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Histomorphometric and Biochemical Study of Liver and Thyroid Hormones Following Administration of MoO_3 Nanoparticles in Female Rats

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Abstract

BACKGROUND: Nanoparticles are popular carriers for gene therapy and drug delivery. Their low toxicity effects, as well as their ability to accumulate and enter mammalian cells, illustrate their importance.

OBJECTIVES: The aim of this experimental study was to investigate the effects of molybdenum trioxide nanoparticles on liver structure and function.

METHODS: Thirty-five adult Wistar rats were studied and placed in five groups. The control group took any drug, the solvent group received normal saline, and groups 3, 4, and 5 received 50, 100, and 200 mg/kgBW molybdenum trioxide nanoparticles (MoO_3 NPs), respectively, by intraperitoneal injection for 35 days. In the end, serum levels of AST, ALT, ALP, T3, T4, TSH, and VLDL were investigated. Moreover, liver tissue was evaluated in terms of morphometrical, histological, histochemical, and image analysis. The Hematoxylin-Eosin, Masson's Trichrome, and Periodic Acid Schiff staining methods were utilized for liver tissue evaluation.

RESULTS: The results showed that molybdenum trioxide nanoparticles significantly increased serum levels of the liver enzymes and thyroid hormones and decreased TSH in MoO_3 NPs groups compared with control and solvent groups. Also, histomorphometric and histochemical evaluation and image analysis of liver tissue indicated adverse effects of MoO_3 NPs on liver tissue. They showed that the accumulation of carbohydrates in hepatocytes was decreased, and collagen fibers stained by Masson's Trichrome staining were increased in MoO_3 NPs groups.

CONCLUSIONS: It can be concluded that nanoparticles such as MoO_3 NPs affect and damage the histological structure of the hepatocytes. Also, MoO3 NPs can alter serum levels of liver enzymes by affecting and damaging hepatocytes.

KEYWORDS: Histomorphometry, Liver enzyme, Liver morphology, Molybdenum trioxide nanoparticle, Thyroid hormone

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Introduction

Nanotechnology science provides nanoscale activities to create a unique product with new features. Nanoparticles refer to a group of materials that are up to 100 nanometers in size. This size is also compatible with the cell scale and its components. While this powerful technology can bring many benefits and advantages, it can also have potentially dangerous disadvantages because the small size of nanoparticles allows these substances to overcome the body's defenses (Khan *et al*., 2019, A Saud *et al*., 2021).

Nanoparticles are popular carriers for gene therapy and drug delivery. Their low toxicity effects and their ability to accumulate and enter mammalian cells illustrate their importance. Nanoparticles are widely used in medical productions such as antimicrobial bandages due to their antimicrobial properties. Adding a positive charge to nanoparticles may improve their potential to be used as nanoparticle carriers for drug delivery (Behzadi *et al*., 2017, A Saud *et al*., 2021). Also, some studies documented the antitumor activity of nanoparticles such as silver nanoparticles (Abduladheem Jabbar and Neima Hussien, 2021).

Today, molybdenum trioxide is one of the nanoparticles that are synthesized and sold in pharmaceutical companies. Due to its antimicrobial properties, this nanoparticle is used to disinfect medical devices. A study conducted in 2016 showed that the heat method is used to synthesize molybdenum trioxide nanoparticles. The synthesized molybdenum trioxide nanoparticles are spherical in shape with a size of about 57 nm. Afterward, this study was presented to demonstrate synthesized molybdenum trioxide nanoparticles for antibacterial activity against gram-negative and positive bacteria (Fakhri and Afshar Nejad, 2016).

The liver is the largest organ in the body, anatomically divided into right, left, caudal, and square lobes, which has nothing to do with its functional division. Each lobe consists of some lobules with a lobular central vein in the center and between 3 and 6 port spaces around it. After entering into the lobular central vein from sinusoids and connecting to the central vein and lobes, the blood exits the liver in the form of three veins and enters the inferior vena cava. The port space, which has a branch of the hepatic artery, portal vein, and bile ducts, includes the autonomic nerves and lymphatic vessels (Alessandrino *et al*., 2019).

Researchers have studied liver enzymes to investigate liver function because a change in any of the liver enzymes could signify a change in some of the liver's functions. The most common liver enzymes are alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin. Liver cell injury is diagnosed by an abnormal rise in ALT and AST levels. Increased circulation of bilirubin as unconjugated bilirubin and elevated levels of conjugated bilirubin indicate liver cell disease. Numerous studies have shown that increased ALT is associated with increased liver-related deaths (Kwo *et al*., 2017).

Nanoparticles are nanometer-sized particles that accumulate in cells when entering the body and can have positive or negative effects on organs, including the liver. So, the aim of this experimental study was to investigate the effects of molybdenum trioxide nanoparticles on the histomorphometric and biochemical study of liver and thyroid hormones following administration of MoO3 nanoparticles in female rats.

Materials and Methods

In this experimental study, thirty-five adult Wistar rats (weight 180-250 gr) were studied and placed in five groups. The control group took any drug, the solvent group received normal saline, and groups 3, 4, and 5 received 50, 100, and 200 mg/kgBW molybdenum trioxide nanoparticles (MoO_3 NPs), respectively, by intraperitoneal injection for 35 days. The animals were obtained from Pasteur Institute of Tehran, Iran, and housed in polycarbonate cages in an air-conditioned room (temperature: 25±2°C, relative humidity: 50±10%, and 12 h light/12 h dark photoperiod) free from any sources of chemical contamination with free access to standard diet and water throughout the experimental period. At the end of the treatment, animals were weighed and anesthetized by ketamine (90 mg/kgBW) + xylazine (10

mg/kgBW). The blood samples were collected from the heart to prepare the serum and determine blood factors. Afterward, animals were dissected, and the liver tissue was immediately excised and weighed and, after washing in normal saline, was fixed with 4% formalin solution for histological evaluation. Tissue samples were embedded in paraffin blocks and sliced into 5 µm thick sections. The slices were stained using Hematoxylin-Eosin, Periodic Acid Schiff, and Masson's Trichrome for histological and histochemical analysis. Five sections from each sample and three microscopic fields of view from each section were investigated. Histomorphometric evaluations were carried out with a digital camera Dino-Lite lens and Dino-capture 2 software. The hepatocyte nucleus diameter, hepatocyte diameter, sinusoid diameter, hepatocytes number, Kupffer cells number, and deformity cells number were measured. The number of cells was calculated in a circle with a radius of 1500 micrometers. Image analysis results were evaluated by image pro-plus V. 6.0 software.

