

Curcuma reduces kidney and liver damage induced by titanium dioxide nanoparticles in male Wistar rats

Mandana Shirdare^{1,†}, Fatemeh Jabbari^{1,†}, Maryam Salehzadeh², Nasrin Ziamajidi³, Alireza Nourian⁴, Shirin Heidarisan³, Azar Ghavimishamekh³, Masoumeh Taheri Azandariani⁵, Roghayeh Abbasalipourkabir^{3,*}

¹Department of Medical Laboratory, School of Paramedicine, Hamadan University of Medical Sciences, Hamadan, Iran

²Department of Orthodontics, School of Dentistry, Hamadan University of Medical Sciences, Hamadan, Iran

³Department of Biochemistry, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

⁴Department of Pathology, School of Veterinary Medicine, Bu-Ali Sina University, Hamadan, Iran

⁵Neurophysiology Research Center, School of Medicine, Hamadan University of Medical Sciences, Hamadan, Iran

Article history:

Received: Nov 19, 2020

Received in revised form:

Jan 11, 2021

Accepted: Feb 20, 2021

AJP, Vol. 12, No. 5, Sep-Oct

2022, 537-547.

[https://dx.doi.org/10.22038/](https://dx.doi.org/10.22038/AJP.2021.53346.2727)

[AJP.2021.53346.2727](https://dx.doi.org/10.22038/AJP.2021.53346.2727)

† Equal first author

* Corresponding Author:

Tel: +98-81-38380583

Fax: +98-81-38380916

rpourkabir@hotmail.com

Keywords:

Curcuma

Titanium dioxide nanoparticles

Toxicity

Wistar rats

Abstract

Objective: The current study was designed to investigate the protective effects of curcuma caplet against titanium dioxide nanoparticles (nTiO₂)-induced damage in liver and kidney of male Wistar rats.

Materials and Methods: Thirty adult (7-8 week old) male rats (200 g) were randomly divided into 5 groups of 6 each. The first and second groups received olive oil and nTiO₂ (300 mg/kg body weight) as control and nTiO₂ groups, respectively. The third, fourth, and fifth groups received Curcuma at concentrations of 100, 200, and 300 mg/kg body weight in addition to 300 mg/kg body weight of nTiO₂, respectively. The treatment was performed through gavage for 3 weeks. Rats' blood was examined for total antioxidant capacity (TAC), total oxidant status (TOS), and malondialdehyde (MDA) levels as well as antioxidant enzymes superoxide dismutase (SOD), and glutathione peroxidase (GPx), and activity of liver enzymes alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), and renal factors (urea, uric acid, and creatinine). Histological analyses were also performed to estimate the extent of hepatic and renal injury.

Results: nTiO₂-induced liver and kidney damage by decreased serum SOD, GPx, and TAC ($p < 0.05$). Furthermore, nTiO₂ increased serum MDA and TOS, and renal (Creatinine, Urea and Uric acid) and liver parameters (ALT, AST, ALP and LDH) ($p < 0.05$). However, Curcuma treatment was able to moderate these changes dramatically ($p < 0.05$). The results were confirmed by histopathological data.

Conclusion: This study showed the antioxidant properties of curcuma against the side effects of nTiO₂.

Please cite this paper as:

Shirdare M, Jabbari F, Salehzadeh M, Ziamajidi N, Nourian A, Heidarisan S, Ghavimishamekh A, Taheri Azandariani M, Abbasalipourkabir R. Curcuma reduces kidney and liver damage induced by titanium dioxide nanoparticles in male Wistar rats. *Avicenna J Phytomed*, 2022; 12(5): 537-547.

Introduction

With the advent of nanotechnology, most nanoparticles can be released into the environment; hence, the effects of nanoparticles on humans and the environment have become a matter of concern for a number of scientists and organizations (Wang *et al.*, 2007). Meanwhile, the use of these nanoparticles in medicinal products and edible pigments has subjected the general public, especially children to health-related hazards (Weir *et al.*, 2012). Also, nanoparticles have a long life span in the environment and in the food chain, leading to the persistence of their toxicity (Peter *et al.*, 2004).

One of these compounds is titanium dioxide nanoparticles. Approximately 95% of titanium is present as titanium dioxide, which is completely insoluble, stable at constant temperatures and non-flammable (Mital and Manoj, 2011). Nowadays, titanium dioxide is employed in the production of paints, cosmetics, targeted drug delivery (Ren *et al.*, 2013; Du *et al.*, 2015), photothermal therapy of cancer (Ren *et al.*, 2015), pigments, optical electronic devices, ceramics, photocatalysts, water and wastewater treatment, and many more applications (Mital and Manoj, 2011; Li *et al.*, 2011). Due to its small size, it easily crosses the surface of biological membranes and causes an imbalance in the body's antioxidant system, thereby inducing oxidative stress in various organs of the body (Liu and Yang, 2013). These nanoparticles can cause liver and kidney injury, hepatocyte necrosis, and lung function damage in mice (Wang *et al.*, 2007). Oxidative stress is caused by an imbalance between the production of free radicals and reactive oxygen species (including superoxide anion, hydroxyl free radical, hydrogen peroxide, etc.) on the one hand and antioxidant defense system on the

other. Oxidative stress has detrimental effects on macromolecules, including DNA, proteins, and lipids (Chandra *et al.*, 2015). From long ago, the significant therapeutic effects of medicinal plants have been considered by researchers (Stener-Victorin, and Lindholm, 2004). Turmeric is widely used as a food additive. This spice and food coloring is known throughout Asia as a herbal medicine (Bala *et al.*, 2006). The low cost of this spice and its beneficial effects have made it a necessary part of the daily diet (Aggarwal, 2010). Studies have shown that turmeric protects the liver against a variety of toxins, including carbon tetrachloride, galactose amine, pentobarbital, acetaminophen, thioacetamide, and aflatoxin (Aggarwal *et al.*, 2003). Liver protection can be effective in preventing the adverse effects of carbon tetrachloride-induced liver damage in rats (Deshpande *et al.*, 1998).

