Regulatory Toxicology and Pharmacology 98 (2018) 240–244

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Protection of manganese oxide nanoparticles-induced liver and kidney damage by vitamin D

Asghar Ashrafi Hafez[a], Parvaneh Naserzadeh[b], Khadijeh Ashtari[c,d], Amir Mohammad Mortazavian[e,**], Ahmad Salimi[f,*]

[a] Cancer Research Center, Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[b] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[c] Radiation Biology Research Center, Iran University of Medical Sciences, Tehran, Iran
[d] Department of Medical Nanotechnology. Faculty of Advanced Technology in Medicine, Iran University of Medical Sciences, Tehran, Iran
[e] Department of Food Science and Technology, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[f] Department of Pharmacology and Toxicology, School of Pharmacy, Ardabil University of Medical Sciences, Ardabil, Iran

ARTICLE INFO

Keywords:
Vitamin D
Liver
Kidney
Nanoparticles
Manganese oxide-nanoparticles

ABSTRACT

Metal nanoparticles (NPs) have been extensively used in industry as well as in biomedical application. Manganese oxide-nanoparticles (MnO_2-NPs) one of these materials, have many applications. This study was designed to evaluate the protective role of vitamin D against MnO_2-NPs -induced toxicity in the BALB c mice. These mice were randomly assigned to 4 (n = 10). In this study, MnO_2-NPs (10 mg/kg), vitamin D (10 mg/kg) and MnO_2-NPs plus vitamin D were administered interperitoneally once daily for 50 consecutive days. The liver and kidney functions, the levels of serum glucose, albumin (ALB), bilirubin (BIL) and total protein were studied. The results indicated that MnO_2-NPs administration significantly decreased liver and kidney functions, and increased glucose and bilirubin serum levels compared to control group ($P < 0.05$). However, vitamin D administration significantly boosted liver and kidney functions, decreased glucose and bilirubin serum level compared to the group received MnO_2-NPs ($P < 0.05$). It seems that vitamin D administration could protect the liver and kidney damage induced by MnO_2-NPs. Probably, given the use of these nanoparticles as a contest agent in humans, having normal levels of vitamin D or receiving it at the time of the test can inhibit liver and kidney toxicity induced by MnO_2-NPs.

1. Introduction

Evaluation of toxicity effect of nanoparticles in living organism is essential due to its hazardous. Nanoparticles with size of particle from 1 to 100 nm, possess unique physicochemical characteristics (Singh and Nalwa, 2011). Interactions of these materials with living cells induced degenerative and cancer diseases (Oberdörster et al., 2005). Manganese oxide (MnO_2)-NPs one of these materials, are favorable materials utilized in drug delivery, waste water treatment, ionization-assisting reagent in mass spectroscopy, consumer products such as batteries and as contrast agents for magnetic resonance imaging (MRI) (Chen and He, 2008; Na et al., 2007; Rutz, 2009; Shin et al., 2009). The increase in the manufacturing and application of MnO_2-NPs in various fields raises the risk of human exposure Karmakar et al. reported functional neurotoxicity in adult male Wistar rat after instilled MnO_2-NPs (Karmakar et al., 2014). Singh and colleagues compared toxicity of manganese oxide micro and nanoparticles in Wistar rat. They showed, that prolonged exposure to MnO_2 has the potential to cause genetic damage, biochemical alterations and histological changes (Singh et al., 2013). The neurotoxicity of MnO_2-NPs in the brain and red blood cells, as determined through acetylcholinesterase activity (Singh et al., 2013). Previous study reported that cell membrane was damaged in BRL 3A rat liver cells at 100–250 μg/ml by MnO_2-NPs (Hussain et al., 2005). A mechanistic approach in Alarifi's study showed that MnO_2-NPs produce reactive oxygen species (ROS) and declined in mitochondrial membrane potential in the SH-SY5Y cell in dose and duration dependent manner. Moreover, lipid peroxide (LPO), superoxide dismutase (SOD), and catalase (CAT) activities increase and glutathione reduce in

* Corresponding author. Assistant Professor of Toxicology and Pharmacology, School of Pharmacy, Ardabil University of Medical Science, P.O. Box: 56189-53141, Ardabil, Iran.
** Corresponding author. Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences, P.O. Box 19395-4741, Tehran. Iran.
E-mail addresses: Mortazn@sbmu.ac.ir (A.M. Mortazavian), salimikd@yahoo.com, a.salimi@pharmacy.arums.ac.ir (A. Salimi).

https://doi.org/10.1016/j.yrtph.2018.08.005
Received 18 March 2018; Received in revised form 8 August 2018; Accepted 9 August 2018
Available online 10 August 2018

dose and time dependent manner. Also, caspase-3 activity, DNA strand breaks and apoptosis increases due to MnO_2-NPs in these cells (Alarifi et al., 2017).