Blood samples were centrifuged at 3,000 rpm for 10 min. Following centrifugation, serum from each sample was collected and frozen at -20°C. Serum levels of aspartate transaminase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) enzymes, T3, T4, and TSH hormones, very-low-density lipoprotein (VLDL), and albumin were determined using spectrophotometry technique.

All data were represented as the mean ± standard deviation. Data distribution was controlled by the K-S test, and since the distribution of all data was normal, parametric tests were used to analyze them. The variables were analyzed by one-way analysis of variance followed by Tukey test for post hoc comparisons using SPSS version 18.0 (SPSS Inc, Chicago, Illinois, USA). The statistical significance level was set at P-value<0.05.

Results

Weight

The weight parameters measurement demonstrated that the liver in MoO_3 NPs 50, 100, and 200 groups had significantly low weight compared to control and solvent groups. Also, weight alterations in MoO_3 NPs 50, 100, and 200 groups were significantly more than control and solvent groups. Moreover, weight alterations of the MoO_3 NPs 200 group indicated significant discrepancy compared to other groups (P<0.05) (Table 1).

Table 1. Liver weight, Primary body weight, Secondary body weight, and Weight alterations in the study groups.

	Liver weight (gr)	Primary body weight (gr)	Secondary body weight (gr)	Weight alterations
Control	10.16 ± 1.01 [a]	235 ± 19.68 [a]	244.16 ± 20.35 [a]	9.16 ± 1.26 [a]
Solvent	9.89 ± 0.70 [a]	220 ± 18.23 [a]	231 ± 19.35 [a]	11.12 ± 2.27 [a]
MoO_3 NPs 50 mg/kg	7.26 ± 1.95 [b]	203.66 ± 9.83 [a]	194 ± 13.87 [a]	-9.3 [b]
MoO_3 NPs 100 mg/kg	8.22 ± 0.98 [b]	215 ± 24.08 [a]	209.16 ± 29.15 [a]	-6 ± 5.07 [b]
MoO_3 NPs 200 mg/kg	8.62 ± 1.14 [b]	205.75 ± 23.6 [a] 5	161.66 ± 31.25 [a]	-44 ± 7.6 [c]

Dissimilar letters in each parameter indicate significant differences between the groups (P<0.05).

Histomorphometry

In histometrical analysis, hepatocyte nucleus diameter, hepatocyte diameter, and sinusoid diameter illustrated no remarkable discrepancy between groups. The number of deformed cells in MoO_3 NPs 200 increased significantly compared to control, solvent, and MoO_3 NPs 50 groups, but had no significant difference with MoO_3 NPs 100. Also, deformed cells number in MoO_3 NPs 100 group did not show any diversities compared with other groups. The number of the kupffer cells measurement represented a significant increase in MoO_3 NPs 100 and 200 groups in comparison with other groups. The assessment of the hepatocytes number displayed a

significant decrease in MoO_3 NPs 100 and 200 groups compared to control groups. Also, the hepatocytes number had no significant differences between solvent, MoO_3 NPs 50, MoO_3 NPs 100, and MoO_3 NPs 200 groups (P<0.05) (Table 2).

Table 2. Hepatocyte nucleus diameter, Hepatocyte diameter, sinusoid's diameter, Deformity cells number, Kupffer cells number, and Hepatocytes number in the study groups.

	Hepatocyte nucleus diameter (µm)	Hepatocyte diameter (µm)	Sinusoid's diameter (µm)	Deformity cells number	Kupffer cells number	Hepatocytes number
Control	7 ± 1.41 [a]	17 ± 2.82 [a]	9.36 ± 0.93 [a]	21 ± 3.57 [a]	5.50 ± 1.38 [a]	51.83 ± 5.19 [a]
Solvent	8 ± 1.41 [a]	17.63 ± 2.20 [a]	9.12 ± 0.91 [a]	21.83 ± 3.71 [a]	6.77 ± 1.57 [a]	49.83 ± 5.77 [ab]
MoO_3 NPs 50 mg/kg	7.5 ± 1.87 [a]	18.33 ± 2.58 [a]	8.93 ± 81 [a]	22.83 ± 3.43 [a]	6 ± 1.41 [a]	45 ± 5.14 [ab]
MoO_3 NPs 100 mg/kg	7.5 ± 1.05 [a]	18.83 ± 2.32 [a]	8.13 ± 0.73 [a]	25.16 ± 4.02 [ab]	9 ± 1.41 [b]	41.83 ± 5.49 [b]
MoO_3 NPs 200 mg/kg	7.83 ± 1.17 [a]	19.23 ± 1.66 [a]	6.35 ± 0.86 [a]	28 ± 2.09 [cb]	9 ± 0.89 [b]	41 ± 5.85 [b]

Dissimilar letters in each parameter indicate significant differences between the groups (P<0.05).

Histological Assessment

The histomorphological evaluation of the liver tissue in all groups indicated that the structure of hepatocyte cells, sinusoids, veins, bile ducts, and dispersion of Kupffer cells were normal in control, solvent, MoO_3 NPs 50, and 100 mg/kg groups. But, in MoO_3 NPs 100 mg/kg group, Kupffer cells number was increased, and mild lobular inflammation was also observed. In MoO_3 NPs 200 mg/kg group, the hepatocellular ballooning, mild lobular inflammation, decreased volume of sinusoids, increase in the number of Kupffer cells, and normal veins and bile ducts were observed (Figure 1).

