Iranian Journal of Veterinary Science and Technology

Received: 2022- Oct- 15
Accepted after revision: 2023- Apr- 03
Published online: 2023-Apr- 23

RESEARCH ARTICLE

DOI: 10.22067/ijvst.2023.78900.1194

Effects of Oral Exposure to Titanium Dioxide Nanoparticles on the Liver, Small Intestine, and Kidney of Rats assessed by light microscopy and Transmission Electron Microscopy

Rahele Javaheri [a], Ahmad Reza Raji [b], Amir Moghaddam Jafari [b], Hossein Nourani [c]

[a] PhD student of comparative Histology, School of veterinary medicine, Ferdowsi University of Mashhad, Mashhad, Iran.
[b] Department of Basic Sciences, Faculty of Veterinary medicine, Ferdowsi University of Mashhad, Mashhad, Iran.
[c] Department of Pathobiology, School of Veterinary Medicine, Ferdowsi University of Mashhad, Mashhad , Iran

ABSTRACT

The TiO2 NPs are widely used in many commercial products, nanomedicine, agriculture, personal care products, different industries, and pharmaceutical preparations with potential risks to human health and the environment. The present study investigated the effects of different doses of TiO2 NPs on the liver, small intestine, and kidney tissues in the rat. The TiO2 NPs were administrated daily through gavage at the doses of 10, 20, and 50 mg/kg BW for 2 months. A total of 32 male rats were divided into four groups. After 60 days, rats were euthanized with CO_2 gas (Code of Ethics: IR UM.REC.1400.327). Histopathological examination of the kidney, small intestine, and hepatic tissues treated with TiO2 NPs showed toxic changes compared to the control group. Histopathological examination revealed hemorrhage in the liver, swelling in the kidney glomerulus, as well as inflammation and damage to the mitochondria in enterocytes. Further evaluations are needed to understand the impact of different doses of NPs on human health.

Keywords

Small intestine, Kidney, Liver, Rat, TiO2 nanoparticles

Number of Figures: 6
Number of Tables: 0
Number of References:: 35
Number of Pages: 8

Abbreviations

LM: light microscope
TEM: Transmission electron microscopy
TiO2 NPs: Titanium dioxide nanoparticles

Corresponding author: *Ahmad Reza Raji*
Email: *rajireza@um.ac.ir*
Tel: *+98(51)3880-5614*

Introduction

Currently, the use of nanotechnology, including NPs, in various fields, such as medicine, cosmetics, energy, chemicals, and textile industries has increased significantly. The size of nanomaterials varies from 1 to 100 nm [2]. Some NPs, if they are based on certain metals, can interact with hydrogen peroxide present in cells, resulting in the production of hydroxyl radicals that can enter the nucleus and cause DNA damage. The TiO2 NPs are reported to be cytotoxic. Several reports have indicated that these NPs can induce oxidative stress and ROS leading to membrane and DNA damage. This structural damage causes apoptosis or genetic alteration in cells affecting the overall health of the organism [3]. NPs can enter through various routes such as the digestive or respiratory system and reach the blood or major organs. They can enter the body through various routes, such as the digestive or respiratory systems, and reach the blood or major organs. Therefore, it is necessary to understand the long-term effects of TiO2 NPs on various biological systems [4]. The TiO2 NPs are mostly used in a large panel of applications, such as manufacturing plastics, paints, cosmetics, sunscreens, and toothpaste, as an adjuvant in pharmaceutical pills, and as bleaching agents in the paper industry [3]. Oral absorption of TiO2 NPs depends on the particle type, size, surface charge, surface coating, protein binding, dose, and species. It may increase with smaller size, negative charge, and appropriate coatings. As for other engineering nanomaterials, the potential toxicological hazards of nano-sized TiO2 are related to intracellular bioaccessibility, the ability to react with macromolecules, and the generation of free radicals [4]. Toxicokinetic studies in rodents administered intravascular and oral NPs showed accumulation predominantly in the spleen, liver, intestine, and kidneys [5, 6]. Absorption of TiO2 can be different according to the exposure routes and there is little knowledge on how the kinetic relates to physicochemical characteristics, such as size [7]. Recent studies showed that TiO2 has very low oral bioavailability and slow tissue elimination which might result in the long run in tissue accumulation [8]. Moreover, a study performed on humans stated that TiO2 NPs are likely to agglomerate in gastric fluid, reducing the bioavailability in nanoform during oral exposure and there is no evidence of significant absorption regardless of particle size [9]. After short-term (5 days) oral exposure to TiO2 NPs (0, 1, and 2 mg/kg BW per day) in rats, deposition of TiO2 (aggregates of test nanomaterial) was shown in the spleen, selected as a putative indicator of TiO2 NP deposition in tissues [10, 11]. The gastrointestinal tract represents a route of entry for several NPs both directly through intentional ingestion or indirectly via NP dissolution from food contact materials or by the secondary ingestion of inhaled particles. In addition, the growing use of NPs may lead to increased environmental contamination and unintentional ingestion via water, food animals, or fish [12]. Due to the high use of NPs, we decided to study the histopathological effects of these particles on the intestinal, liver, and kidney tissues in the rat.

