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The Impact of Metformin on Dust-Induced Histopathological Changes and Oxidative Stress in the Liver: An Insight into Dust Concentration and Liver Biomarkers in Animal Models

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Abstract

Background: Environmental pollution has a profound impact on both human and animal life. Khuzestan province, which has been plagued by intense dust storms and pollution for decades, is the focus of this study. The research aims to investigate the protective effects of metformin against the toxicity of particulate matter in the livers of rats.

Methods: Male Wistar rats were selected for the study and divided into six groups: a control group, Metformin-treated groups, Iraqi dust-exposed group (Iraqi-D), Local dust-exposed group (Local-D), Iraqi dust-exposed with Metformin treatment group (Iraqi-D+Metformin), and Local dust-exposed with Metformin treatment group (Local-D+Metformin). The rats were exposed to local and Iraqi dust through a nebulizer and received oral metformin for a duration of 21 days. At the end of the intervention, liver biomarkers and oxidative stress factors were evaluated enzymatically.

Results: The study revealed that rats exposed to Iraqi and local dust experienced a significant increase in liver biomarkers, including aspartate aminotransferase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALK) levels, alongside a decrease in glutathione (GSH) concentrations and an increase in malondialdehyde (MDA) levels. However, treatment with metformin was effective in preventing the increase in these biomarkers, restoring GSH levels, and averting the rise in MDA levels, as compared to the control group.

Conclusion: Exposure to particulate matter from Iraq and the local region can induce alterations in biomarkers and oxidative stress levels in the rat liver, and these effects can be mitigated through metformin treatment.

Keywords: Dust, Liver Biomarker, Metformin, Oxidative Stress, Pollution.

Introduction

An important challenge faced by the field of public health is the increase in diseases and fatalities caused by environmental toxins, particularly in developing nations. Particulate

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matter (PM) refers to atmospheric pollutants with varying sizes and compositions based on their natural or human-derived sources. These particles are categorized into three distinct sizes based on their aerodynamic diameter: ultrafine, fine, and coarse, with diameters less than 0.1 μm, 1 μm, and greater than 1 μm, respectively.

Previous research has indicated that PM can adversely affect organs such as the kidneys, liver, and nervous system (1-3). However, the mechanisms of PM exposure on non-target tissues like the liver remain poorly understood. Recent scholarly investigations have been conducted to examine the relationship between hepatic toxicity and air pollution (4). Liver enzymes are commonly used to assess liver function in clinical settings (5). It has been observed that individuals living near oil drilling sites experienced elevated levels of aspartate transaminase (AST) and alanine transaminase (ALT) due to prolonged exposure to air pollutants (6). Zhang et al. found a correlation between high PM levels over two years and increased AST and ALT levels in participants of adult medical screening programs (7).

Studies have indicated that rats exposed to PM exhibited increased serum AST and ALT levels and liver histopathological changes (8). Exposure to particulate matter induces oxidative stress, which is a crucial factor in liver disease (9, 10). The inhalation of PM can generate reactive oxygen species (ROS) in the lungs, leading to oxidative stress through redox reactions with lung antioxidants (9). Several studies have reported a reduction in glutathione (GSH) levels in lung tissue or cells following exposure to PM, as well as an increase in oxidized glutathione (GSSG) (11). Levels of malondialdehyde (MDA) in urine, serum, or exhaled breath condensate (EBC) have been closely monitored as indicators of oxidative stress induced by air pollution within the human body. Numerous investigations have established a correlation between increased exposure to PM and elevated MDA levels. For example, an increase in airborne PM was associated with a 10% to 20% rise in urinary MDA levels per interquartile range (IQR) (12).

This research aimed to gain a deeper understanding of the potential impact of air pollution on the liver by exploring the relationship between short-term exposure to PM and the levels of liver enzymes and oxidative stress in male Wistar rats. The researchers hope that the findings of this study will shed light on the mechanisms connecting air pollution with PM to human health and, subsequently, aid in the development of effective pollution mitigation strategies that promote public health.

Materials and Methods

Biochemical analysis

Metformin was procured from Dr. Abidi's pharmaceutical company in Iran. Formaldehyde, Ellman's reagent (DTNB), Hematoxylin-eosin, and thiobarbituric acid were obtained from Sigma-Aldrich Company. Furthermore, Pars Azmoon Company in Iran provided kits for the determination of ALT, AST, and ALK activities.

PM collection

Dust sampling was conducted in Ahvaz, Iran, at the Agricultural and Natural Resources Research Center, using the glass table method. A glass surface measuring one square meter, with edges of 10 cm in height, was constructed. The particles that settled on this glass surface during dust events were subsequently collected with a spatula and packed into sampling containers before strong winds occurred.

