in comparison to the Group A animals. Additionally, when compared to Group A, the pMDA activity of the animals in Group B was seen to be significantly higher ($p < 0.05$), whereas the pMDA activity of the animals in Group C did not show any statistical difference ($p > 0.05$) (Table 1).

Histopathological examinations and lesion scoring of animal Groups A and B

In this study, the histological lesions present in the liver tissue samples examined and the findings of all the experiments were compiled. The findings showed that the liver slices extracted from Group A animals displayed a normal level, wherein the tissues showed the presence of normally placed hepatocytes that surrounded the central vein, in addition to general sinusoidal capillaries (Figs. 1 and 4) (Table 2). However, the liver tissue slices extracted from the animals in Group B displayed significant treatment-induced histopathological changes, which included vacuolation, degeneration, and necrosis of hepatocytes with the accumulation of inflammatory cells, especially mononuclear cells; also noted clear swelling of hepatocytes, or became like balloons. Some samples displayed histological changes related to capsular and advanced septal fibrosis. Further histopathological analysis revealed that the rabbits had hepatitis since the infiltration of inflammatory cells was noted in addition to their congestion (Figs. 2A–G and 5A–C) (Table 2). On the other hand, the analysis of the liver sections extracted from the Group C animals did not display any structural variations (Figs. 3A and B, 6A and B) (Table 2).

Discussion

In this work, the enzymatic and histological investigations were employed to determine if the extended exposure of the experimental rabbits to Pb had caused liver damage. The findings showed that the Pb-administered rabbits (Group B) had higher levels of pMDA activity (Table 1). Comparable findings were previously reported by Hasan (2024), who observed a marked elevation in plasma enzyme activities, comprising alkaline phosphatase, alanine transaminase, and aspartate aminotransferase, along with increased hepatic pMDA levels. Elevated lipid peroxidation coupled with reduced GSH concentrations pointed to lead-induced oxidative stress within liver tissues (Hasan, 2024). The Pb-exposed animals absorb and retain the Pb ions within their soft tissues, particularly the liver (Hashim *et al.*, 2024). The liver is the first organ in the body that gets exposed to the toxins and absorbed nutrients, which enter via the portal vein (Okediran *et al.*, 2019; Mueed *et al.*, 2023). As a result, we conducted a histological analysis of the liver tissue to investigate

Table 2. Sub-chronic lesion scoring for liver tissue obtained from treated and untreated groups.

Liver tissue	Lesions	Cx	2% LA(Pb)	2% LA(Pb)+ Moringin
Perivenous zone	Congestion	0.00	0.23 ± 0.01	0.10 ± 0.00
	SSD	0.00	0.47 ± 0.01*	0.13 ± 0.01
	HHP	0.00	0.45 ± 0.01*	0.10 ± 0.00
	HN	0.00	0.45 ± 0.01*	0.09 ± 0.00
	C& FD	0.00	0.05 ± 0.01	0.00 ± 0.00
	KCPA	0.00	0.3 ± 0.02*	0.09 ± 0.00
	Total score of zone	0.00	1.96	0.51
Midzonal	Congestion	0.00	0.17 ± 0.01	0.08 ± 0.01
	SSD	0.00	0.42 ± 0.01*	0.11 ± 0.01
	HHP	0.00	0.21 ± 0.01	0.05 ± 0.01
	HN	0.00	0.23 ± 0.01	0.07 ± 0.00
	C& FD	0.00	0.01 ± 0.00	0.00
	KCPA	0.00	0.18 ± 0.01	0.01 ± 0.00
	Total score of zone	0.00	1.22	0.32
Periportal zone	Congestion	0.00	0.11 ± 0.01	0.08 ± 0.01
	SSD	0.00	0.34 ± 0.01*	0.10 ± 0.00
	HHP	0.00	0.26 ± 0.01	0.07 ± 0.01
	HN	0.00	0.18 ± 0.00	0.02 ± 0.02
	C& FD	0.00	0.02 ± 0.00	0.01 ± 0.00
	KCPA	0.00	0.19 ± 0.00	0.01 ± 0.01
	Total score of zone	0.00	1.10	0.28
Liver total score		0.00	4.29	1.11

SSD: Sinusoidal space dilation, HN: Hepatocellular necrosis, HHP: Hepatocellular hypertrophy, C&FD: Cystic and fatty degeneration, KCPA: Kupffer cells phagocytic activity. Data are expressed as the mean ± SE.