This study was designed to investigate the effect of curcuma on titanium dioxide-induced liver and kidney damage.

Materials and Methods

Titanium dioxide nanoparticles (white, crystal form, size 20 nm, specific surface area 10-45 m²/g) were prepared from Iranian Nanomaterials Pioneers Company, NANOSANY (Mashhad, Iran). The characteristics of titanium dioxide nanoparticles (nTiO₂) are presented in Table 1 and Figure 1. Curcuma caplet (turmeric caplet) was purchased from Dineh Company (Iran). Each caplet of curcuma contains 450 mg of *Curcuma longa* rhizome powder and 50 mg of *Curcuma longa* extract, which is standardized based on 47.5 mg of curcumin. nTiO₂ (Moradi *et al.*, 2019) and curcuma (Lee *et al.*, 2016) doses were selected based on previous studies.

Curcuma decreases TiO₂ nanoparticles damage

Table 1. Characteristics of nTiO₂ used in the present study.

| Particle size nm | Specific surface area m ² /g | Color | Crystal form | pH | Bulk density |
|------------------|---|-------|----------------------------------|---------|--------------|
| 20 nm | 10-45 | White | 80 vol% anatase + 20 vol% rutile | 5.5-6.0 | 0.46 g/ml |

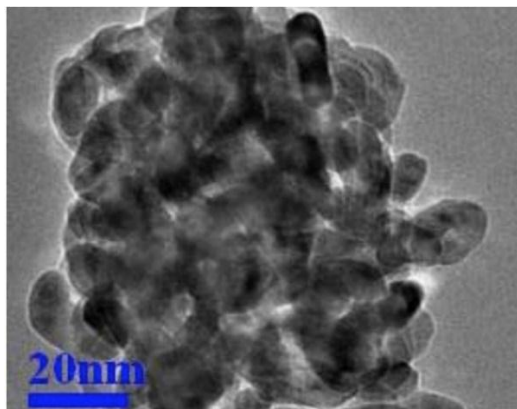


Figure 1. A micrograph of titanium dioxide nanoparticles by transmission electron microscope (TEM).

Animals and study design

Thirty adults male Wistar rats aged 7- 8 weeks old (200 g) were randomly divided into 5 groups of 6 each. The control group (C group) received olive oil, the TiO₂ group was treated with nTiO₂ at 300 mg/kg body weight dissolved in olive oil, the TiO₂+ T100 group received nTiO₂ at 300 mg/kg body weight + Curcuma caplet at 100 mg/kg body weight dissolved in olive oil, the TiO₂+ T200 group received nTiO₂ at 300 mg/kg body weight + Curcuma caplet at 200 mg/kg body weight and the TiO₂+ T300 group received nTiO₂ at 300 mg/kg body weight + Curcuma caplet at 300 mg/kg body weight. The treatment was performed through 1 ml/day gavage for 3 weeks. At the end of the treatment period, the serum of the rats was prepared, and the activity of the liver enzyme including alanine transaminase (ALT), aspartate transaminase (AST), alkaline phosphatase (ALP), and lactate dehydrogenase (LDH) as well as renal factors including urea, uric acid, and creatinine was measured. The animal study was conducted according to the guidelines for the care and use of laboratory animals of the Hamadan University of Medical Sciences, Hamadan, IRAN (IR.UMSHA.REC.1397.523).

Biochemistry of serum

The serum biochemical parameters, creatinine, uric acid, urea, alkaline phosphatase (ALP), alanine transaminase (ALT), aspartate transaminase (AST) and lactate dehydrogenase were measured by an Autoanalyzer (Mindray-BS 480, USA) using Pars Azmun kits (Iran).

Serum oxidative stress

The serum was studied for total antioxidant capacity (TAC), total oxidant status (TOS), and malondialdehyde (MDA) level as well as antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GPx) according to a previous research (Heidarisan et al., 2018).

Histopathology study

The liver and kidney of the animals were removed, washed with physiologic serum, fixed in PBS 10%, and finally stained with Hematoxylin and Eosin (H&E). Histological analyses of the tissue sections were performed using a light microscope (ProWay, China) for examining the tissue changes.

Statistical analysis

The obtained data were statistically analyzed using SPSS 20 software. The results are presented as mean±standard deviation. One-way analysis of variance (ANOVA) followed by Tukey's test was carried out to compare the differences of means among the groups. A $p < 0.05$ was appointed as the level of significance.

Results

Effect of nTiO₂ and curcuma caplet on body weight of the rats

Table 2 reports significant increases in weight of the rats during the study ($p < 0.05$). However, there was no meaningful difference between the weight of the animals at the end of the study ($p > 0.05$).