Particle characterization

The chemical elements of the particles were determined using Inductively Coupled Plasma Mass Spectrometry (ICP-MS), and the measurement of the concentration of metals and chemical compounds was conducted on the collected Iraqi and local particles. Teflon containers were filled with a specific weight of particles, to which 2.5 ml of nitric acid, 2.5 ml of perchloric acid, and 5 ml of concentrated hydrofluoric acid were

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added. These containers were then placed in an oven at a temperature of 170 °C for 4 hours. The resulting cold solution was subsequently dried on a heater at 95 °C, with 2.5 mL of nitric acid being added, and the volume increased to 50 mL using distilled water. The final solution was then utilized in the Spectra ICP-MS machine to identify the heavy metals present. The particle's size, shape, and dominant compounds were determined through scanning electron microscopy (SEM) and X-Ray diffraction (XRD) analysis (Philips Model).

Dust exposure

A clear and sturdy plastic enclosure, measuring 40 cm in length, 30 cm in width, and 22 cm in height with an air capacity of 26,400 cm^3, was created to simulate a dusty environment. A dust vent was positioned on the top of the enclosure to allow for the entry of dust particles, which was kept under laboratory conditions to prevent air exchange during the trial. Rats were exposed to PM for 21 consecutive days using a nebulizer while being anesthetized with ketamine and xylazine and monitored with a portable dust monitor.

Dust concentration

Different suspension agents were tested at varying concentrations to suspend dust particles. Tragacanthin proved unsuitable due to its thickness and limited suspension time. Carboxymethyl cellulose (CMC) was found to be effective at suspending dust particles at concentrations of 1%, 0.5%, and 0.2%, with increasing concentrations leading to longer suspension times.

In vivo analysis

Forty-two adult male Wistar rats (250-300 g) with 6-8 weeks of age were obtained from the animal house of AJU MS and maintained under standard conditions, including a 12 h dark-light cycle, a temperature of 22 ± 3 °C, and a humidity of 40-50%. The rats were fed a rat chow diet and provided with free access to water. The study involved randomly dividing the rats into two groups: the control group and the Iraqi and local PM-receiving groups (n=7). The rats' weights were measured before and after the experiment, and the permissible dose of metformin (250 mg/kg) was determined based on mg/kg. Distilled water gavage was used to homogenize the stress condition between the four animal groups: dust, treated, control, and metformin groups. Metformin powder was dissolved in 1 mL of distilled water for the study. The first group, known as the Control Group, was given 1 mL of distilled water an hour before being exposed to the nebulizer. Nebulization was then performed using 0.5% CMC. The second group, known as the Metformin Group, was given 1 mL of metformin solution an hour before exposure to the nebulizer. Nebulization was then performed with 0.5% CMC. The third group, Iraq-D (Iraq Dust Group), was given distilled water before exposure to the nebulizer. The rats in this group were then exposed to 100 mg of Iraqi dust dissolved in 0.5% CMC solution for an hour. Finally, the Local-D (Local Dust Group) received distilled water before exposure to the nebulizer. The rats were subjected to a dose of 100 mg of local dust dissolved in a 5% CMC solution for one hour. In the Iraq-D + Met group, an hour before exposure to the nebulizer, metformin was administered to the rats via gavage. Subsequently, the rats were exposed to 100 mg of Iraqi dust dissolved in a 5% CMC solution for 1 h. The Local-D + Met group also received metformin via gavage an hour before exposure to the nebulizer. The rats were then exposed to 100 mg of local dust dissolved in a 5% CMC solution for 1 h. After 21 days of exposure, the rats were euthanized, with all subjects anesthetized using ketamine and xylazine (100 and 10 mg/kg) and prepared for further investigation.

Tissue extraction and analysis

At the end of the treatment period, animals were anesthetized to collect blood and dissect the liver. Liver sections were collected and stained with Hematoxylin-Eosin for

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evaluation of histopathology. A liver tissue sample was frozen for oxidative stress evaluation. Blood samples were also collected and sera were frozen for biochemical tests, which were thawed and analyzed for ALT, AST, and ALK enzymatically using the Pars Azmoon kit as per the manufacturer's instructions.

Liver oxidative stress assessment

Frozen liver tissues were mixed with phosphate buffer and centrifuged. The supernatant was used to evaluate GSH, while the homogenized solution was utilized for the MDA test. The MDA level was measured using thiobarbituric acid interaction and a UV spectrophotometer (SPEKOL 2000, Korea). Moreover, GSH was assessed based on Ellman's reagent, which produced a yellow color.

Liver histopathological analysis

Liver tissues were preserved with formaldehyde and cut into 4µm sections using a microtome after being embedded in paraffin. The stained sections were utilized to detect inflammation and Masson-trichrome was used to quantify collagen deposition and fibrosis severity. Histopathological assessments were conducted blindly using a light microscope.