*Significant difference at the 0.05 level.

*Bold values significant difference at the 0.05 level.

the resultant morphological and ultrastructural changes by using a light and transmission electron microscope, which indicated the toxic impact of Pb on hepatocytes. Our results showed that the hepatocytes displayed several significant changes, such as degeneration, vacuolation, and necrosis, with a higher fibrosis level, and hepatitis caused by the infiltration of inflammatory cells. A prior investigation (Mueed *et al.*, 2023) documented comparable outcomes, noting that lead exposure through contaminated water triggered various pathological changes, including hepatic vein dilation, vascular congestion, and widespread hepatocellular degeneration and necrosis. Multiple studies (Shalan *et al.*, 2023) have also highlighted similar hepatotoxic impacts on liver tissues, revealing histological alterations such as enlarged blood vessels, dilated central veins, and sinusoidal hemorrhaging. Furthermore, many researchers claimed that Pb was very detrimental to liver tissue because it caused fibrosis and inflammation of hepatocytes. Lead (Pb) toxicity led to many pathological changes/ abnormalities in the liver, which differed according to

exposure duration, administration route, and animal model type (Shalan, 2024). The microscopy analysis of hepatic tissue samples in Group C animals revealed that many of the histopathological abnormalities observed in Group B had been significantly reduced. Group C animals (Figs. 3A and B, 6A and B) demonstrated a significant decrease in hepatic tissue cellular deteriorations in comparison to Group B (Figs. 2A and G and 5A and C), (Table 2). These findings indicated that Moringin displayed a protective effect against the different pathological events that occurred in the rabbits because of Pb-hepatotoxicity. Previous presentations of comparable findings have shown that Moringin successfully prevented hepatotoxicity (Sharida *et al.*, 2012; Singh *et al.*, 2014). Additionally, comparable outcomes were reported by Saalu *et al.*, (2012),; Sharifudin *et al.* (2013)), where it was demonstrated that animals treated with *M. oleifera* leaf extract experienced notable protection against hepatic injury, showing no significant rise in lipid peroxidation levels even after exposure to multiple toxins and liver-damaging agents. They concluded that *M. oleifera*