Effect of nTiO₂ and curcuma caplet on serum biochemical parameters

According to Tables 3 and 4, treatment with nTiO₂ resulted in a significant increase in renal indices creatinine, urea, and uric acid as well as liver function

parameters ALT, AST, ALP, and LDH ($p < 0.05$). Treatment with curcuma at 100 mg/kg body weight better than curcuma 300 mg/kg body weight, improved renal parameters ($p < 0.05$). According to the results, curcuma at 300 mg/kg body weight further reduced the serum levels of AST and ALT ($p < 0.05$). However, regarding ALP and LDH, the effect of 100 mg/kg body weight was better than that of 300 mg/kg body weight ($p < 0.05$).

Table 2. Effect of titanium dioxide nanoparticles and curcuma caplet on body weight (g) of the rats.

| Groups | Week 1 | Week 2 | Week 3 | Week 4 |
|------------------------|-------------|--------------|--------------|--------------|
| C | 211.33±5.75 | 246.33±12.73 | 262.83±11.87 | 282.50±15.82 |
| TiO ₂ | 208.16±3.97 | 243.00±10.75 | 260.50±11.04 | 276.50±14.51 |
| TiO ₂ +T100 | 201.83±6.36 | 236.50±13.33 | 253.66±22.06 | 271.00±28.51 |
| TiO ₂ +T200 | 211.00±7.32 | 260.83±20.73 | 262.66±18.40 | 272.00±15.92 |
| TiO ₂ +T300 | 203.16±3.31 | 234.16±8.15 | 249.16±14.45 | 268.83±15.90 |
| p value | 0.016 | 0.021 | 0.504 | 0.744 |

All values are expressed as Mean±SD. TiO₂ (nTiO₂ 300 mg/kg bw.); TiO₂+T100 (nTiO₂ 300 mg/kg bw + curcuma caplet 100 mg/kg bw.); TiO₂+T200 (nTiO₂ 300 mg/kg bw + curcuma caplet 200 mg/kg bw.); and TiO₂+T300 (nTiO₂ 300 mg/kg bw + curcuma caplet 300 mg/kg bw.).

Table 3. Effect of titanium dioxide nanoparticles and curcuma caplet on kidney parameters in serum of rats

| Groups | Creatinine mg/dl | Urea mg/dl | Uric acid mg/dl |
|------------------------|------------------|------------|-----------------|
| C | 0.57±0.15 | 36.33±2.16 | 1.26±0.023 |
| TiO ₂ | 0.94±0.29 | 75.33±2.73 | 1.57±0.027 |
| TiO ₂ +T100 | 0.62±0.19 | 45.16±3.06 | 0.70±0.023 |
| TiO ₂ +T200 | 0.75±0.14 | 52.16±2.56 | 0.81±0.021 |
| TiO ₂ +T300 | 0.83±0.19 | 60.33±1.75 | 1.01±0.057 |
| p value | 0.000 | 0.000 | 0.000 |

All values are expressed as Mean±SD. TiO₂ (nTiO₂ 300 mg/kg bw.); TiO₂+T100 (nTiO₂ 300 mg/kg bw + curcuma caplet 100 mg/kg bw.); TiO₂+T200 (nTiO₂ 300 mg/kg bw. + curcuma caplet 200 mg/kg bw.); and TiO₂+T300 (nTiO₂ 300 mg/kg bw. + curcuma caplet 300 mg/kg bw.).

Table 4. Effect of titanium dioxide nanoparticles and curcuma caplet on serum liver enzymes

| Groups | ALP(U/L) | AST(U/L) | ALT(U/L) | LDH(U/L) |
|------------------------|-------------|-------------|-------------|---------------|
| C | 455.00±4.28 | 69.66±4.80 | 47.33±2.06 | 789.00±3.89 |
| TiO ₂ | 639.00±6.54 | 139.16±3.12 | 106.17±2.92 | 1015.33±37.83 |
| TiO ₂ +T100 | 352.16±3.31 | 104.83±2.92 | 83.33±2.58 | 548.33±3.20 |
| TiO ₂ +T200 | 379.80±3.86 | 96.00±1.67 | 69.40±2.42 | 595.4±3.93 |
| TiO ₂ +T300 | 426.33±5.20 | 81.83±2.13 | 59.50±1.87 | 667.50±6.74 |
| p value | 0.000 | 0.000 | 0.000 | 0.000 |

All values are expressed as Mean±SD. TiO₂ (nTiO₂ 300 mg/kg bw.); TiO₂+T100 (nTiO₂ 300 mg/kg bw. + curcuma caplet 100 mg/kg bw.); TiO₂+T200 (nTiO₂ 300 mg/kg bw. + curcuma caplet 200 mg/kg bw.); and TiO₂+T300 (nTiO₂ 300 mg/kg bw. + curcuma caplet 300 mg/kg bw.). ALP: Alkaline phosphatase; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase, and LDH: Lactate dehydrogenase.

Curcuma decreases TiO2 nanoparticles damage

Effect of nTiO2 and curcuma caplet on serum oxidative stress

As Tables 5 and 6 show, nTiO2 significantly increased TOS and MDA and significantly decreased TAC, SOD, and GPx compared to the control group ($p < 0.05$). Curcumin improved these changes ($p < 0.05$) but did not restore the values to those of the control group.

Effect of nTiO2 and curcuma caplet on the tissue structure of liver

In Figure 2, the microstructural image of the control group shows the tissue structure of the liver consisting of a normal lobular structure with portal areas, hepatic cords, and normal central veins. Treatment with nTiO2 led to liver tissue damage including inflammation, hyperemia, Kupffer cell proliferation, sinusoidal dilatation, and hepatocyte necrosis. Damages were

reduced in the groups treated with curcuma at the selected doses.