Statistical analysis

The results were presented as means, maximum, and minimum. An ANOVA test was applied to study the groups and find significant differences using IBM SPSS Statistics 22.

Results

ICP-MS analysis identified 52 heavy metals in the dust. The most toxic heavy metals identified in Iraqi and local dust were, in descending order of concentration, S, Ti, P, Mn, Sr, Ba, Zr, Zn, Ni, and Cr, respectively. The concentration of P, S, Ti, Mn, Sr, and Ba was higher in both Iraqi and local dust (Fig. 1.) Furthermore, Figure 2 displays the SEM image of Iraqi and local dust.

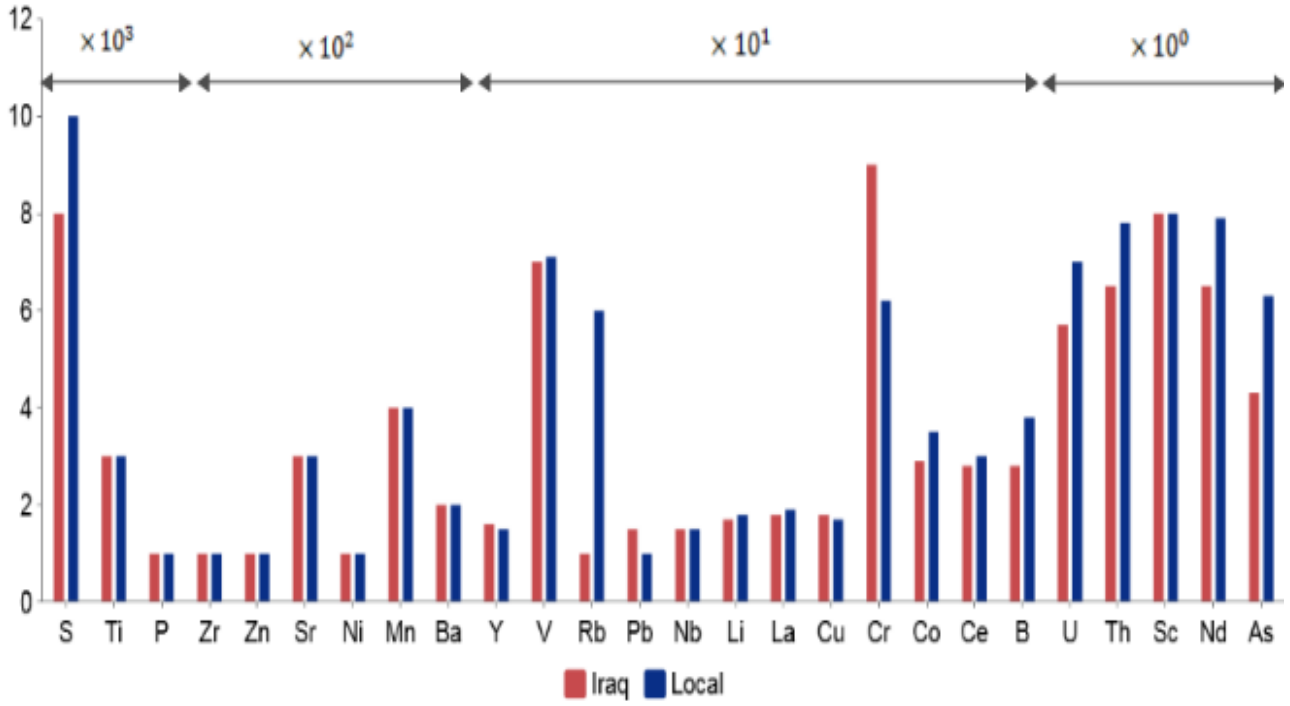

Fig. 1. The concentration of elements found in Iraq and local dust comparison.