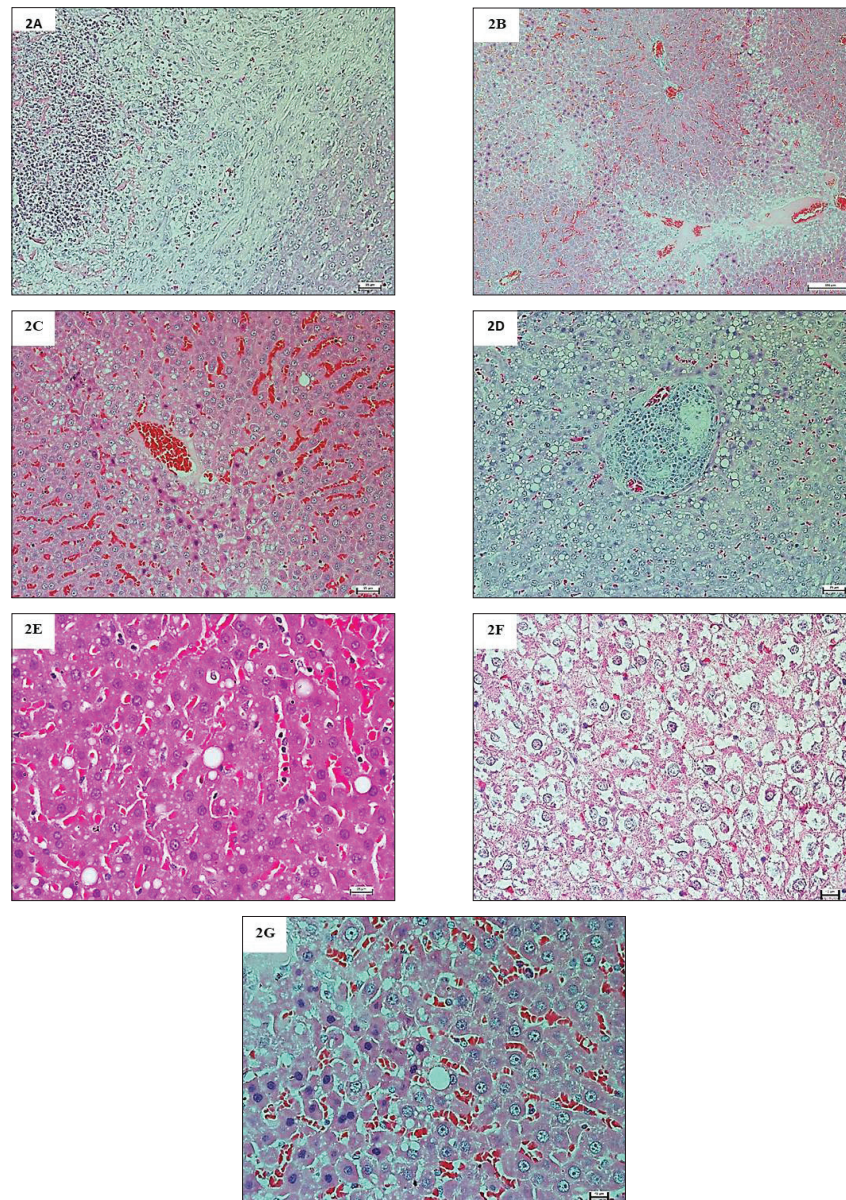


Fig. 2. (A). Photomicrographs of H&E-stained livers in the sub-chronic trial at 10× magnification. The livers in Group B were abnormal, appeared hepatocellular necrosis, with periductal fibrosis surrounding the bile ducts and severe dilation of sinusoidal spaces. (B). Photomicrographs of H&E-stained livers, at 10× magnification. The livers in Group B were abnormal, the central vein and sinusoidal spaces were severely dilated and congested, while appeared severe steatosis in the centrilobular zone. A huge number of inflammatory cells had infiltrated, especially in the periportal region. (C). Photomicrographs of H&E-stained livers at 20× magnification. The livers in Group B were abnormal, the central vein and sinusoidal spaces were severely dilated and congested, while severe steatosis was in the centrilobular zone. Hepatocellular necrosis was also observed, with periductal fibrosis surrounding the bile ducts. (D). Photomicrographs of H&E-stained livers at 20× magnification. The livers in Group B were abnormal, hepatocellular necrosis was observed, with periductal fibrosis surrounding the bile ducts. A highly infiltrated area of inflammatory cells especially in the periportal region, which formed non-small nodules. (E). Photomicrographs of H&E-stained livers at 40× magnification. The livers in Group B were abnormal, clear ballooned hepatocytes, with Mallory-Denk bodies, and a huge number of inflammatory cells had infiltrated, especially in the periportal region, as well as the Kupffer cells, hypertrophy and hyperplasia. (F). Photomicrographs of H&E-stained livers at 40× magnification. The livers in Group B were abnormal, clear ballooned hepatocytes, with Mallory-Denk bodies, and a huge number of inflammatory cells had infiltrated, especially in the periportal region, as well as periductal fibrosis surrounding the bile ducts. (G). Photomicrographs of H&E-stained livers at 40× magnification. The livers in Group B were abnormal, and hepatocellular necrosis was observed, with periductal fibrosis and clear ballooned hepatocytes, with Mallory-Denk bodies, as well as the Kupffer cells, hypertrophy and hyperplasia.