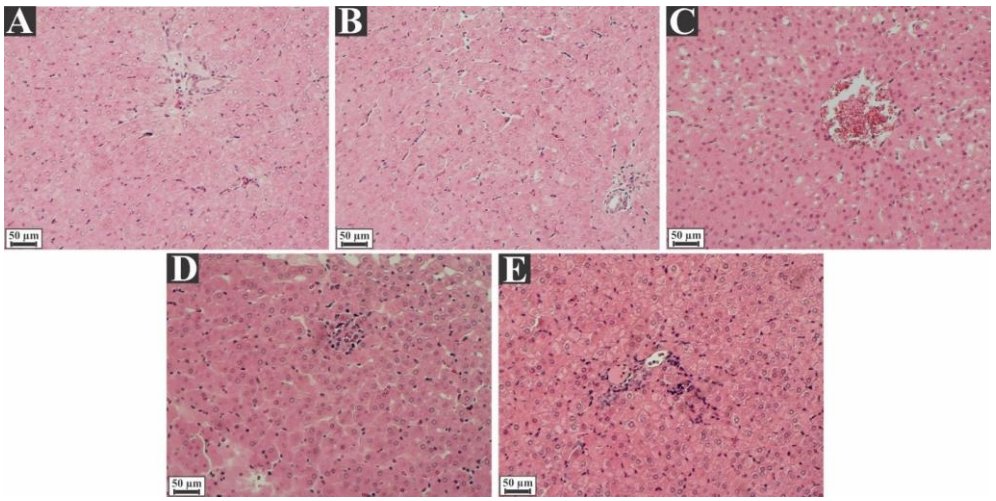

Figure 1. Histology of liver stained by H&E in control and treatment groups (×100). A, control group; B, Solvent group; C, MoO_3 NPs 50 mg/kg group; D, MoO_3 NPs 100 mg/kg group; E, MoO_3 NPs 200 mg/kg group.

Histomorphometric Image Analysis

In the image analysis of H & E slides, a significant decrease of sinusoid volume and a significant increase of cell nucleus volume in MoO_3 NPs 100 and 200 mg/kg groups were determined compared with control, solvent, and MoO_3 NPs 50 mg/kg groups. Also, the decrease of the sinusoid volume of the MoO_3 NPs 200 mg/kg group was significantly more than MoO_3 NPs 100 mg/kg group. Furthermore, the cell cytoplasm volume showed no differences between all groups (P<0.05) (Figure 2, Table 3).

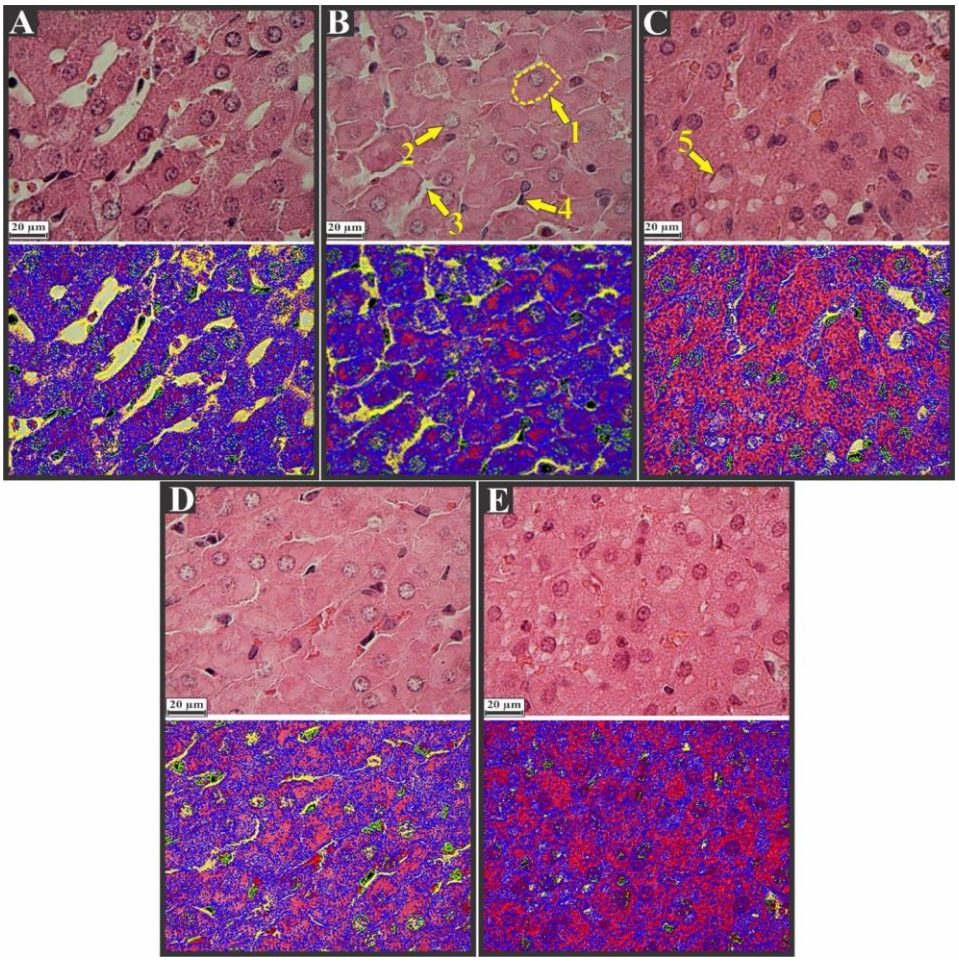

Figure 2. Histology of liver stained by H&E in control and treatment groups and Image analysis (×400). A, control group; B, Solvent group; C, MoO_3 NPs 50 mg/kg group; D, MoO_3 NPs 100 mg/kg group; E, MoO_3 NPs 200 mg/kg group. No. 1: Hepatocyte – No. 2: Hepatocyte nucleus – No. 3: Hepatic sinusoid – No. 4: Kupffer cell – No. 5: Deformity cell.