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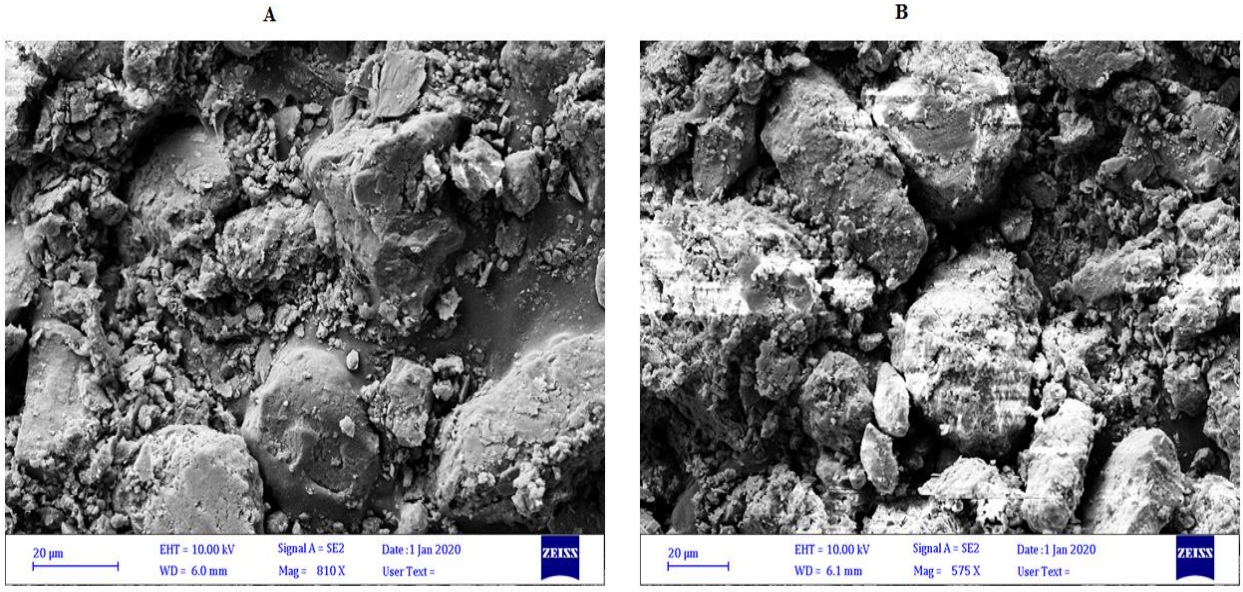

Fig. 2. The SEM result A. Iraq. B. local dust.

Dust size during exposure

Table 1 presents statistical data on PM10, PM2.5, and PM1 concentrations derived from local and long-range dust sources. It is evident that long-range transport exhibited lower average mass concentrations compared to local dust. Both types of dust displayed varying maximum and minimum mass concentrations. Notably, the highest mass concentrations of PM10, PM2.5, and PM1 differed between dust originating from long-range transport and local emission sources. Rats were exposed to notably higher particle concentrations of dust from local emission sources in comparison to long-range transport.

Table 1. Descriptive statistics of dust originating; the local and long-range emission resources.

Parameters	Unit	Long-range transport dust			Local dust		
		Max	Mean	Min	Max	Mean	Min
PM_1	($\mu g/m^3$)	2713.10	1262.91	5.90	2488.30	992.57	10.60
$PM_{2.5}$	($\mu g/m^3$)	15895.30	5726.55	9.80	11287.30	2879.89	16.20
PM_{10}	($\mu g/m^3$)	101739.90	32722.88	27.90	187197.90	58858.49	32.00
$PM_1/PM_{2.5}$	-	0.1706	0.2205	0.6020	0.2204	0.3446	0.6543
PM_1/PM_{10}	-	0.0266	0.0385	0.2114	0.0132	0.0168	0.3312
$PM_{2.5}/PM_{10}$	-	0.1562	0.1750	0.3512	0.0602	0.0489	0.5062

Liver weight assessment

No significant discrepancies were detected in the liver weight to body weight proportion between the exposed and control cohorts ($P > 0.05$), indicating an insignificant influence of PM on liver weight alterations (Fig. 3). Nevertheless, scrutinizing the body weight displayed a more significant reduction in the body weight of Iraq-D rats compared to the control cohort.

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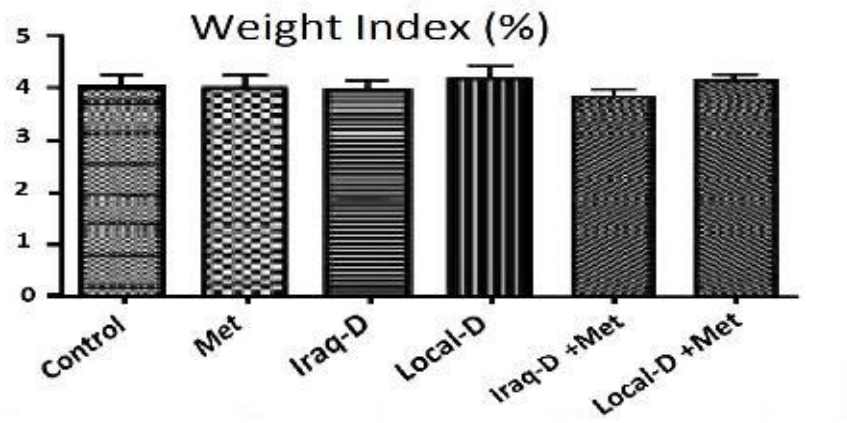

Fig. 3. The impact of dust and metformin treatment on the ratio of liver weight to body weight (n=7). Data are indicated as mean±SD deviation.