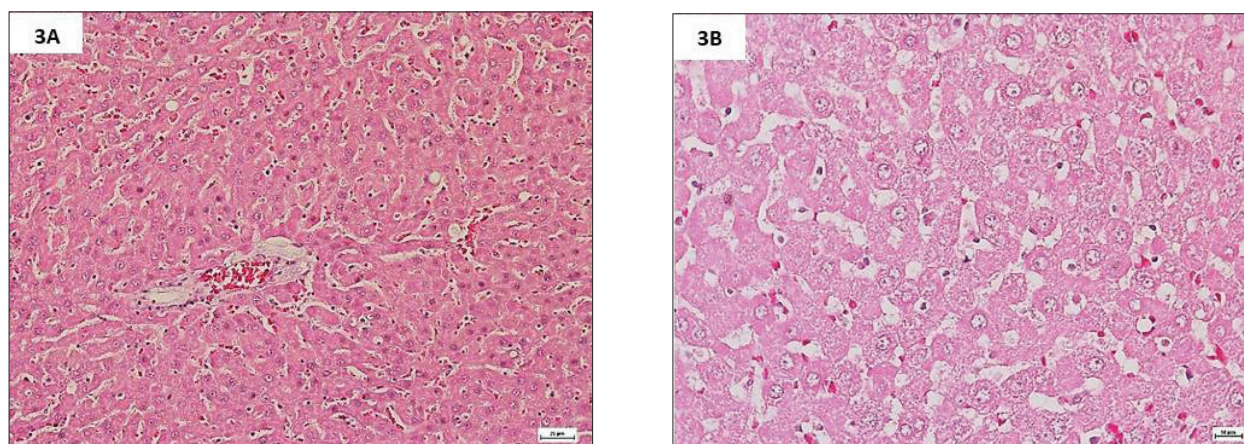


Fig. 3. (A). Photomicrographs of H&E-stained livers in the sub-chronic trial at 20× magnification. The livers in Group C had significantly smaller hepatotoxic lesions with minimal necrotic cells, no cystic or fatty degeneration, and no inflammatory cells infiltrations. (B). Photomicrographs of H&E-stained livers in the sub-chronic trial at 40× magnification. The livers in Group C, a fewer hypertrophic and hyperplastic periportal Kupffer cells and hepatocytes, with minimal necrosis, no cystic or fatty degeneration, and no inflammation, despite necrosis and mild congestion. Moringin can therefore counteract the negative effects of Pb-induced liver damage and has a strong protective effect.

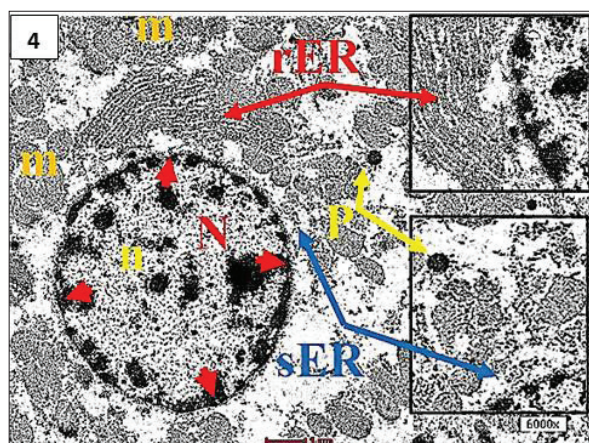


Fig. 4. TEM. from control group, showing normal appearance of hepatocyte with a euchromatic nucleus (N) as well as developed a nuclear membrane (red head arrow), and the cytoplasm contains normal mitochondria (m), an array of rough endoplasmic reticulum (rER) and smooth endoplasmic reticulum (sER), and normal peroxisome (p).

significantly decreased the animals' oxidative stress caused by alcohol or paracetamol, or other ROS and RNS inducers. Several studies have postulated that ROS are key contributors to lead-induced toxicity (Gurer-Orhan *et al.*, 2004). Previous research has extensively examined how different antioxidant enzymes and molecules influence Pb-triggered oxidative stress in both humans and animals. Diminished levels of GSH and glutathione disulfide, along with altered pSOD activity, were frequently cited as primary indicators of Pb-related hepatotoxicity in blood and tissue samples (Okediran *et al.*, 2019). Some researchers