Effect of nTiO2 and curcuma caplet on tissue structure of the kidney

According to Figure 3, the control group presented the normal tissue structure of the kidney, including the renal glomeruli and normal nephron tubes. Glomerular wrinkling and atrophy, vascular hyperemia, interstitial tissue inflammation around the renal tubules, necrosis in the kidney, small blood vessel hyperemia, neuronal apoptosis, and gliosis occurred in the renal tissue of TiO2-treated group compared to the healthy control rats. Treatment with curcumin improved the tissue damage as only a few areas of white blood cell and hyperemia in small blood vessels were observed.

Table 5. Effect of titanium dioxide nanoparticles and curcuma caplet on oxidative stress parameters.

| Groups | TAC (mmole/ml) | TOS (mmole/ml) | MDA (μ M/l) |
|-----------|-----------------|------------------|-------------------|
| C | 8.86 \pm 0.25 | 3.88 \pm 0.67 | 0.213 \pm 0.025 |
| TiO2 | 3.93 \pm 0.22 | 20.68 \pm 0.49 | 0.601 \pm 0.022 |
| TiO2+T100 | 1.67 \pm 0.20 | 2.48 \pm 0.19 | 0.460 \pm 0.021 |
| TiO2+T200 | 2.79 \pm 0.36 | 5.46 \pm 0.10 | 0.386 \pm 0.027 |
| TiO2+T300 | 6.86 \pm 0.35 | 7.64 \pm 0.45 | 0.305 \pm 0.028 |
| p value | 0.000 | 0.000 | 0.000 |

All values are expressed as Mean \pm SD. TiO2 (nTiO2 300 mg/kg bw.); TiO2+T100 (nTiO2 300 mg/kg bw. + curcuma caplet 100 mg/kg bw.); TiO2+T200 (nTiO2 300mg/kg bw. + curcuma caplet 200 mg/kg bw.); and TiO2+T300 (nTiO2 300 mg/kg bw. + curcuma caplet 300 mg/kg bw.). TAC: Total antioxidant capacity; MDA: Malondialdehyde; and TOS: Total oxidant status.

Table 6. Effect of titanium dioxide nanoparticles and curcuma caplet on serum enzymatic antioxidants.

| Groups | SOD (U/L) | GPx (U/L) |
|-----------|------------------|-------------------|
| C | 1.93 \pm 0.037 | 190.5 \pm 5.68 |
| TiO2 | 0.66 \pm 0.149 | 115.33 \pm 4.03 |
| TiO2+T100 | 1.27 \pm 0.043 | 143.83 \pm 3.76 |
| TiO2+T200 | 1.51 \pm 0.027 | 164.00 \pm 4.18 |
| TiO2+T300 | 1.71 \pm 0.022 | 176.83 \pm 3.31 |
| p value | 0.000 | 0.000 |

All values are expressed as Mean \pm SD. TiO2 (nTiO2 300 mg/kg bw.); TiO2+T100 (nTiO2 300 mg/kg bw. + curcuma caplet 100 mg/kg bw.); TiO2+T200 (nTiO2 300 mg/kg bw. + curcuma caplet 200 mg/kg bw.); and TiO2+T300 (nTiO2 300 mg/kg bw. + curcuma caplet 300 mg/kg bw.). SOD: Superoxide dismutase; and GPX: Glutathione peroxidase.

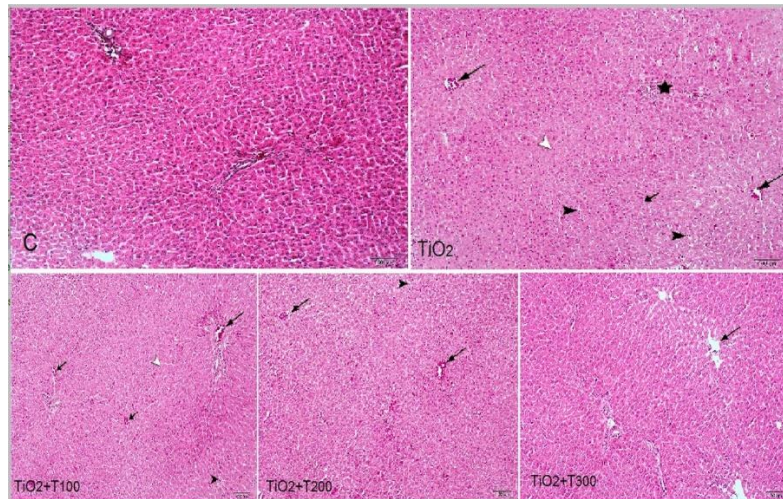


Figure 2. H&E staining photomicrograph of liver tissue of rats (10 x). C: The control group shows tissue structure of the liver containing the normal lobular structure with portal areas, hepatic cords and normal central veins. TiO₂ (nTiO₂ 300 mg/kg bw.) shows portal inflammation with infiltration of white blood cells (stars), central vein hyperemia (large arrows), enlargement of Kupffer cells (small arrow), dilation of sinusoids associated with inflammatory cells accumulation (black arrowhead), and hepatocyte necrosis (white arrow head); TiO₂+T100 (nTiO₂ 300 mg/kg bw. + curcuma caplet 100 mg/kg bw.) shows portal inflammation with venous liver bleeding (larger arrow), lobule center venous bleeding (small arrows), sinusoidal dilatation, and inflammatory cell aggregation (black arrow head), and liver parenchymal cell necrosis (white arrow head), TiO₂+T200 (nTiO₂ 300 mg/kg bw. + curcuma caplet 200 mg/kg bw.) shows center of vein hypertension (arrows) and sinusoidal dilatation (arrowhead), and TiO₂+T300 (nTiO₂ 300 mg/kg bw. + curcuma caplet 300 mg/kg bw.) shows microscopic structure of normal liver lobes, inflammation, hyperemia and enlargement of sinus capillaries.