Vitamin D exhibits direct and indirect antioxidant effects. Vitamin D is a membrane antioxidant. It also affects the antioxidant defense system, by up-regulating endogenous antioxidant effectors like glutathione peroxidase, glutathione, catalase and superoxide dismutase. Major sources of vitamin D are exposure to ultraviolet radiation and diet (Mokhtari et al., 2017). Resect study by Özerkan and colleagues showed that vitamin D appears to act as an antioxidant and anti-fibrotic to protect the rat liver against damage (Özerkan et al., 2017). Another study showed that vitamin D protects hyperoxia-induced lung injury in newborn rats (Kose et al., 2017).

Previous studies showed that exposure to nanoparticles can have an adverse effect on human and environment health. The biological properties of MnO_2-NPs used in medicine applications such as in bioimaging and therapeutics can be very important. MnO_2-NPs may enter the body by passage through the skin, injection into the bloodstream, and inhalation. They also may have the potential to penetrate the blood–brain barrier due to their size. Other studies suggested that MnO_2-NPs can interact with proteins and enzymes, alter gene expression, and thus affect the biological behavior at the organ, tissue, cellular, subcellular, and protein levels. We investigated the protective effects of vitamin D treatment against liver and kidney caused by MnO_2-NPs.

2. Materials and methods

2.1. Animals

All studies and animal procedures were carried out in accordance with the local ethics committee for animal experimentation and in compliance with guidelines of Shahid Beheshti University of Medical Sciences. The animals were kept in temperature controlled (22 ± 2 °C) environment with free access to food and water ad libitum and under 12 light/dark cycle. The mice were adapted to the animal house for 10 days, and then the research protocol started.

2.2. Chemicals and reagents

The assay kits for AST (aspartate transaminase), ALT (alanine transaminase), ALP (Alkaline phosphatase), ALB (albumin), BIL (Bilirubin), CREA (creatinine), blood urea nitrogen (BUN), serum glucose concentration, and uric acid were obtained from Randox Laboratory Limited (Crumlin, United Kingdom). All other reagents used were of analytical grade and supplied by Sigma Aldrich Inc. (St. Louis, MO, USA).

2.3. Characterization of nanoparticles

MnO_2 nanoparticles of size < 40 nm and purity ≥98.1% were measured by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Images of MnO_2-NPs were taken to obtain morphology and size on a TEM (JEM-2100) from JEOL Ltd., Tachikawa, Tokyo, Japan.

2.4. Study design

Forty males (4–5 weeks with an average weight of 17.76 g) were purchased from the Pasteur Institute. The animals were divided into four groups as follows: G1 (n = 10) normal mice were served as control, which received no medications; G2 (n = 10) were normal mice treated intraperitoneally with MnO_2-NPs only (10 mg/kg, daily); G3 (n = 10) were normal mice treated intraperitoneally with vitamin D only (10 mg/kg) and G4 were normal mice treated intraperitoneally with MnO_2-NPs (10 mg/kg, daily) and vitamin D (10 mg/kg, daily). The duration of the treatment was for 7 weeks and biochemical analysis were measured at weeks 1, 3 and 7. MnO_2-NPs were suspended in deionized water and vortexed before every treatment of the mice.

2.5. Blood biochemical

The activities of AST (aspartate transaminase), ALT (alanine transaminase), ALP (Alkaline phosphatase), ALB (albumin), BIL (Bilirubin), CREA (creatinine), blood urea nitrogen (BUN), and serum glucose concentration was assayed using the Randox assay kits (Randox Laboratory Limited) (Warnick et al., 1990). Total protein content of the serum was determined using the Biuret method as previously described by Sulaiman and Adeyemi. All measurements were done using a Spectronic spectrophotometer (Bausch and Lomb, Rochester, NY, USA) (Kalantari et al., 2011a, 2011b; Sulaiman et al., 2015).