Liver biomarkers alteration

A positive correlation was found between ALT, AST, and ALK levels and exposure to Iraqi dust (P< 0.05). Figure 4 reveals the impact of PM and Metformin on enzyme levels in rats' liver tissue. Pretreatment with metformin had a protective effect on ALT (P< 0.05), AST (P> 0.05), and ALK (P< 0.05) levels, preventing their elevation.

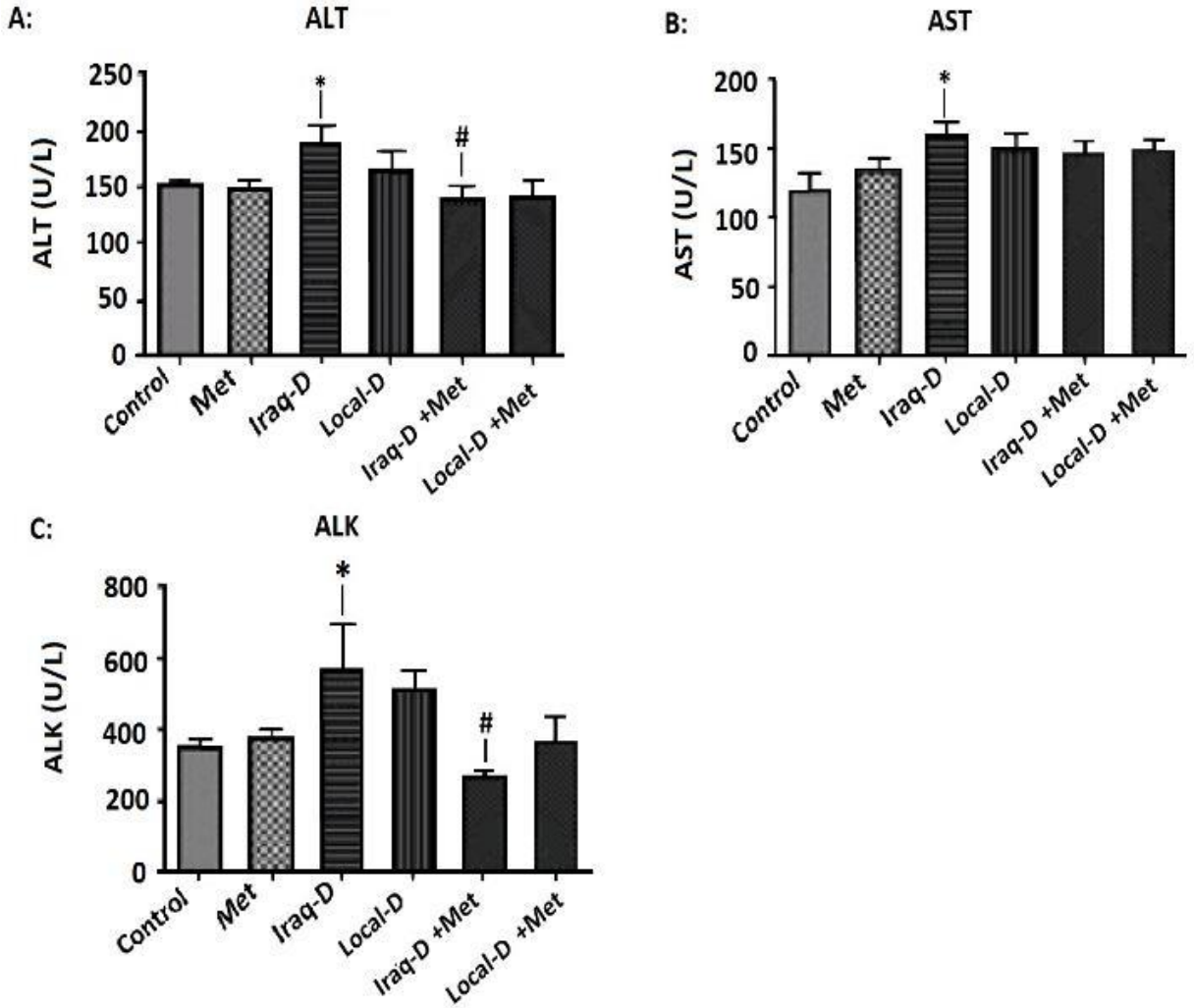

Fig. 4. The impact of particulate matter exposure on the liver enzymes in rat liver tissue. A. ALT enzyme. B. AST enzyme. C. ALK enzyme. Data are demonstrated as mean± SEM deviation. *Significant increase compared to the control group (p<0.05). #Significant decrease compared to Iraq-D group (P< 0.05).