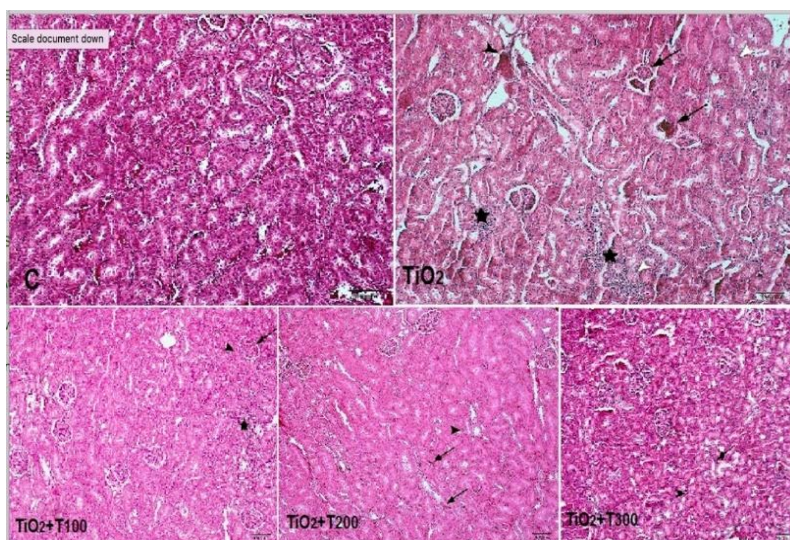


Figure 3. H&E staining photomicrograph of renal tissue of rats (10 x). C: The control group shows the normal tissue structure of the renal glomeruli and nephron tubes. TiO₂ (nTiO₂ 300 mg/kg bw.) shows glomerular wrinkling and atrophy (arrows), vascular hyperemia (black arrowhead), inflammation of the interstitial tissue surrounding the renal tubules with infiltration and accumulation of white blood cells in the area (stars), and necrosis of the epithelial cells of the adjacent renal tubules (white arrows head). TiO₂+T100 (nTiO₂ 300 mg/kg bw. + curcuma caplet 100 mg/kg bw.) shows wrinkles and atrophy of the glomerulus (arrow), inflammation of the interstitial tissue around the tubes with the influence of white blood cells (stars), and necrosis of the epithelial cells of the nearby renal collecting tubules (black arrowhead), TiO₂+T200 (nTiO₂ 300 mg/kg bw. + curcuma caplet 200 mg/kg bw.) shows venous hyperpigmentation (arrows) and mild infiltration of inflammatory cells into the interstitial tissue (arrowhead), TiO₂+T300 (nTiO₂ 300 mg/kg bw. + curcuma caplet 300 mg/kg bw.) shows the microscopic structure of the organ is near-normal and only in some areas of infiltration of white blood cells (arrow) and hyperemia in small blood vessels (arrowhead).

Discussion

In this study, the toxicity of nTiO₂ and protective effects of 100, 200 and 300 of curcuma powder/kg body weight of the rats were evaluated for three weeks in adult Wistar rats based on serum antioxidant enzymes as well as liver and kidney function parameters. We found hepatocyte necrosis in the liver tissue and epithelial cells necrosis in the renal tubules. Previous studies have shown that nTiO₂ can cause liver damage and induce oxidative stress in rats' liver (Ma et al., 2009). Due to its physicochemical properties, titanium dioxide may cause liver dysfunction. These nanoparticles induce cell death and liver necrosis upon entry into the cell and deployment in the cytoplasm (Sharma et al., 2012; Rezaei-Zarchi et al., 2012). nTiO₂ can enter the body through the mouth, thereby affecting the function of the stomach and intestinal epithelium. In a study, absorption of nTiO₂ through the small intestine has been reported (Al-Jubory and Handy, 2013). Studies have shown that nTiO₂ may potentially enter the tissues through the intestine (Brun et al., 2014). Wang et al. (2007) reported that two weeks after feeding nTiO₂ to adult rats, the nanoparticles had a toxic effect at 25 and 80 nm at a dose of 1 g/kg. They performed this experiment through intravenous and intraperitoneal injection of nTiO₂ and observed nephrotoxicity as renal glomeruli inflammation due to nTiO₂ accumulation in the kidney. They concluded that nTiO₂ could penetrate into body tissues and be absorbed by other tissues through the intestines and stomach. It has been shown that in many toxicities, the liver and kidney are more susceptible to damage due to their active role in the metabolism and biochemical changes of environmental pollutants as well as their high blood supply (Mohamed, 2009). In another study, the effect of nTiO₂ on rat liver enzyme activity was investigated. Elsewhere, the silver nanoparticles were orally administered to mice and the liver enzymes activity was measured. The results showed elevated

serum levels of liver enzymes ALT and AST due to the toxic effect of nanoparticles on the body (Rezaei-Zarchi et al., 2013). These enzymes are naturally present in the liver cells, and are released into the circulation due to damages to the plasma membrane or cell death, causing elevated serum levels of these enzymes. Thus, a higher serum level of these enzymes is an indicator for assessing the extent of liver cell injury (Liao et al., 2015).