3. Results

3.1. Characterization of nanoparticles

The physicochemical characteristics of MnO_2 particles were determined by TEM and SEM techniques. The data obtained are shown in Fig. 1A–B. The primary particle size of the MnO_2-NPs was determined by TEM and SEM images. The shape of particles was found to be

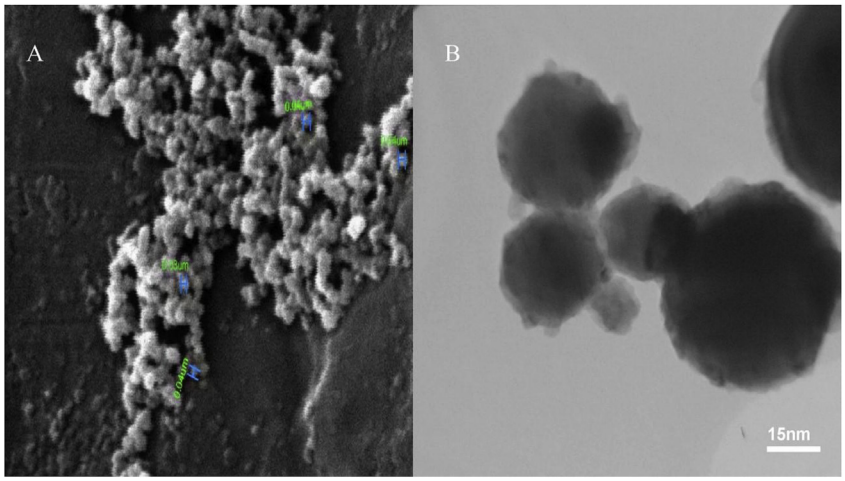

Fig. 1. The purity and morphological characteristics of nanoparticles (A and B). The prepared MnO_2 nanoparticles powder was characterized by scanning electron microscopy (SEM) and transmission electron microscopy (TEM).

Table 1
Effect of MnO_2 nanoparticles on the level of mice serum AST and protective effect of vitamin D.

Groups	AST (U/L)		
	First week	Third week	Seventh week
Control	12 ± 3.4	13 ± 4.1	13 ± 2.4
MnO_2-NP (10 mg/kg)	287 ± 6.4[a]	312 ± 5.1[a]	395 ± 10.4[a]
MnO_2-NP + Vitamin D (10 mg/kg)	102 ± 2.4[b]	97 ± 5.8[b]	98 ± 7.1[b]
Vitamin D (10 mg/kg)	11 ± 1.4	12 ± 1.8	10 ± 2.3

Values are expressed as mean ± SEM (n = 10).
[a] AST significantly (P 0 < 0.05) increased compared with control group.
[b] AST significantly (P 0 < 0.05) decreased compared with MnO_2-NPs plus vitamin D group. Results were analyzed using *t*-test student.

Table 2
Effect of MnO_2 nanoparticles on the level of mice serum ALT and protective effect of vitamin D.

Groups	ALT (U/L)		
	First week	Third week	Seventh week
Control	24 ± 1.0	27 ± 3.1	29.5 ± 4.4
MnO_2-NP (10 mg/kg)	342 ± 10.4[a]	379 ± 6.1[a]	476 ± 9.4[a]
MnO_2-NP + Vitamin D (10 mg/kg)	150 ± 2.3[b]	113 ± 5.2[b]	100 ± 6.2[b]
Vitamin D (10 mg/kg)	16 ± 1.6	18 ± 1.6	20 ± 3.7

Values are expressed as mean ± SEM (n = 10).
[a] ALT significantly (P 0 < 0.05) increased compared with control group.
[b] ALT significantly (P 0 < 0.05) decreased compared with MnO_2-NPs plus vitamin D group. Results were analyzed using *t*-test student.

spherical. The observed average mean size diameter of MnO_2-NPs was lower than 40 nm.

3.2. Liver function

The enzymes such as AST (Table 1), ALT (Table 2) and ALP (Table 3) are responsible for the proper functioning of the liver. Thus, the effect of MnO_2-NPs over the level of different metabolic enzymes shaping the effective functioning of the liver through the serum analysis was analyzed and their protective effect of vitamin D over the liver damage is shown in Tables s1–3 The enzymes ALT, AST, and ALP significantly elevated in the G2 group in comparison to control group. Following treatment of vitamin D, the G3 group presented a partial decrease significantly in comparison to the G2 group, which directly reveals the protective/regenerative effect over the exaggerated activity of liver.

Table 3
Effect of MnO_2 nanoparticles on the level of mice serum ALP and protective effect of vitamin D.