Image analysis; Green: Hepatocyte nucleus – yellow: Hepatic sinusoids – blue: cells cytoplasm.

Histochemical Assessment

PAS Image Analysis

Assessing the accumulation of carbohydrates showed that the density of PAS-positive particles in hepatocytes was reduced in the MoO_3 NPs 100 and 200 mg/kg groups compared with control, solvent, and MoO_3 NPs 50 mg/kg groups. Moreover, reduction of the density of PAS-positive particles in the MoO_3 NPs 200 mg/kg group was significant compared with other groups (P<0.05) (Figure 3, Table 3).

Masson's Trichrome Image Analysis

Evaluation of Masson's Trichrome positive area in all groups indicated that the formation of collagen fibers was significantly increased in MoO_3 NPs 100 and 200 mg/kg groups compared to other groups. The comparison of other groups did not show a significant difference (P<0.05) (Figure 4 Table 3).

Table 3. Percentage of Sinusoid volume, Cell nucleus volume, Cell cytoplasm volume (in H&E staining) and the accumulation of carbohydrates (in PAS staining) and collagen fibers (in Masson's Trichrome staining) in control and treatment groups.

	Sinusoid volume (%)	Cell nucleus volume (%)	Cell cytoplasm volume (%)	The accumulation of carbohydrates (%)	Collagen fibers stained by Masson's Trichrome staining (%)
Control	7.04 ± 0.51 [a]	4.01 ± 0.41 [a]	88.95 ± 3.11 [a]	32.29 ± 2.19 [a]	3.02 ± 0.42 [a]
Solvent	6.65 ± 0.45 [a]	4.40 ± 0.81 [a]	89.17 ± 5.67 [a]	30.17 ± 4.99 [a]	4.09 ± 0.61 [a]
MoO_3 NPs 50 mg/kg	6.43 ± 0.34 [a]	9.23 ± 0.62 [b]	84.12 ± 4.52 [a]	42.72 ± 5.02 [b]	4.85 ± 1.38 [a]
MoO_3 NPs 100 mg/kg	4.14 ± 0.98 [b]	11.91 ± 1.13 [c]	83.95 ± 7.35 [a]	23.73 ± 5.81 [a]	16.78 ± 1.23 [b]
MoO_3 NPs 200 mg/kg	0.73 ± 0.11 [c]	13.08 ± 0.85 [c]	86.19 ± 6.15 [a]	9.45 ± 2.70 [c]	18.98 ± 1.82 [b]

Dissimilar letters in each parameter indicate significant differences between the groups (P<0.05).

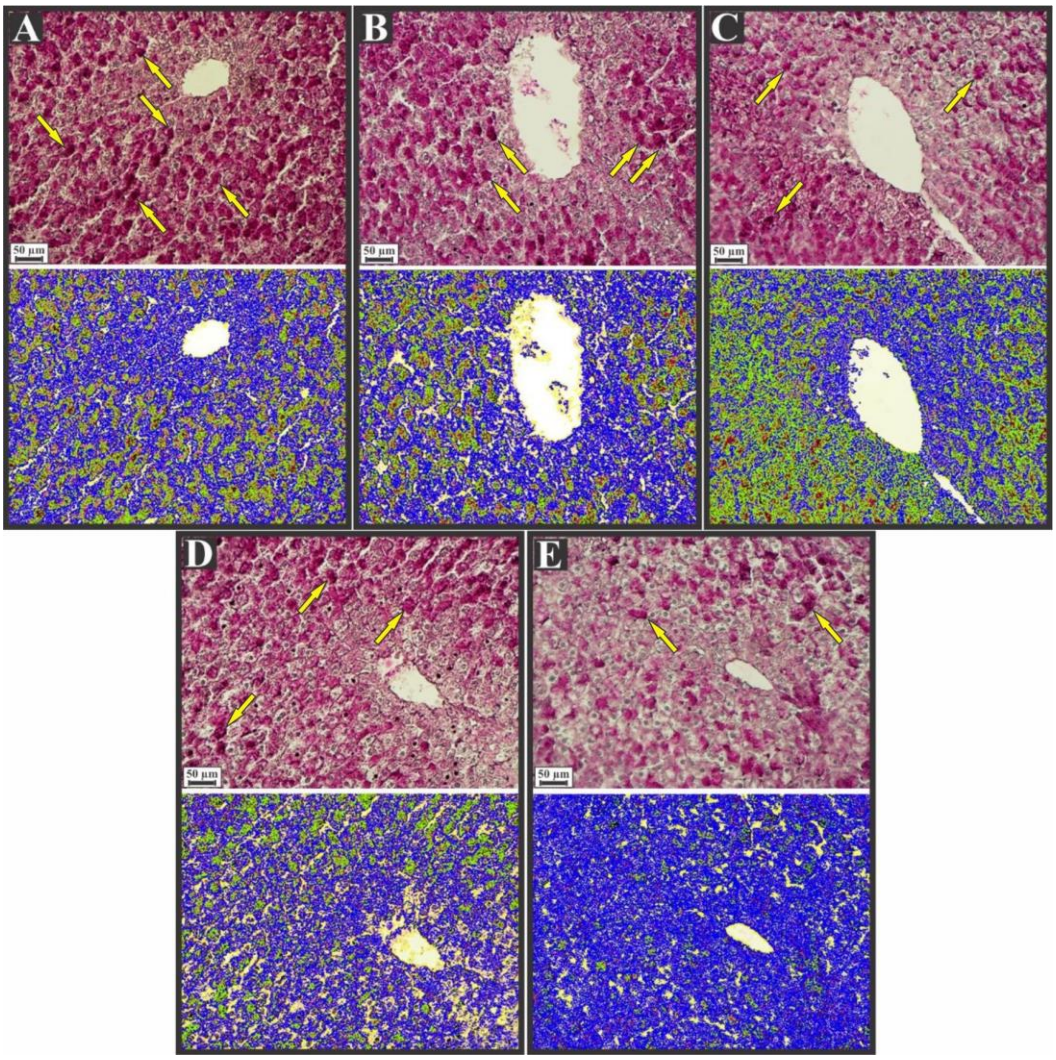

Figure 3. Histology of liver stained by PAS in control and treatment groups and Image analysis (×100). A, control group; B, Solvent group; C, MoO_3 NPs 50 mg/kg group; D, MoO_3 NPs 100 mg/kg group; E, MoO_3 NPs 200 mg/kg group. Arrows: the accumulation of carbohydrates (PAS-positive particles).