Researchers have shown that the Curcuminoids from *Curcuma longa* L. (Zingiberaceae) is able to protect the skin's epidermal cells from the stress of oxygen radicals (Bonte, 1997). Based on recent studies, curcumin reduces oxidative damage and apoptosis. Cellular-molecular analysis has shown that exposure of astrocyte and oligodendrocyte from rat glioma to a low dose of curcumin regulated the pentose phosphate pathway by activating glutathione and aldehyde oxidase (Panchal et al., 2008). Curcumin may lower the levels of serum enzymes such as ALT, AST and LDH which are secreted more during inflammation (Manjunatha and Srinivasan, 2006). ALT, AST, and ALP are present in the cell cytosol and cell membrane, respectively. These enzymes are released into the blood in response to liver cell destruction. Thus, elevation of these enzymes is a sign of liver cell destruction. ALT and AST are indicators of hepatocyte function while ALP reflects bile duct injury, especially extracellular duct injury (Feldman et al., 2002; Okechukwu and Segun, 2004). The results of our study showed that administration of curcuma caused a significant reduction in the acute rise in serum transaminases induced by nTiO₂. In a study, Park et al. (2000) reported the inhibitory effect of turmeric (curcuma) on carbon tetrachloride-induced liver toxicity, which is consistent with the results of the present study. Turmeric has also been shown to improve acute hepatic toxicity due to beta-de-galactose amine and iron, reducing necrosis, and lipid peroxidation in the liver (Park et al., 2000;

Lin SC, 1996; Ready AC, Lokesh 1999). In our study, ALP level in the nTiO₂ recipient group was significantly elevated, indicating liver damage induced in rats. ALP has been proposed as a tumor marker or marker of liver disease as well as liver injury (Moss DW, 1999). In our study, the serum level of ALP activity began to decrease from the beginning of the treatment. In addition, LDH levels were significantly lower in the curcuma-treated groups in comparison with the control and titanium dioxide groups, which may be due to the antioxidant and anti-inflammatory properties of curcumin (Sadoughi, 2016; Sharma, 2007). Curcumin curbs the activity of inflammatory enzymes, such as cyclooxygenase-2 and lipoxygenase-5, by reducing gene expression of NF- κ B as inflammatory parameter (Sharma, 2007). According to the results, the serum level of urea, uric acid, and creatinine significantly rose in the group treated with titanium dioxide compared to the control group. After treatment with curcuma at 100, 200, and 300 mg/kg, their serum levels were significantly reduced in a dose-dependent manner. The results of this study are consistent with a study where the serum urea, creatinine, and uric acid levels diminished dose-dependently in experimental diabetic groups treated with 100 and 200 mg/kg bw. curcumin (Sadoughi, 2017).

It is suggested that different mechanisms are involved in nTiO₂ damage such as reactive species oxygen (ROS) production followed by oxidative stress (Li et al., 2014). In the current study, SOD and Gpx significantly fell in the group treated with titanium dioxide. Lower levels of antioxidant indices can be due to the higher levels of free radicals. SOD has a key role against oxidative damage (Ighodaro and Akinloye, 2017). The levels of the two enzymes, SOD and GPx, were elevated in groups treated with curcuma at 100, 200, and 300 mg/kg bw. Also, 300 mg/kg bw. of curcuma further increased SOD and GPx and brought them closer to levels observed

in the control group. Curcumin suppresses cellular glutathione depletion, increases its levels, and enhances internal antioxidant enzymes activity, while SOD inhibits lipid peroxidation and prevents ROS production (Ognjanović et al., 2010; Bucak et al., 2010). Studies by Avci et al. (2012) and Kalpana et al. (2007) also reported increased levels of CAT, GPx, SOD, and tissue glutathione (GSH) by curcumin in the liver, kidney, and muscles of rats (Avci et al., 2012; Kalpana et al., 2007). Kalpana et al. (2007) suggested that curcumin could exert its protective effect against nicotine-induced oxidative stress. The results of the present study are in line with the findings of El-Demerdash et al. (2009) who reported the antioxidant effect of curcumin on oxidative damage induced by sodium arsenite toxicity in rats' plasma, liver, kidney, lung, testis, and brain through enhanced antioxidant enzymes activity. In a study, in male Wistar rats exposed to curcumin at 100 mg/kg for four weeks, increased sperm count, plasma testosterone level, glutathione and glutathione peroxidase levels, catalase and superoxide dismutase activity, and expression of inflammatory cytokines were observed (Sharma, 2007). In the present study, curcuma at 100, 200, and 300 mg/kg dose-dependently elevated the level of TAC in comparison to the group treated with nTiO₂. Recent studies have shown that curcumin has a phenolic ring and a beta-diketone moiety on one molecule, both of which have antioxidant potentials (Palma et al., 2001; Wang and Huang, 2007).

The decreased antioxidant activity along with the increased oxidizing parameters is associated with the toxicity of compounds such as nTiO₂. These parameters can be useful in monitoring their toxicity. With the increasing use of nanoparticles in industry, the use of protective and antioxidant herbal compounds such as curcuma can reduce the toxicity caused by nTiO₂. The findings of the present study suggest the role of curcuma caplet in controlling oxidative stress indices and preventing lipid

peroxidation as well as tissue damage and apoptosis in rats exposed to nTiO₂.

Acknowledgment

The study was funded by Vice-chancellor for Research and Technology, Hamadan University of Medical Sciences (Grant No. 9708295073).