(Borekar *et al.*, 2024) suggested that antioxidant supplementation might serve as a viable alternative to chelation therapy, as Pb exposure typically generates free radicals during disease progression. Numerous studies have highlighted that ascorbic acid, commonly known as vitamin C, functions effectively as a chelating agent with antioxidant properties, offering cellular defence against oxidative stress (Borekar *et al.*, 2024). Additionally, tomatoes and their derivatives are excellent sources of antioxidants due to their rich content of vitamins A, C, and lycopene (Abdollahi *et al.*, 2014). The experimental results revealed no significant variation ($p > 0.05$) in the pSOD activities of Groups C and A. However, the animals in Group B showed significantly lower pSOD activities ($p < 0.05$) than Group A. Comparable observations were documented previously (Simatupang *et al.*, 2024). Animals in Group B showed a marked decline ($p < 0.05$) in their plasma catalase pCAT activity compared to those in Group A. Conversely, there was no notable difference ($p > 0.05$) in pCAT activity levels between Groups A and C. Based on the above findings, we concluded that even though the animals in Group C were exposed to Pb toxicity, the dosage of Moringin that was administered to the animals could reduce their Pb-based oxidative stress. Additionally, no significant variation ($p > 0.05$) was found in both tissue and plasma MDA concentrations between Groups A and C. However, Group B revealed a significantly elevated ($p < 0.05$) pMDA concentration. These results suggest that Moringin extract, abundant in antioxidants, effectively countered the oxidative damage triggered by lead exposure in the animals receiving Moringin supplementation. In summary, since Moringin contains several types of antioxidants, it can effectively mitigate