Image analysis; Green: PAS-positive particles – yellow: Hepatic sinusoids and central veins – blue: PAS negative cytoplasm.

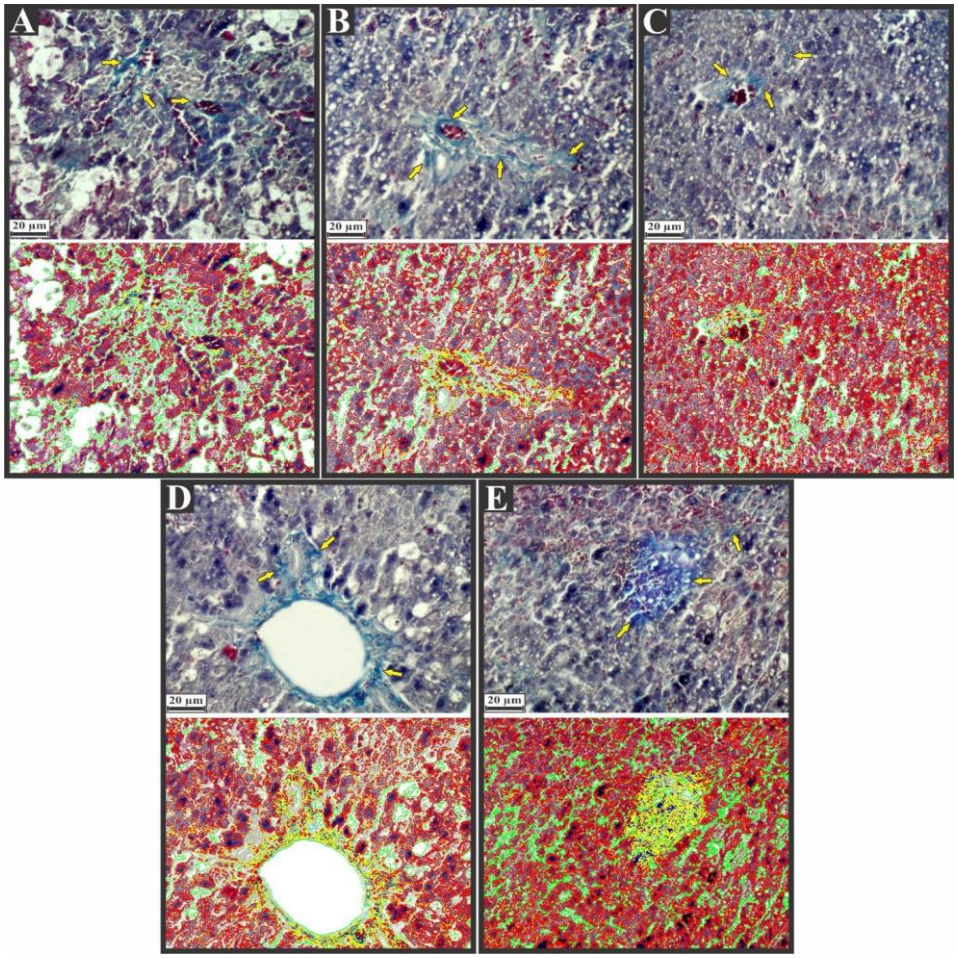

Figure 4. Histology of liver stained by Masson's Trichrome staining in control and treatment groups and Image analysis (×400). A, control group; B, Solvent group; C, MoO_3 NPs 50 mg/kg group; D, MoO_3 100 NPs mg/kg group; E, MoO_3 NPs 200 mg/kg group. Arrows: the accumulation of Collagen fibers (Masson's Trichrome positive area).

Image analysis; Yellow: Masson's Trichrome positive area (Collagen fibers) – Green: Hepatic sinusoids and central veins – Blue: cytoplasm and nucleus.

Liver Enzymes

The enzymes of the liver and albumin in this study were investigated and compared among the experimental groups. The albumin evaluation did not indicate any significant differences among all groups. Comparison of ALT levels in all groups showed that MoO_3 NPs 50, 100, and 200 were increased significantly compared to control and solvent groups. ALP level was significantly enhanced only in MoO_3 NPs 200 compared to other groups. The AST enzyme level evaluation in experimental groups demonstrated that MoO_3 NPs 50 and 100 were heightened significantly beside control and solvent groups. Also, MoO_3 NPs 200 had a significant enhancement compared to other groups (P<0.05) (Table 4).

Thyroid Hormones

The assessment of thyroid hormones such as T3 and T4 was presented in Table 5. The levels of T3 and T4 hormones were heightened significantly in MoO_3 NPs 200 group compared to other groups. The TSH level was decreased in MoO_3 NPs 100 and 200 groups in comparison with control and solvent groups. This decline was significantly more in MoO_3 NPs 200 group. Finally, VLDL levels in MoO_3 NPs 50, 100, and 200 groups represented a significant increase in comparison with control and solvent groups. Likewise, in MoO_3 NPs 100 and 200 groups, VLDL level had a significant enhancement compared to MoO_3 NPs 50 mg/kg, control, and solvent groups (P<0.05) (Table 5).

Table 4. Serum levels of Albumin, ALT, ALP, and AST in the study groups.