Conflicts of interest

The authors have declared that there is no conflict of interest.

References

- Al-Jubory AR, Handy RD. 2013. Uptake of titanium from TiO₂ nanoparticle exposure in the isolated perfused intestine of rainbow trout: nystatin, vanadate and novel CO₂-sensitive components. *Nanotoxicology*, 7: 1282-1301.
- Aggarwal BB. 2010. Targeting inflammation-induced obesity and metabolic diseases by curcumin and other nutraceuticals. *Annu Rev Nutr*, 30: 173-199.
- Aggarwal BB, Kumar A, Bharti AC. 2003. Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Res*, 23: 363-398.
- Avcı G, Kadioglu H, Sehirli AO, Bozkurt S, Guclu O, Arslan E, Muratli SK. 2012. Curcumin protects against ischemia/reperfusion injury in rat skeletal muscle. *J Surg Res*, 172: 39-46.
- Bala K, Tripathy B, Sharma D. 2006. Neuroprotective and anti-ageing effects of curcumin in aged rat brain region. *Biogerontology*, 7: 81-89.
- Bucak MN, Sariözkan S, Tuncer PB, Sakin F, Ateşşahin A, Kulaksız R, Çevik M. 2010. The effect of antioxidants on post-thawed Angora goat (*Capra hircus ancyrensis*) sperm parameters, lipid peroxidation and antioxidant activities. *Small Rumin Res*, 89: 24-30.
- Bonte F, Noel-Hudson MS, Wepierre J, Meybeck A. 1997. Protective effect of curcuminoids on epidermal skin cells under free oxygen radical stress. *Planta Med*, 63: 265-266.
- Brun E, Barreau F, Veronesi G, Fayard B, Sorieul S, Chanéac C, Carapito C, Rabilloud T, Mabondzo A, Herlin-Boime N, Carrière M. 2014. Titanium dioxide nanoparticle impact and translocation through ex vivo, in vivo and in vitro gut epithelia. *Part Fibre Toxicol*, 11:1-16.
- Chandra K, Salman AS, Mohd A, Sweetly R, Ali KN. 2015. Protection against FCA induced oxidative stress induced DNA damage as a model of arthritis and In vitro anti-arthritis potential of *costus speciosus* rhizome extract. *Int J Pharma Phyto Res*, 7: 383-389.
- Deshpande UR, Gadre SG, Raste AS, Pillai D, Bhide SV, Samuel AM. 1998. Protective effect of turmeric (*Curcuma longa* L.) extract on carbon tetrachloride-induced liver damage in rats. *Indian J Exp Biol*, 36: 573-577.
- Du Y, Ren W, Li Y, Zhang Q, Zeng L, Chi C, Wu A, Tian J. 2015. The enhanced chemotherapeutic effects of doxorubicin loaded PEG coated TiO₂ nanocarriers in an orthotopic breast tumor bearing mouse model. *J Mater Chem B*, 3: 1518-1528.
- El-Demerdash FM, Yousef MI, Radwan FM. 2009. Ameliorating effect of curcumin on sodium arsenite-induced oxidative damage and lipid peroxidation in different rat organs. *Food Chem Toxicol*, 47: 249-254.
- Feldman M, Friedman LS, Sleisenger MH. 2002. Gastrointestinal and liver disease. In: Sleisenger & Fordtran's (Eds). 7th Ed. pp. 1227-39, 1310-11, Elsevier.
- Gupta SM, Tripathi M. 2011. A review of TiO₂ nanoparticles. *Chinese Sci Bull*, 56: 1639-1657.
- Heidarisan S, Ziamajidi N, Karimi J, Abbasalipourkabir R. 2018. Effects of insulin-loaded chitosan-alginate nanoparticles on RAGE expression and oxidative stress status in the kidney tissue of rats with type 1 diabetes. *IJBMS*, 21: 1035-1042.
- Hoet PH, Brüske-Hohlfeld I, Salata OV. 2004. Nanoparticles—known and unknown health risks. *J Nanobiotechnology*, 2:12.
- Ighodaro O, Akinloye O. 2017. First line defence antioxidants-superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX): their fundamental role in the entire antioxidant defence grid. *Alex J Med* 54: 287-293.
- Lee HY, Kim SW, Lee GH, Choi MK, Jung HW, Kim YJ, Kwon HJ, Chae HJ. 2016. Turmeric extract and its active compound, curcumin, protect against chronic CCl₄-