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Oxidative stress related biomarkers

In the Iraq-D group, a significant positive correlation was observed between exposure to PM1, PM2.5, and PM10 and elevated levels of MDA, compared to the control and metformin groups (P< 0.05). The use of metformin displayed a noticeable preventive effect on MDA elevation (P< 0.05). Figure 5A illustrates the impact of PM and metformin on MDA levels in the liver tissue of rats. Furthermore, exposure to PM was significantly associated with decreased GSH levels in the Iraq-D group (P< 0.05). Although the positive association between GSH and Iraqi PM was reduced after metformin treatment, the changes were not statistically significant (P> 0.05). Figure 5B demonstrates the effect of Iraq PM and metformin on GSH levels.

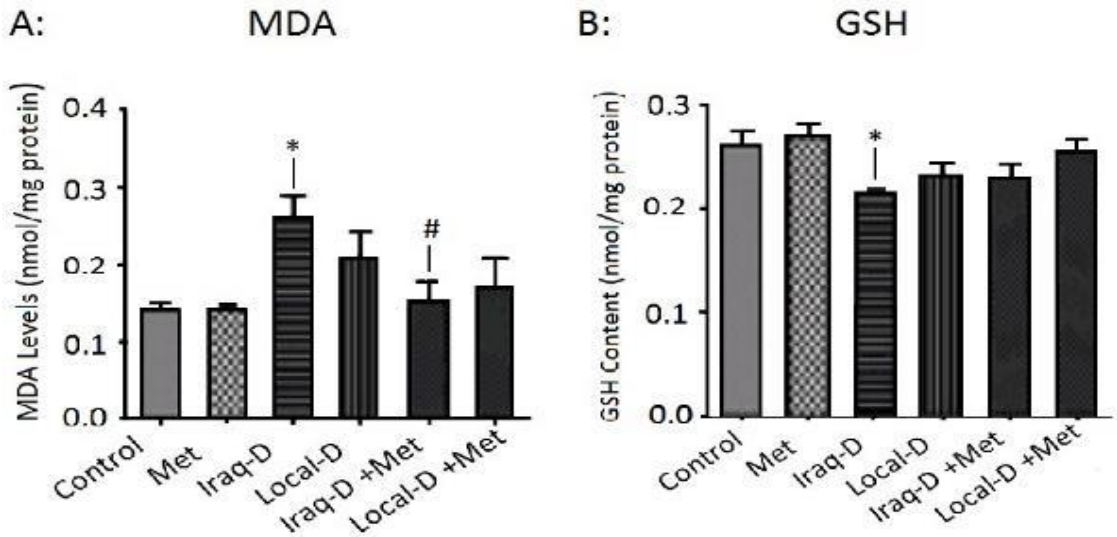

Fig. 5. A. The effect of particulate matter and Metformin on MDA levels in rats' liver tissue. B. The effect of particulate matter and Metformin on GSH level in rats' liver tissue. Data are shown as mean±SEM deviation. *Significant increase compared to the control group (P< 0.05). #Significant decrease compared to Iraq-D group (P< 0.05).

Liver histopathological alteration

There are no histopathological changes in control and metformin groups but significant changes in Iraq-D and local-D groups. The local-D group had more serious liver damage than the control group (Fig. 6). Local-D group had higher hyperemia and sinusoidal dilatation than the Iraq-D group. Dust and metformin-receiving groups had lower liver damage than only dust-receiving rats (Table 2).

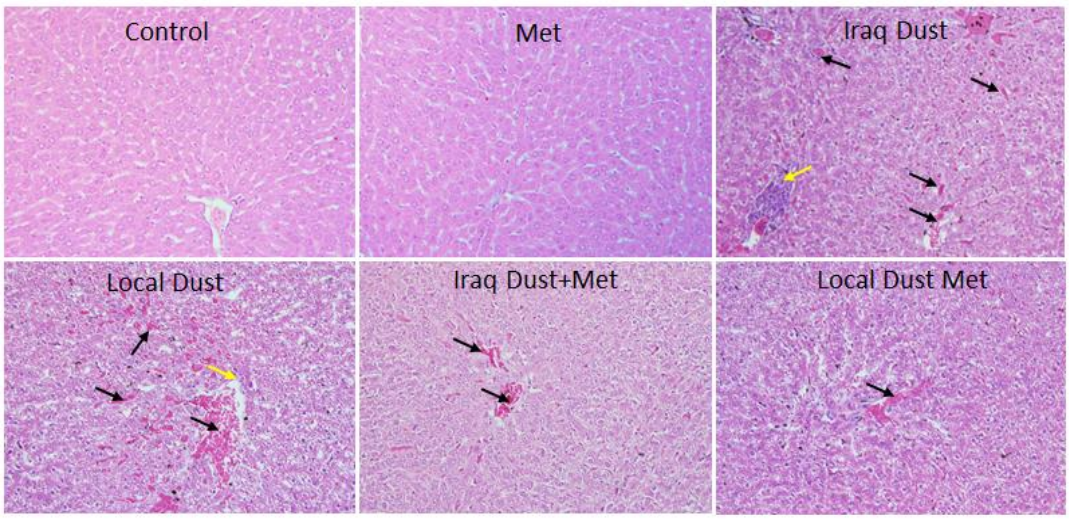

Fig. 6. The impact of particulate matter on liver histology in rats. Hepatic tissue from rats exposed to particles stained with H&E. Inflammation (yellow arrow) and Hyperemia (black arrow) of the liver after particle exposure.