	Albumin (g/dL)	ALT (IU/L)	ALP (IU/L)	AST (IU/L)
Control	3.74 ± 0.17 [a]	64.42 ± 2.69 [a]	337.00 ± 139.06 [a]	110.43 ±3.78 [a]
Solvent	3.45 ± o.83 [a]	62.12 ± 2.77 [a]	342.42 ± 84.90 [a]	115.57±4.37 [a]
MoO_3 NPs 50 mg/kg	3.14 ± 0.171 [a]	72.14 ± 33.32 [b]	312.42 ± 50.937 [a]	129.71 ±5.32 [b]
MoO_3 NPs 100 mg/kg	3.28 ± 0.195 [a]	69.28 ± 21.98 [b]	321.85 ± 165.51 [a]	133.14 ±4.65 [b]
MoO_3 NPs 200 mg/kg	3.54 ± 2.23 [a]	71.00 ± 12.36 [b]	383.14 ± 81.04 [b]	240.57 ±50.9 [c]

Dissimilar letters in each parameter indicate significant differences between the groups (P<0.05).

Table 5. T3, T4, and VLDL levels in the study groups.

	T3 (pg/mL)	T4 (ng/dL)	TSH (u/L)	VLDL (mg/dL)
Control	1.25 ± 0.6 [a]	3.77 ± 0.75 [a]	6.65 ± 1.09 [a]	10 ± 2.34 [a]
Solvent	1.28 ± 0.46 [a]	2.95 ± 0.64 [a]	6.27 ± 0.82 [a]	9.85 ± 1.98 [a]
MoO_3 NPs 50 mg/kg	1.05 ± 0.46 [a]	3.51 ± 0.64 [a]	5.34 ± 0.82 [ab]	15.57 ± 1.98 [b]
MoO_3 NPs 100 mg/kg	1.54 ± 0.46 [a]	3.54 ± 0.64 [a]	4.87 ± 0.77 [b]	24 ± 1.98 [c]
MoO_3 NPs 200 mg/kg	3.32 ± 0.43 [b]	5.50 ± 0.59 [b]	2.88 ± 0.98 [c]	20.37 ± 1.85 [c]

Dissimilar letters in each parameter indicate significant differences between the groups (P<0.05).

Discussion

The results obtained in the study of the effect of different amounts of Molybdenum trioxide nanoparticles on the amount of liver enzymes showed that MoO_3 NPs NPs caused changes in liver enzymes, histomorphometry, and thyroid hormones. There is limited information to suggest that approximately 20-25% of the oral dose of molybdenum is excreted in the urine. Water-soluble molybdenum compounds are readily absorbed through the lungs, stomach, and intestines, but insoluble compounds are not like this. After absorption throughout the body, molybdenum is distributed in high amounts, mainly in the liver, kidneys, spleen, and bone. Most of the molybdenum found in the liver accumulates in the outer membrane of the mitochondria, where it is available as a cofactor for enzymatic reactions. Some points can affect molybdenum toxicity, such as the chemical and physical forms of molybdenum, how to deal with it, and dietary compounds like copper and sulfur. The mechanism of molybdenum toxicity is unknown. Still, it has been hypothesized that molybdenum, as the primary factor in the formation of the tetrathiomolybdate complex in the regenerative medium of the gastrointestinal tract, reduces the biological properties of copper (EFSA *et al.*, 2019).

The study results of the effect of intraperitoneal injection of molybdenum nanoparticles show that no symptoms of morbidity and mortality were observed in the doses used. Also, AST and ALT enzymes showed a significant increase in the three groups of 50, 100, and 200 mg/kgBW compared to the control and solvent groups. Moreover, the ALP enzyme indicated a significant increase in the 200 mg/kgBW group compared with other groups. The ALT enzyme is specific for the liver, and damage to liver cells increases the serum level of this enzyme. In addition, bile duct obstruction increases the serum concentration of the ALP enzyme. Also, increased serum concentrations of ALT and AST may be due to increased anabolism or decreased catabolism (Lorestani *et al.*, 2020).

In recent years, many studies have been conducted on the toxicity of various nanoparticles. In a study of evaluation of the acute toxicity effect of nanoparticles and microparticles of zinc in adult mice by administrating 5 mg/kgBW through the gavage and histological and hematological studies after two weeks, it was shown that in the early days, symptoms such as diarrhea, vomiting and drowsiness developed. Serum tests of liver function also showed that

ALP, AST, ALT, and LDH levels in mice exposed to zinc microparticles and ALT, ALP, and LDH levels in mice exposed to zinc nanoparticles increased significantly compared to the control group, which indicates hepatic damage by the studied nanoparticles (Bing *et al*., 2006). Also, in 2013, the evaluation of the zinc oxide nanoparticles' effect on liver enzymes ALP, AST, and ALT indicated that intraperitoneal injection of zinc oxide nanoparticles with doses 25, 50, 100, and 200 ppm for seven days caused a significant increase in liver enzymes (Fazilati, 2013). The present study confirmed that MoO_3 nanoparticles, like nanoparticles and microparticles of zinc and zinc oxide nanoparticles, caused hepatic damage and high levels of liver enzymes.

The investigation of the Molybdenum nanoparticles' effects on plasma levels of liver enzymes with 5, 10, and 15 mg/kgBW doses in rats indicated that Molybdenum nanoparticles at low concentrations because of their antagonistic effects on copper metabolism are not acutely toxic (Heidari *et al*., 2014). But, in our study, MoO_3 nanoparticles with 50, 100, and 200 mg/kgBw made a significant increase in liver enzyme levels.

In the evaluation of acute toxicity of titanium dioxide (TiO_2) nanoparticles and biodistribution of these nanoparticles with different dimensions (25 and 80 nm) in adult mice, it was obtained that prescription of 5 mg/kgBW of TiO_2 nanoparticles as suspension by gavage for two weeks, had no acute toxicity. Changes in serum biochemical parameters (ALT / AST, LDH) and liver pathology indicated that these particles caused liver injury in mice after exposure. There was a significant change in serum LDH and α-HBDH in the 25 and 80 nm particle groups compared to the control group, indicating myocardial damage (Wang *et al*., 2007). Also, in this experimental study, the hepatic morphological injuries were caused by MoO3 nanoparticles.