Groups	ALP (U/L)		
	First week	Third week	Seventh week
Control	65 ± 6.8	68 ± 7.5	71 ± 5.8
MnO_2-NP (10 mg/kg)	450 ± 21.3[a]	580 ± 16.8[a]	700 ± 19.7[a]
MnO_2-NP + Vitamin D (10 mg/kg)	280 ± 23.4[b]	370 ± 27.3[b]	298 ± 12.7[b]
Vitamin D (10 mg/kg)	81 ± 11.6	76 ± 9.6	70 ± 11.1

Values are expressed as mean ± SEM (n = 10).
[a] ALP significantly (P 0 < 0.05) increased compared with control group.
[b] ALP significantly (P 0 < 0.05) decreased compared with MnO_2-NPs plus vitamin D group. Results were analyzed using *t*-test student.

Table 4
Effect of MnO_2 nanoparticles on the level of mice serum BUN and protective effect of vitamin D.

Groups	BUN (mg/dL)		
	First week	Third week	Seventh week
Control	18 ± 2	19 ± 1.9	21 ± 1.7
MnO_2-NP (10 mg/kg)	56 ± 1.3[a]	72 ± 6.8[a]	89 ± 8.6[a]
MnO_2-NP + Vitamin D (10 mg/kg)	34 ± 9.4[b]	48 ± 8.1[b]	38 ± 5.4[b]
Vitamin D (10 mg/kg)	18 ± 1.6	20 ± 2.6	19 ± 4.2

Values are expressed as mean ± SEM (n = 10).
[a] BUN significantly (P 0 < 0.05) increased compared with control group.
[b] BUN significantly (P 0 < 0.05) decreased compared with MnO_2-NPs plus vitamin D group. Results were analyzed using *t*-test student.

Table 5
Effect of MnO_2 nanoparticles on the level of mice serum Creatinine and protective effect of vitamin D.

Groups	Creatinine (mg/dL)		
	First week	Third week	Seventh week
Control	1.2 ± 0.4	1 ± 0.2	0.9 ± 0.2
MnO_2-NP (10 mg/kg)	6.2 ± 1.1[a]	8.2 ± 2.1[a]	16 ± 1.2[a]
MnO_2-NP + Vitamin D (10 mg/kg)	3.1 ± 0.6[b]	3.1 ± 0.4[b]	4.2 ± 0.5[b]
Vitamin D (10 mg/kg)	1.4 ± 0.3	0.9 ± 0.1	1.1 ± 0.2

Values are expressed as mean ± SEM (n = 10).
a Creatinine significantly (P 0 < 0.05) increased compared with control group.
b Creatinine significantly (P 0 < 0.05) decreased compared with MnO_2-NPs plus vitamin D group. Results were analyzed using *t*-test student.

3.3. Kidney function

The level of BUN (Table 4) and creatinine (Table 5) symptomatic of the renal functions were decreased significantly near to normal in the G3 groups in comparison to G2 group. The vitamin D treated mice did not show any significant changes of creatinine and BUN levels in comparison to the control ($p < 0.05$). These results obtained over the restorative effect of vitamin D over these biomarkers confirm the ability of vitamin D to protect the kidney from damage due to MnO_2-NPs.

3.4. Other biochemical indices

The daily administration of MnO_2-NPs to mice caused increase in the level of serum ALB and BIL relative to the control (Figs. 2–3). By contrast, the level of serum ALB and BIL were reduced by the vitamin D treatment.

3.5. Blood glucose

The effect of the MnO_2-NPs over high glucose conditions was studied. The blood glucose level in all groups are represented in Fig. 4. Blood glucose levels, estimated in overnight G2 group (only MnO_2-NPs) were significantly elevated. However, this level was reduced significantly upon treatment with vitamin D at a dosage of 10 mg/kg b. wt/day.

3.6. Total protein

The level of mice serum total protein was in consistently altered by the MnO_2-NPs treatment when compared with the control groups (G1). MnO_2-NPs plus vitamin D group showed significant changes of total protein in comparison to the MnO_2-NPs treated group ($p < 0.05$). The vitamin D treated mice did not show any significant changes of total protein in comparison to the control ($p < 0.05$) (Fig. 5).