- induced liver damage by enhancing antioxidation. *BMC Complement Altern Med*, 16: 316.
- Li LZ, Zhou DM, Peijnenburg WJ, van Gestel CA, Jin SY, Wang YJ, Wang P. 2011. Toxicity of zinc oxide nanoparticles in the earthworm, *Eisenia fetida* and subcellular fractionation of Zn. *Environ Int*, 37: 1098-1104.
- Li M, Yin JJ, Wamer WG, Lo YM. 2014. Mechanistic characterization of titanium dioxide nanoparticle-induced toxicity using electron spin resonance. *J Food Drug Anal*, 22: 76-85.
- Liao CC, Chiu YS, Chiu WC, Tung YT, Chuang HL, Wu JH, Huang CC. 2015. Proteomics analysis to identify and characterize the molecular signatures of hepatic steatosis in ovariectomized rats as a model of postmenopausal status. *Nutrients*, 7: 8752-8766.
- Lin SC, Teng CW, Lin CC, Lin YH, Supriyatna S. 1996. Protective and Therapeutic Effect of the Indonesian Medicinal Herb *Curcuma xanthorrhiza* on β -D-Galactosamine-induced Liver Damage. *Phytother Res*, 10:131-135
- Liu S, Yang Z. 2013. Evaluation of the effect of acute and subacute exposure to TiO₂ nanoparticles on oxidative stress. In: *Oxidative Stress and Nanotechnology*, pp: 135-145. Totowa, NJ, Humana Press,
- Ma L, Zhao J, Wang J, Liu J, Duan Y, Liu H, Li N, Yan J, Ruan J, Wang H, Hong F. 2009. The acute liver injury in mice caused by nano-anatase TiO₂. *Nanoscale Res Lett*, 4: 1275-1285
- Manjunatha H, Srinivasan K. 2006. Protective effect of dietary curcumin and capsaicin on induced oxidation of low-density lipoprotein, iron-induced hepatotoxicity and carrageenan-induced inflammation in experimental rats. *FEBS J*, 273: 4528-4537.
- Mohamed FA. 2009. Histopathological studies on *Tilapia zillii* and *Solea vulgaris* from Lake Qarun, Egypt. *WJFMS*, 1: 29-39.
- Moradi A, Ziamajidi N, Ghafourikhosroshahi A, Abbasalipourkabir R. 2019. Effects of vitamin A and vitamin E on attenuation of titanium dioxide nanoparticles-induced toxicity in the liver of male Wistar rats. *Mol Biol Rep*, 46:2919-32.
- Moss DW, Henderson R. 1999. Clinical enzymology. In: Burtis CA, Ashwood ER (Eds), *Tietz textbook of Clinical Chemistry and Molecular Diagnostics*, pp: 617-721, Philadelphia, Elsevier Saunders.
- Ognjanović BI, Marković SD, Đorđević NZ, Trbojević IS, Štajn AŠ, Saičić ZS. 2010. Cadmium-induced lipid peroxidation and changes in antioxidant defense system in the rat testes: Protective role of coenzyme Q10 and Vitamin E. *Reprod Toxicol*, 29: 191-197.
- Okafor O, Ojo S. 2004. A comparative analysis of six current histological classification schemes and scoring systems used in chronic hepatitis reporting. *Rev Esp Patol*, 37: 269-277.
- Palma M, Piñeiro Z, Barroso CG. 2001. Stability of phenolic compounds during extraction with superheated solvents. *J Chromatogr A*, 921: 169-174.
- Panchal HD, Vranizan K, Lee CY, Ho J, Ngai J, Timiras PS. 2008. Early anti-oxidative and anti-proliferative curcumin effects on neuroglioma cells suggest therapeutic targets. *Neurochem Res*, 33: 1701-1710.
- Park EJ, Jeon CH, Ko G, Kim J, Sohn DH. 2000. Protective effect of curcumin in rat liver injury induced by carbon tetrachloride. *J Pharm Pharmacol*, 52: 437-440.
- Ready AC, Lokesh BR. 1999. Effect of curcumin on iron-induced hepatic toxicity in rats. *Toxicology*, 107: 39-45.
- Rezaei-Zarchi S, Taghavi-Foumani MH, Sheshdeh SA, Negahdary M, Rahimi G. 2012. The effect of silver nano-particles on blood cells in rats. *J Biol*, 1: 17-22.
- Ren W, Zeng L, Shen Z, Xiang L, Gong A, Zhang J, Mao C, Li A, Paunesku T, Woloschak GE, Hosmane NS. 2013. Enhanced doxorubicin transport to multidrug resistant breast cancer cells via TiO₂ nanocarriers. *RSC Adv*, 3: 20855-20861.
- Ren W, Yan Y, Zeng L, Shi Z, Gong A, Schaaf P, Wang D, Zhao J, Zou B, Yu H, Chen G. 2015. A near infrared light triggered hydrogenated black TiO₂ for cancer photothermal therapy. *Adv Healthc Mater*, 4: 1526-1536.
- Sadoughi SD. 2017. The effect of curcumin on the hormones of pituitary-adrenal axis and renal indices in alloxan-induced diabetic rats. *Daneshvar Med*, 24: 79-91.
- Sharma V, Singh P, Pandey AK, Dhawan A. 2012. Induction of oxidative stress, DNA damage and apoptosis in mouse liver after sub-acute oral exposure to zinc oxide

Curcuma decreases TiO₂ nanoparticles damage

- nanoparticles. *Mutat Res Genet Toxicol Environ Mutagen*, 745: 84-91.
- Sharma RK. 2007. Physiology of male gametogenesis. In: *Clinical reproductive medicine and surgery*, pp. 73-83. Philadelphia, MOSBY ELSEVIER.
- Stener-Victorin E, Lindholm C. 2004. Immunity and β -endorphin concentrations in hypothalamus and plasma in rats with steroid-induced polycystic ovaries: effect of low-frequency electroacupuncture. *Biol Reprod*, 70: 329-333.
- Wang F, Huang W. 2007. Determination of curcumin by its quenching effect on the fluorescence of Eu³⁺-tryptophan complex. *J Pharm Biomed Anal*, 43: 393-398.
- Wang J, Zhou G, Chen C, Yu H, Wang T, Ma Y, Jia G, Gao Y, Li B, Sun J, Li Y. 2007. Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. *Toxicol Lett*, 168: 176-185.
- Weir A, Westerhoff P, Fabricius L, Hristovski K, Von Goetz N. 2012. Titanium dioxide nanoparticles in food and personal care products. *Environ Sci Technol* 46: 2242-2250.