A report by Kostka et al. (1999) stated that increased VLDL in the liver affected the activity and function of the sodium-potassium pump, causing water to accumulate and transfer into the cell, thereby increasing hepatocyte volume and reducing sinusoid diameter (Kostka et al., 1999). The results of the present study concerning histomorphometric features of the liver showed that the diameter of hepatocytes in the groups consuming molybdenum trioxide nanoparticles increased compared to the control and solvent groups. On the other hand, the diameter of sinusoids and their volume in the groups receiving nanoparticles, especially at higher doses, decreased compared to the control and solvent groups. Blood flow reduction to the hepatic sinusoids due to decrease in their diameter, causes serum levels of liver enzymes to increase.. Also, increasing the diameter of hepatocytes, which can be due to their hypertrophy or inflammation, and leads to more pressure on the sinusoids and a decrease in their diameter, especially at higher doses. This change in the morphology of hepatocytes, which will ultimately affect their function, has led to their degradation and deformity and a decrease in their number. In connection with this matter, in this study, the increase in deformed hepatocytes and the decrease in the number of hepatocytes in the consumer groups compared to the control group prove these results. Consistent with the present study, Khidr *et al*. (2017) showed that some foods such as aspartame in high doses, if used chronically, would significantly reduce the diameter of sinusoids and increase the diameter of hepatocytes due to hypertrophy (Khidr *et al*., 2017).

Kupffer cells have been shown to increase after consuming harmful substances and subsequent inflammatory reactions in the liver to defend and produce cytokines (Li *et al*., 2017). Also, in the present study, there was a significant increase in the number of Kupffer cells in the groups receiving MoO_3 NPs compared to the control and solvent groups, which could be related to the defense function of Kupffer cells.

It is stated that the destruction of liver tissue is mainly due to the formation of free radicals and disturbance of the ratio between active species of oxygen and antioxidants in liver tissue (Ramos-Tovar & Muriel, 2020). It has also been shown that in liver tissue, free radicals bind to proteins and lipids in the cell membrane of hepatocytes, causing instability of the cell membrane and ultimately the destruction and necrosis of hepatocytes and intracellular organelles (Daher *et al*., 2009). So, the key to these changes may be due to the release of free radicals produced by harmful substances in the liver. Also, in a study that investigated the effect of silver nanoparticles on 45 male rats orally on liver tissue,

they found that hepatocytes indicated inflammation in addition to degeneration (Heydarnejad *et al*., 2015). Consistent with this study, in our study, the hepatocellular ballooning and mild lobular inflammation were seen in liver tissue of rats that received a high dose of MoO_3 NPs.

The activity of the thyroid gland is regulated with a negative feedback mechanism. The hypothalamic neurons unleash thyrotropin-releasing hormone (TRH) into the hypothalamic-hypophyseal portal blood, and it links to its receptors in the adenohypophysis. Thyroid-stimulating hormone (TSH) is secreted by the stimulation of TRH. The TSH makes the thyroid gland generate and abandon thyroid hormones. Iodine deficit in the thyroid gland increases T4 into T3 transformation.

Moreover, the deiodination of T4 causes synthesis and demolition of T3 (Qatanani *et al*., 2005; Blanco-Muñoz *et al*., 2016; Bervini *et al*., 2021). The information about the effects of NPs on the function of the thyroid is contradictory and very narrow. There is a study which indicated a decline in levels of transcripts encoding the TH-induced receptor β (TRβ) and TH-repressed Rana larval keratin type I (RLKI) after exposing to 10 nM of silver NPs and 0.1 nM of Quantum Dots (QDs) alone, while TRβ and RLKI transcript levels had not been affected by zinc oxide nanoparticles (Amaral *et al*., 2019). Contradistinctionly, the consumption of Chromium (III) nanoparticles in rats at heat-stressed did not significantly alter serum TSH, T3, and T4 levels, denoting that thyroid hormone metabolism is not affected by these NPs (Zha *et al*., 2009). The T3 and T4 serum levels results in this study showed that the levels of these hormones in the groups receiving MoO_3 NPs at a dose of 200 mg/kg showed a significant increase compared to other groups. Also, TSH levels showed a significant decrease in MoO_3 NPs 200 mg/kg group compared to other groups. These results indicate the effect of nanoparticles on the thyroid gland as well as the brain-pituitary-thyroid axis. Due to the significant decrease in TSH and a significant increase in the concentration of T3 and T4 hormones, it should be said that due to the concentration of T3 and T4 hormones, the concentration of TSH is expected to decrease and due to the fact that the T3 hormone receptor is located in the anterior pituitary gland. These nanoparticles can affect both the hypothalamus and the pituitary gland, resulting in changes in the hormone TSH. It can also be said that MoO_3 NPs can cause follicular destruction and release of T3 and T4 and increase their concentration by affecting the thyroid gland. In a study by Tassinari *et al*. on the effect of titanium dioxide nanoparticles, they found that the concentration of T3 decreased (2014). In another study by Afkhami-Ardakani *et al*. (2013) on the effect of iron oxide nanoparticles on the thyroid gland, the concentration of T4 increased, and at a higher concentration a decrease in the concentration of T4 was observed. Also, the study of the effect of nanoparticles on the thyroid showed that the reduction in TSH led to disruption of the hypothalamic-pituitary-endocrine pathway and liver damage. These changes impair the secretion of the monoamine oxidase enzyme. Moreover, due to nanoparticles, increasing the concentration of T3 and T4 reduces TSH or affects the brain-pituitary-thyroid axis and causes disruption in this axis, and the amount of TSH is reduced (Afkhami-Ardakani *et al*., 2013).

The monoamine oxidase inhibitors reduce TSH synthesis (Noureddine *et al*., 2005). The nanoparticles probably inhibit the monoamine oxidase enzyme, and as a result, TSH is reduced, which is in line with the present study. Therefore, according to previous reports and the present study, it can be stated that nanoparticles can increase the concentration of T3 and T4 hormones and also damage the cells of thyroid follicles and cause the release of hormones.