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Table 2. Histological findings of hepatic tissue following exposure to PM from Iraq and the local area, as well as treatment with metformin, were analyzed.

Groups	Histological results			
	Congestion of RBCs	Inflammation	Sinusoidal dilation	Pyknotic nuclei
Control	(-)	(-)	(-)	(-)
Met	(-)	(-)	(-)	(-)
Iraqi dust	(++)	(++)	(+)	(++) to (+++)
Local dust	(++) to (+++)	(+)	(++)	(++)
Iraqi-D+Met	(+)	(-) to (+)	(-) to (+)	(+) to (++)
Local-D+Met	(+)	(-) to (+)	(+) to (++)	(+) to (++)

Animal ethology

The Iraq-D and Iraq-D + Met groups showed skin loosening and wrinkles after two weeks, as well as darker feces compared to the control and treatment groups, and higher water consumption in the dust receiving groups, with wheezing and watery feces observed in the Iraq-D group on day 21.

Discussion

Current study found that exposure to dust in Iraq caused liver damage in rats, but pretreatment with metformin prevented oxidative stress and improved liver function. Ambient air pollution, caused by dust particles and industrial activities, presents a significant threat to human health, particularly the respiratory system. The origin of dust affects its composition, which has a direct correlation with potential side effects on health; evidence has shown that individual components of dust can be harmful to health, and the pathways of long- and locally-ranged dust masses have been identified in specific areas using satellite technology and wind speed models. The direct association between the development of NAFLD and heavy metal presence, including cadmium, cobalt, chromium, nickel, lead, zinc, and aluminum, has been established (1, 2). The analysis showed that the dust samples had higher levels of heavy metals, which could potentially cause histological changes in liver tissue, skin loosening, and wrinkles in rats exposed to the dust (1, 3). No difference in liver weight compared to body weight. Ineffectiveness of PM on liver weight. The Iraq-D group showed weight loss. A prior study found rats exposed to dust lost weight due to a lack of appetite. Various regulatory mechanisms affect animal feeding, including internal and external factors. External factors include palatability and environmental temperature. Cytokines, leptin, estrogen, and cholecystokinin play a role in regulating animal feeding. Exposure to dust likely impacts physiological mechanisms related to regulating feeding (4). To avoid negative consequences, it is important to explore the mechanisms of particle toxicity and discover new treatments, as demonstrated by the confirmation of liver damage caused by PM in this study. Elevated levels of the proteins AST and ALT in the bloodstream are indicative of severe liver damage and impaired liver function (3, 5). The study found that dust exposure led to increased levels of ALT, AST, and ALK biomarkers in the Iraq-D group, but metformin treatment helped to improve this. No significant differences were observed in Local-D and control groups. Mandal et al. also reported increased levels of AST and ALT in male construction workers exposed to PM (6). Additionally, Noroozi et al. found that road asphalt paving workers exhibited higher levels of serum enzymes AST and ALT than healthy individuals (7). A study by Qiu et al. evaluated 3892 residents from Wuhan and Zhuhai. The participants showed elevated liver enzymes AST and ALT due to exposure to PM2.5 and PM10 (8). Dey et al. measured serum levels of