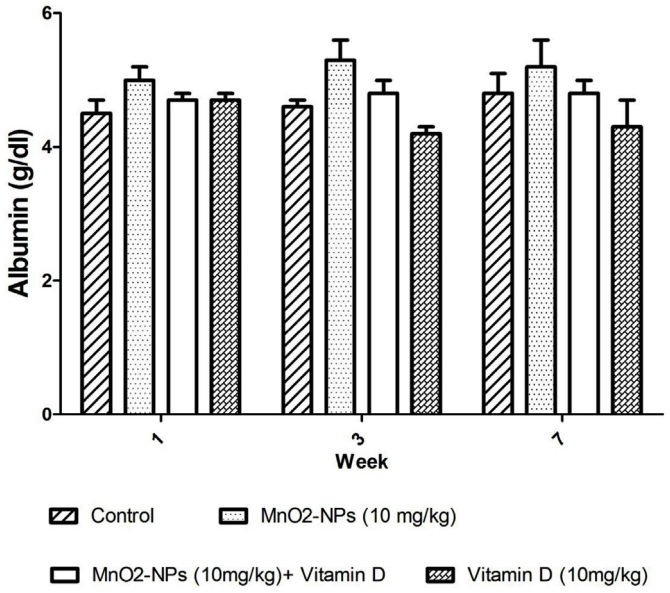

Fig. 2. Effect of MnO_2 nanoparticles on the level of mice serum albumin and protective role of vitamin D against liver and kidney damages caused by MnO_2 nanoparticles. Values are expressed as mean ± SEM (n = 10). There are significant in between groups.

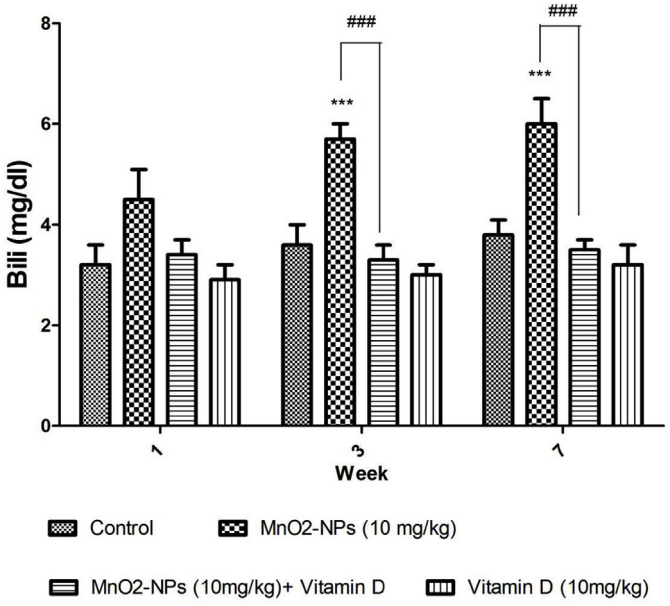

Fig. 3. Effect of MnO_2 nanoparticles on the level of mice serum bilirubin and protective role of vitamin D against liver and kidney damages caused by MnO_2 nanoparticles. Values are expressed as mean ± SEM (n = 10). *** indicates the significant with control group and ### indicates the significant with MnO_2-NPs plus vitamin D group.

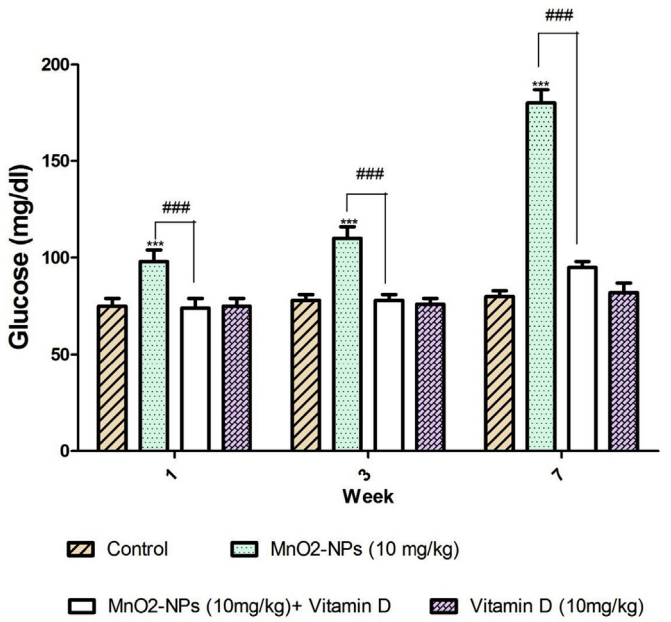

Fig. 4. Effect of MnO_2 nanoparticles on the level of mice serum glucose and protective role of vitamin D against liver and kidney damages caused by MnO_2 nanoparticles. Values are expressed as mean ± SEM (n = 10). *** indicates the significant with control group and ### indicates the significant with MnO_2-NPs plus vitamin D group.