Disorders in hormone levels cause changes in the amount of carbohydrate accumulation (Vornanen *et al*., 2011). In the present study, an increase in T3 and T4 levels was evident. Naturally, an increase in the levels of metabolic hormones increases liver function and the use of carbohydrates as an energy source. The present study results showed a decrease in the density of carbohydrates in the liver of the MoO_3 NPs 200 group.

Masson's trichrome staining is used as an indicator for measuring liver fibrosis in tissue sections (Ghaedi *et al*., 2014). A study illustrated that oxidative stress, cytotoxicity, and genotoxicity in mouse skin fibroblast cells (L929) were made by molybdenum nanoparticles (Siddiqui *et al*., 2015). In the

present study, the increase in liver staining by Masson's trichrome staining in the MoO_3 NPs groups, especially the 200 mg/kg group, indicates the induction of fibrosis. This can be due to nanoparticle damage or overactive liver cells due to hormonal changes.

Nanoparticles have special and unexampled physiochemical characteristics since their tiny size (<100 nm), high surface-to-mass ratio, singular quantum features (Patra *et al*., 2018), and therefore exclusive biological attributes. Crossing through cellular and nuclear membranes is a unique feature of smaller nanoparticles, and they can perforate cells and intracellular constructions and aim at delineated points within the body (Sharma *et al*., 2020; Augustine *et al*., 2020). Because of the very small size of NPs, they can cross from the body's entrances into the circulatory and lymphatic systems and finally into tissues and organs. In addition, diverse NPs cause irremeable cell lesions by oxidative stress and/or organelle damage owing to multiple agents containing size, shape, composition, and surface chemistry (De Matteis, 2017; Rajput *et al*., 2018; Gupta & Xie, 2018). The feasibility of NPs entering biological systems is the principal concern of the public according to potential toxicity to biological systems and development (Brohi *et al*., 2017).

Conclusion

In conclusion, the consumption of nanoparticles has various outcomes. Because of their tiny size, they can cross through membranes and affect cells. Therefore, finding safe doses of nanoparticles needs more investigations. Furthermore, MoO_3 NPs have adverse effects and damage on hepatocytes which causes alterations in serum levels of liver enzymes and thyroid hormones. But, in some studies, low doses of MoO_3 NPs had a slight effect on liver tissue and enzymes.

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All procedures performed in this study involving animals were in accordance with the ethical standards and considerations of the Faculty of Pharmacy and Pharmaceutical Sciences, Islamic Azad University, Tehran, Iran (Code: IR.IAU.PS.REC.1400.207) at which the study was conducted.

Conflict of Interest

The authors declared no conflict of interest.

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مجله طب دامی ایران، ۱۴۰۰، دوره ۱۶، شماره ۲، ۱۸۹-۲۰۲

مطالعه هیستومورفومتری و بیوشیمیایی کبد و هورمون‌های تیروئید به دنبال تجویز نانوذرات MoO3 در رت‌های ماده

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زمینه مطالعه: نانوذرات حامل‌های محبوبی برای ژن‌درمانی و انتقال دارو هستند. اثرات سمی کم، توانایی تجمع و ورود به سلول‌های پستانداران، اهمیت آن‌ها را نشان می‌دهد.

هدف: هدف از این مطالعهٔ تجربی، بررسی تأثیر نانوذرات تری اکسید مولیبدن بر ساختار و عملکرد کبد بود.

روش کار: در این بررسی، سی‌وپنج رت بالغ نژاد Wistar در پنج گروه استفاده شدند. گروه کنترل، دارویی دریافت نکرد؛ گروه حلال نرمال سالین و گروه‌های ۳، ۴ و ۵ به ترتیب ۵۰، ۱۰۰ و ۲۰۰ میلی‌گرم بر کیلوگرم وزن بدن، نانوذرات تری‌اکسیدمولیبدن (MoO_3 NPs) را با تزریق داخل صفاقی به مدت ۳۵ روز دریافت کردند. در پایان، مقدار سطح سرمی AST، ALT، ALP، T3، T4، TSH و VLDL بررسی شد. علاوه بر این، بافت کبد ازنظر ریخت‌شناسی، بافت‌شناسی، هیستوشیمی و آنالیز تصویری ارزیابی شد. روش‌های رنگ‌آمیزی هماتوکسیلین-ائوزین، ماسون تریکروم و پریودیک اسید شیف برای ارزیابی بافت کبد استفاده شد.

نتایج: نانوذرات تری اکسید مولیبدن باعث افزایش قابل‌توجه سطح سرمی آنزیم‌های کبدی و هورمون‌های تیروئیدی، و کاهش TSH در گروه‌های MoO_3 NPs در مقایسه با گروه‌های کنترل و حلال شدند. همچنین، ارزیابی هیستومورفومتری، هیستوشیمیایی و آنالیز تصویری بافت کبد نشان‌دهندهٔ اثرات نامطلوب نانوذرات MoO_3 بر بافت کبد بود و نشان داد که تجمع کربوهیدرات‌ها در سلول‌های کبدی کاهش‌یافته و فیبرهای کلاژن رنگ‌آمیزی شده به‌وسیلهٔ رنگ‌آمیزی ماسون تریکروم در گروه‌های MoO_3 NPs افزایش‌یافته بود.

نتیجه‌گیری نهایی: می‌توان نتیجه گرفت که نانوذرات مانند MoO_3 NPs ساختار بافتی سلول‌های کبدی را تحت تأثیر قرار داده و به آن‌ها آسیب می‌رسانند؛ همچنین، نانوذرات MoO_3 می‌توانند با آسیب رساندن و تأثیر بر سلول‌های کبدی، سطح سرمی آنزیم‌های کبدی را تغییر دهند.

واژه‌های کلیدی: هیستومورفومتری، آنزیم کبدی، مورفولوژی کبد، نانوذرات تری‌اکسیدمولیبدن، هورمون تیروئید

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