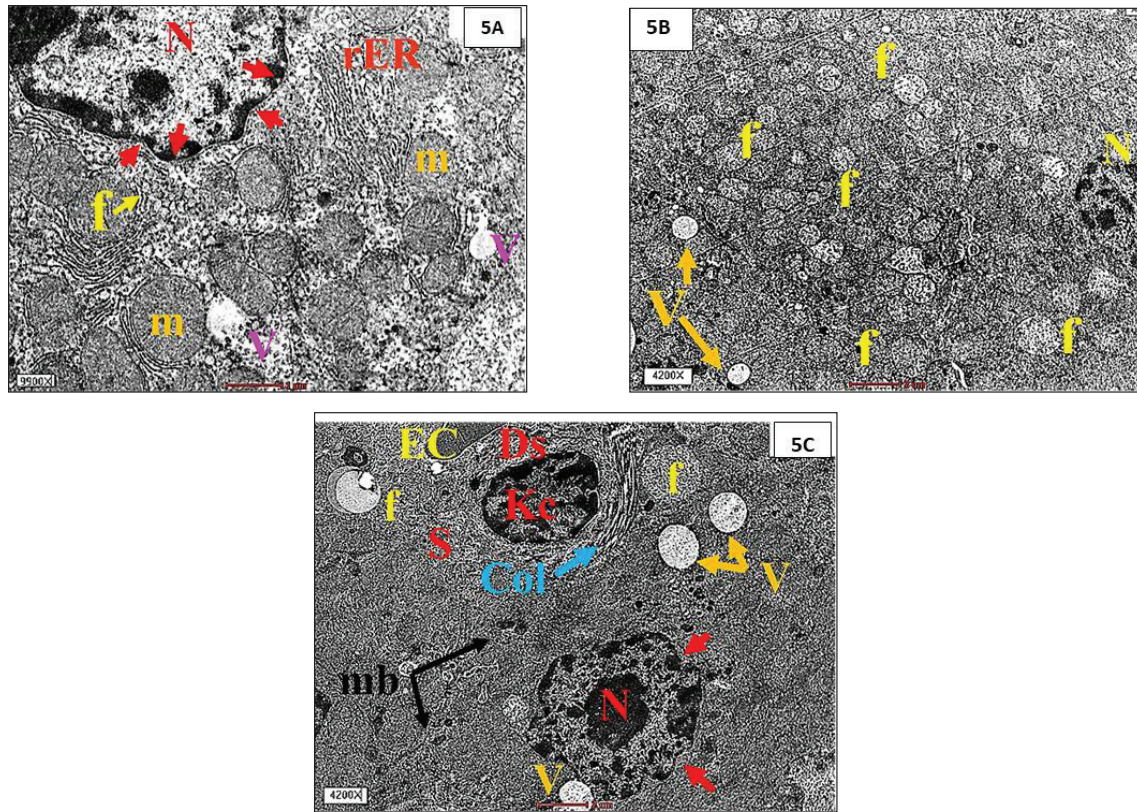


Fig. 5. (A). TEM from the LA-treated group, showing, hepatocytes with intracytoplasmic vacuolization (V), swollen mitochondria (m), electro-dense bodies\ Mallory bodies (mb)\(f) and debris of necrotic nuclei, a lot of lysosomes (Ly). (B). TEM from the LA-treated group, showing, hepatocytes with intracytoplasmic vacuolization (V), swollen mitochondria (m), electro-dense bodies\ Mallory bodies (mb)\(f) and debris of necrotic nuclei, a lot of lysosomes (Ly). (C). TEM from the LA-treated group, showing, dilated blood sinusoids (S) with severe hypertrophic Kupffer cells (KC), severe dilated smooth endoplasmic reticulum (sER) and highly proliferation of peroxisome (P), and a higher magnification of cytosol immediately adjacent to the nucleus and collagen fibers adjacent to Kupffer cells.

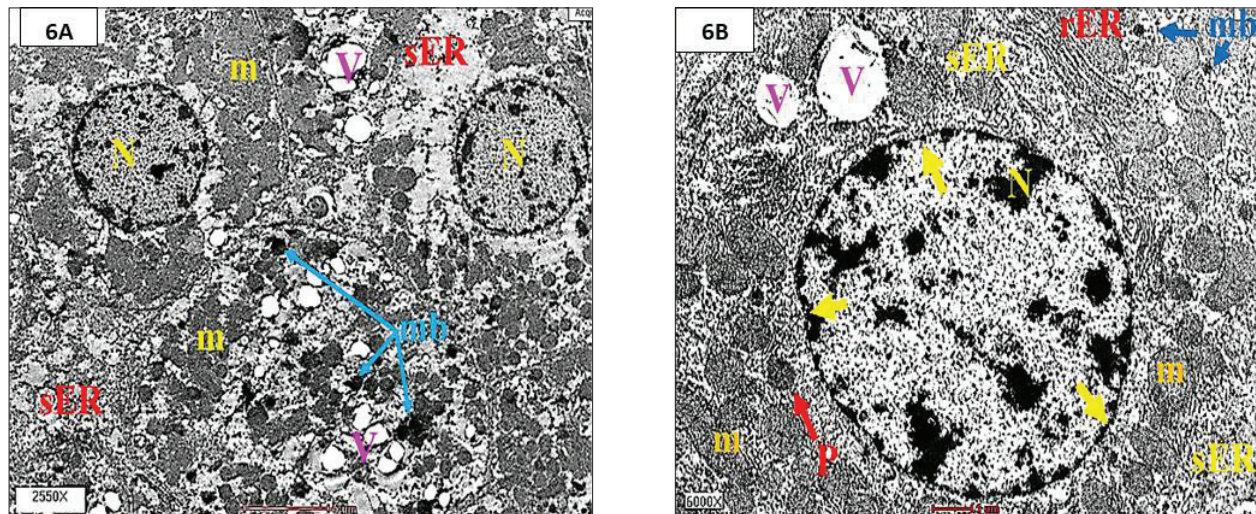


Fig. 6. A and B. TEM from the LA+Moringin group, illustrating pronounced reduction in the hepatocellular degeneration and necrosis and Kupffer cells hypertrophy with significant diminution in the highly increased amount of sER and peroxisome, normal appearance of hepatocyte with an euchromatic nucleus (N) as well as developed a nuclear membrane (yellow head arrow).

the hepatotoxicity resulting from the Pb-induced oxidative damage to the hepatic tissue.

Conclusion

In summary, findings from this study demonstrated that Moringin, derived from *M. oleifera* seeds, exhibits powerful antioxidant, anti-proliferative, and liver-protective effects. Consistent oral dosing of Moringin at 100 mg/kg proved beneficial as both a preventive strategy and supportive therapy against the onset, progression, and persistence of lead-induced liver toxicity in rabbits. Moringin provides substantial hepatoprotective action, contributing to the prevention of hepatic lesions and minimizing their intensity over prolonged exposure periods.

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Conflicts of interest and funding declaration

The manuscript was not funded, and there are no conflicts of interest.

Ethical statement

The Animal Care and Use Committee (ACUC) of the Faculty of Bio-Medical Science at Universiti Putra Malaysia (UPM) approved this study (UPM/IACUC/AUP-R082/2015).

Authors' contribution

The author designed and implemented the research, analysed the results, and wrote the manuscript.

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