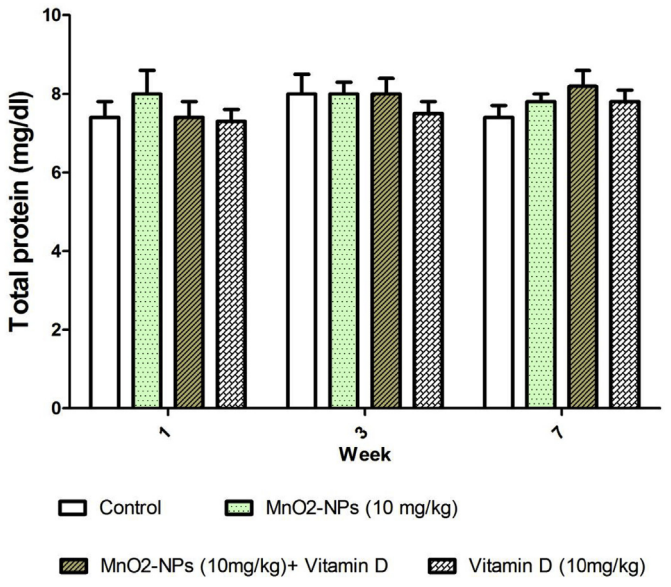

Fig. 5. Effect of MnO_2 nanoparticles on the level of mice serum total protein and protective role of vitamin D against liver and kidney damages caused by MnO_2 nanoparticles. Values are expressed as mean ± SEM (n = 10). There are significant in between groups.

4. Discussion

In the near future, nanotechnology is envisaged for large-scale use. Hence health and safety issues of nanoparticles (NPs) should be promptly addressed (Gao et al., 2017). Resent study screeched oral toxicity, genotoxicity, biochemical alterations, histopathological changes and tissue distribution of nanoparticles (NPs) of manganese oxide (MnO2) in Wistar rats. The obtained results demonstrated a significant increase in AST, ALT and LDH in the liver, kidney and serum in a dose-dependent manner (Singh et al., 2013). Also, MnO_2 nanoparticles induce DNA damage towards the rats liver and kidney cells (Albanese and Chan, 2011). Moreover, another study showed that exposure to nanosized particles at sub chronic doses of MnO_2 causes adverse changes in animal biochemical profiles, especially in glucose level. It seems that the high oxidative power of these particles is the main reason for these disturbances (Mousavi et al., 2016). Our study in here showed that MnO_2 nanoparticles induced liver, kidney damages like previous studies.

Reducing the toxicity of high-consumption and useful compounds like MnO_2 nanoparticles can be an important goal in leading research. As these compounds have shown beneficial effects for example in imaging. Therefore, human exposed to these compounds may show

liver and kidney toxicity according previous studies (Gao et al., 2017). Therefore, compounds that can inhibit the toxicity of these compounds will be of particular importance. Vitamins have always been important in preventing and controlling various toxicities. Due to the use of MnO_2 nanoparticles and the probability of toxicity with them, the effect of vitamin D was studied in this study. Vitamin D, regulates cell differentiation, cell growth, and prevents neoplastic transformation and the immune system (Mangin et al., 2014). It also plays an important role in the secretion of insulin from pancreatic beta cells and in regulating the reconstruction of bone. The most active form of vitamin D, 1,25-dihydroxyvitamin D3 (1,25(OH)2D3), has a beneficial role in calcium homeostasis (Kochupillai, 2008). Recent studies showed that vitamin D has protective effects in cardiovascular and renal diseases. The protective mechanism of vitamin D in renal diseases is mediated by various receptors and is regulated by the renin–angiotensin system (RAS) (Elmubarak and Özsoy, 2016). Elmubarak and Ozsoy showed that treatment with vitamin D reduces the nephrotoxicity resulting from chronic exposure of rats to carbon tetrachloride, and this is in line with the reports of vitamin D nephroprotective in other systems (Elmubarak and Özsoy, 2016). In our study, we showed that the treatment with vitamin D significantly normalized AST, ALT and LDH in the liver. Antioxidant effect of vitamin D is between the newest suggested non-calcemic roles of this compound. Having a homologous structure to cholesterol has proposed that vitamin D may be regarded as an antioxidant (Ktari et al., 2015; Smith, 1991). Vitamin D-mediated protection from oxidative stress is through the expression of numerous enzymes involved in ROS detoxification. Calcitriol (active metabolite of vitamin D) induced the expression of superoxide dismutase 1 (SOD1) and 2 (SOD2) (Lambert et al., 2006; Peehl et al., 2004). Also, calcitriol induced the expression of thioredoxin reductase 1 (TXNRD1), which reduces thioredoxin for its antioxidant function and glucose-6-phosphate dehydrogenase (G6PD), which produces NADPH for glutathione (GSH) regeneration in several cells (Bao et al., 2008; Swami et al., 2003). Moreover, NF-E2-related factor-2 (NRF2), a transcription factor that increases the expression of a diverse array of antioxidant enzymes was shown to be regulated by vitamin D through either increase in its expression, nuclear translocation, or decrease in Kelch-like ECH-associated protein 1(KEAP1)-mediated degradation (Manna and Jain, 2015; Nakai et al., 2013). As NRF2 is known as the master regulator of the expression of antioxidant enzymes, this can be a potential mechanism by which vitamin D can induce antioxidant enzymes and exert antioxidant defenses (Teixeira et al., 2017).