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ALK, ALT, and AST with a spectrophotometer. Their findings suggest a decrease in ALK levels and an increase in ALT levels in the exposed group due to higher concentrations of respiratory-suspended PM and nitrogen dioxide (9). Similarly, Wang et al. found that PM2.5 and PM10 increased ALK levels in mice serum and caused lung tissue cell toxicity (10). Zhang et al. also reported that ALK levels were considerably elevated in $PM_{2.5}$-exposed mice than in the control group (11). The composition of PM is mostly heavy metals. Mechanistic studies propose ROS generation through Fenton reactions, leading to oxidative damage (12, 13). PM has the potential to induce oxidative stress via its oxidative properties or through cellular reactions. Various PM sources have been shown to induce ROS in human lung epithelial cells (14). The current study found a significant decrease in glutathione reductase levels in the Iraq-D group compared to the control group, with a slight prevention of deduction in the Iraq-D+Met and Local-D+Met groups after pretreatment with metformin, and in vivo and in vitro studies confirmed reduced GSH activity and elevated GSSG in lung tissue following exposure to PM (15, 16). Scientists found significant decreases in glutathione biosynthesis and antioxidant activities following PM10 exposure, which is in agreement with previous research (17). Similarly, Ren et al. showed that $PM_{2.5}$ markedly mitigated GSH activity (18). In contrast, wood smoke exposure led to an elevated level of GSH in BALF in healthy volunteers (19). Lipids are among the most targeted oxidative stress molecules, such as ROS (20). Several epidemiological studies have linked lipid peroxidation to cardiovascular and/or respiratory diseases (21). Malondialdehyde (MDA) is a well-established stable lipid peroxidation product and a crucial biomarker for oxidative stress. In cases of illnesses marked by oxidative stress, such as cancer, diabetes, cardiovascular, and respiratory diseases, increased MDA levels have been discovered in plasma, serum, and exhaled breath condensate (EBC) (22). MDA has been used as a marker of oxidative stress in only a few epidemiological studies (23). Our study demonstrated a significant increase in serum MDA levels in the Iraq-D group compared to the control group, with no significant differences seen between the Local-D and control groups, and metformin treatment was found to be effective in preventing increased MDA levels in the Iraq-D-Met group, which is consistent with previous research showing a correlation between increased $PM_{2.5}$ exposure and elevated urine MDA levels (24). A correlation was observed between PM2.5 and urinary MDA in a pilot study conducted on nine volunteers traveling from Germany to China (25). During the Beijing Olympics, it was observed that healthy young adults experienced a decrease in EBC MDA as air quality improved (26). The study of 125 Beijing residents revealed significant correlations between PM2.5 and EBC MDA biomarkers representing respiratory events at lags 3, 4, and 5 (27). Exposure to $PM_{2.5}$ significantly increased MDA levels in animal models, with a 1.60% increase observed for every 10 μg/m3 increase in short-term exposure according to Li et al (28). Li et al.'s (2018) study revealed that prolonged exposure to different concentrations of dust can result in liver histopathological changes and decreased liver function in rats, which supports earlier literature suggesting that heavy metals and dust may cause liver tissue damage (3). Current study found that exposure to dust had a toxic effect on liver tissue in both groups, with greater liver damage observed in the dust and local-D group compared to the Iraq-D group. Antioxidants such as gallic acid were found to reduce inflammation, red blood cell accumulation, and fat deposition in the liver caused by dust exposure, with heavy metals in dust being a likely cause of functional and morphological changes in liver tissue (29). The findings of the present research validate that the administration of metformin along with dust resulted in lower levels of liver damage compared to the groups that only received dust (Table 2). The skin, particularly its epidermis, acts as a barrier and is susceptible to air

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pollutants, both of environmental and anthropogenic origin. Nanosized particles in environmental PM can cause oxidative stress in the skin, leading to extrinsic skin aging, as observed in a study by Vierkötter et al. which found a positive correlation between exposure to PM pollution and skin aging signs. (30-32). Along with these data, we also observed skin loosening in Iraq-D and Iraq-D-Met groups. Airborne particles, such as PM, are linked to various respiratory conditions, both short and long-term, which include cystic fibrosis, pulmonary infections, bronchitis, COPD, and the exacerbation of asthma (33). The study's results indicate that PM exposure can negatively impact lung function, as evidenced by the Iraq-D group exhibiting wheezing symptoms on day 21, which is supported by Nyhan et al.'s suggestion that radionuclides in ambient particles can activate inflammatory pathways and cause oxidative stress that hinders lung function when inhaled and deposited in the respiratory tract (34). The study found significant increases in liver biomarkers AST, ALT, and ALK levels among rats exposed to Iraqi and local dust, which were prevented by metformin treatment. GSH concentrations decreased and MDA increased in both groups, but metformin restored GSH levels and prevented MDA elevation compared to the control group. Finally, it can be considered from the current study findings suggest that exposure to PM can have adverse effects on lung function, as demonstrated by the increased MDA value and decreased GSH level in rat liver after a 21-day exposure to Iraq and local dust, which was alleviated by metformin's protective effect against oxidative stress and inflammation.

In conclusion, the present study has evinced that prolonged exposure to dust from Iraq and the local environment resulted in an increase in MDA levels and a decrease in GSH levels in the liver of rats. However, pretreatment with metformin exhibited a preventive effect by inhibiting oxidative stress and improving liver function concerning dust-induced inflammation. Furthermore, exposure to dust caused a rise in the levels of liver enzymes such as ALT, AST, and ALK. The administration of metformin in rats was found to mitigate almost all the variables studied, thereby suggesting that metformin could be a promising therapeutic agent in managing the adverse effects of dust exposure.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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