Increased oxidative stress is an accepted participant in the induced toxicity by MnO_2-NPs (Alarifi et al., 2017). Hyperglycemia-induced increase in free radicals, and its impairment of the endogenous antioxidant defense system (Valko et al., 2007). Antioxidant defense mechanisms involve both enzymatic and non-enzymatic strategies (Pham-Huy et al., 2008). Vitamin D have a more significant antioxidant effect (Noureldin et al., 2017). Our results showed that, vitamin D administration significantly decreased glucose MnO_2-NPs treated group.

Conflicts of interest

There are no conflicts to disclose.

Acknowledgement

This study is related to the project NO 1396/68533 From Student Research Committee, Shahid Beheshti University of Medical Sciences, Tehran, Iran. We also appreciate the “Student Research Committee” and “Research & Technology Chancellor” in Shahid r for their financial support of this study. This project was conducted under supervision of Dr. Ahmad Salimi at Department of Pharmacology and Toxicology, School of Pharmacy, Ardabil University of Medical Science and Dr. Amir Mohammad Mortazavian at Department of Food Science and Technology, Faculty of Nutrition Sciences and Food Technology, Shahid Beheshti University of Medical Sciences.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.yrtph.2018.08.005.

References

Alarifi, S., et al., 2017. Oxidative stress-induced DNA damage by manganese dioxide nanoparticles in human neuronal cells. BioMed Res. Int. 2017, 1–10.
Albanese, A., Chan, W.C., 2011. Effect of gold nanoparticle aggregation on cell uptake and toxicity. ACS Nano 5, 5478–5489.
Bao, B.Y., et al., 2008. Protective role of 1α, 25-dihydroxyvitamin D3 against oxidative stress in nonmalignant human prostate epithelial cells. Int. J. Canc. 122, 2699–2706.
Chen, H., He, J., 2008. Facile synthesis of monodisperse manganese oxide nanostructures and their application in water treatment. J. Phys. Chem. C 112, 17540–17545.
Elmubarak, S., Özsoy, N., 2016. Histoprotective effect of vitamin D against carbon tetrachloride nephrotoxicity in rats. Hum. Exp. Toxicol. 35, 713–723.
Gao, S., et al., 2017. Complex effect of zinc oxide nanoparticles on cadmium chloride-induced hepatotoxicity in mice: protective role of metallothionein. Metall 9, 706–714.
Hussain, S., et al., 2005. In vitro toxicity of nanoparticles in BRL 3A rat liver cells. Toxicol. Vitro 19, 975–983.
Kalantari, H., et al., 2011a. Protective effect of Cassia fistula fruit extract against bromobenzene-induced liver injury in mice. Hum. Exp. Toxicol. 30, 1039–1044.
Kalantari, H., et al., 2011b. Protective effect of Cassia fistula fruit extract on bromobenzene-induced nephrotoxicity in mice. Hum. Exp. Toxicol. 30, 1710–1715.
Karmakar, A., et al., 2014. Neurotoxicity of nanoscale materials. J. Food Drug Anal. 22, 147–160.
Kochupillai, N., 2008. The physiology of vitamin D: current concepts. Indian J. Med. Res. 127, 256.
Kose, M., et al., 2017. Protective effect of vitamin D against hyperoxia-induced lung injury in newborn rats. Pediatr. Pulmonol. 52, 69–76.
Ktari, N., et al., 2015. Cholesterol regulatory effects and antioxidant activities of protein hydrolysates from zebra blenny (Salaria basilisca) in cholesterol-fed rats. Food & function. 6, 2273–2282.
Lambert, J.R., et al., 2006. Prostate derived factor in human prostate cancer cells: gene induction by vitamin D via a p53-dependent mechanism and inhibition of prostate cancer cell growth. J. Cell. Physiol. 208, 566–574.
Mangin, M., et al., 2014. Inflammation and vitamin D: the infection connection. Inflamm. Res. 63, 803–819.
Manna, P., Jain, S., 2015. Vitamin D (VD) prevents oxidative stress via regulating NOX4/Nrf2/Trx signaling cascade and upregulates SIRT1-mediated AMPK/IRS1/GLUT4 pathway and glucose uptake in high glucose treated 3T3L1 adipocytes. Faseb. J. 29 253.1.
Mokhtari, Z., et al., 2017. Antioxidant efficacy of vitamin D. Journal of Parathyroid Disease 5, 12.
Mousavi, Z., et al., 2016. Effects of subcutaneous injection MnO2 micro-and nanoparticles on blood glucose level and lipid profile in rat. Iran. J. Med. Sci. 41, 518.
Na, H.B., et al., 2007. Development of a T1 contrast agent for magnetic resonance imaging using MnO nanoparticles. Angew. Chem. 119, 5493–5497.
Nakai, K., et al., 2013. Vitamin D activates the Nrf2-Keap1 antioxidant pathway and ameliorates nephropathy in diabetic rats. Am. J. Hypertens. 27, 586–595.
Noureldin, E.E.M., et al., 2017. Effect of melatonin versus vitamin D as antioxidant and Hepatoprotective agents in STZ-induced diabetic rats. J. Diabetes Metab. Disord. 16, 41.
Oberdörster, G., et al., 2005. Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ. Health Perspect. 113, 823.
Özerkan, D., et al., 2017. The protective effect of vitamin D against carbon tetrachloride damage to the rat liver. Biotech. Histochem. 1–11.
Peehl, D.M., et al., 2004. Molecular activity of 1, 25-dihydroxyvitamin D3 in primary cultures of human prostatic epithelial cells revealed by cDNA microarray analysis. J. Steroid Biochem. Mol. Biol. 92, 131–141.
Pham-Huy, L.A., et al., 2008. Free radicals, antioxidants in disease and health. International journal of biomedical science: IJBS. 4, 89.
Rutz, A., 2009. Synthesis and properties of manganese oxide nanoparticles for environmental applications. In: The 2009 NNIN REU Research Accomplishments, pp. 98–99.
Shin, J., et al., 2009. Hollow manganese oxide nanoparticles as multifunctional agents for magnetic resonance imaging and drug delivery. Angew. Chem. Int. Ed. 48, 321–324.
Singh, R., Nalwa, H.S., 2011. Medical applications of nanoparticles in biological imaging, cell labeling, antimicrobial agents, and anticancer nanodrugs. J. Biomed. Nanotechnol. 7, 489–503.
Singh, S.P., et al., 2013. Genotoxicity of nano-and micron-sized manganese oxide in rats after acute oral treatment. Mutat. Res. Genet. Toxicol. Environ. Mutagen 754, 39–50.
Smith, L.L., 1991. Another cholesterol hypothesis: cholesterol as antioxidant. Free Radic. Biol. Med. 11, 47–61.
Sulaiman, F.A., et al., 2015. Biochemical and morphological alterations caused by silver nanoparticles in Wistar rats. Journal of Acute Medicine 5, 96–102.
Swami, S., et al., 2003. Vitamin D growth inhibition of breast cancer cells: gene expression patterns assessed by cDNA microarray. Breast Canc. Res. Treat. 80, 49–62.
Teixeira, T.M., et al., 2017. Activation of nrf2-antioxidant signaling by 1, 25-dihydroxycholecalciferol prevents leptin-induced oxidative stress and inflammation in human endothelial Cells–3. J. Nutr. 147, 506–513.
Valko, M., et al., 2007. Free radicals and antioxidants in normal physiological functions and human disease. Int. J. Biochem. Cell Biol. 39, 44–84.
Warnick, G.R., et al., 1990. Estimating low-density lipoprotein cholesterol by the Friedewald equation is adequate for classifying patients on the basis of nationally recommended cutpoints. Clin. Chem. 36, 15–19.