Results

The present study explored the potential effects of TiO2 NPs on the jejunum, liver, and kidney following repeated oral administrations in rats, at doses relevant to human dietary intake. Detailed histological and morphometrical examinations of the jejunum, kidney, and liver were performed in the control and treated rats. No mortality occurred in any of the investigated groups of the current study. No effects on animal health and weight gain were observed during the treatments.

Kidney Histopathology

Kidneys of all control rats demonstrated well-preserved and kept intact normal histological components of the glomeruli, renal tubules, and interstitial tissues of the cortex and medulla (Figure 1-A). Kidney histological analysis did not show any significant qualitative changes both in 10 and 20 mg/kg groups,

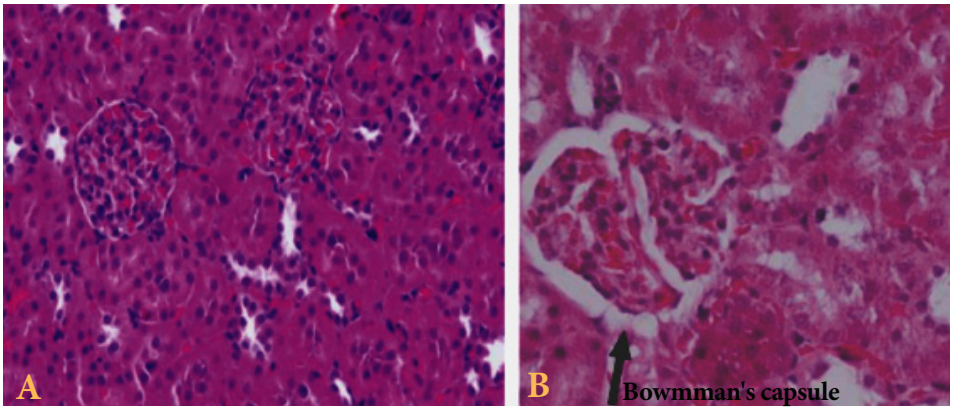

Figure 1.
A: Light micrograph of the kidney in control rats demonstrating normal histological architecture. H & E stain (×400). B: Light micrograph of the kidney in rats exposed to 50 mg/kg TiO_2 NP_s, demonstrating Bowman's capsule swelling and dilatation (arrow). H & E stain (×400).

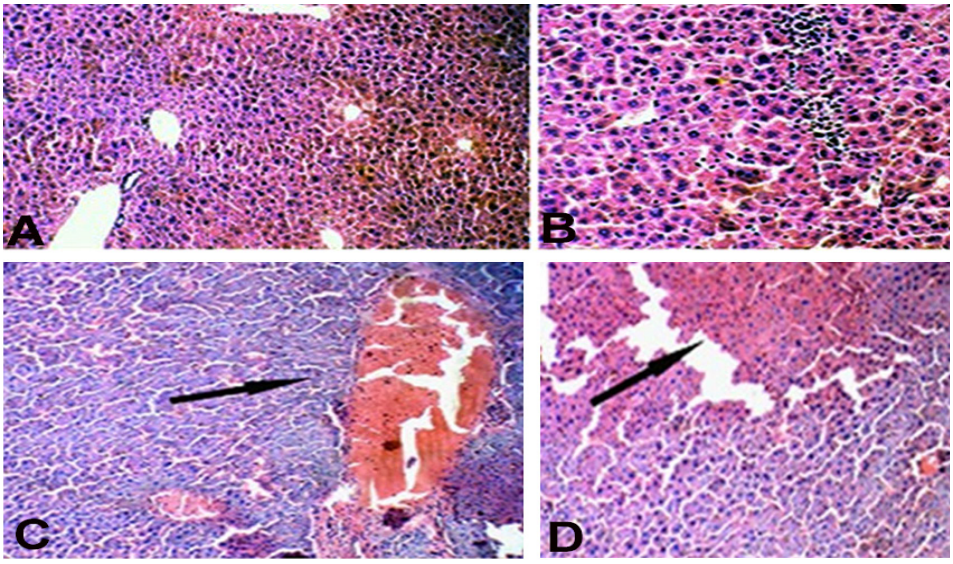

Figure 2.
A: Light micrograph of the liver in control rats demonstrating normal histological architecture. H & E stain (×400). B: Light micrograph of the liver of rats exposed to 10 mg/kg TiO2 NPs. H & E stain (×400). C: Light micrograph of the liver of rats exposed to 50 mg/kg TiO2 NPs. CV: Central Vein congestion (arrow). H & E stain (×400). D: Light micrograph of the liver of rats exposed to 50 mg/kg TiO2 NPs. The obstruction of central veins (arrow). H & E stain (×400).

However, in the group that received 50 mg/kg of NPs, Bowmman's capsule swelling and dilatation were observed. This study indicated the dissociation of junctions between the glomeruli and the renal tubule and might be associated with free radicals induced by TiO2 NPs exposure (Figure 1-B).

Liver Histopathology

In the liver, no histopathological changes were observed in the untreated animals (Figures 2-A). After oral exposure, TiO2 NPs reached the liver via blood circulation. The NP aggregates were internalized in the Kupffer cells and probably into phagolysosomes localized in hepatic sinusoids as well as in the periphery of the portal tract. These different histological alterations occurred in animals exposed to the highest dose (50 mg/kg BW). In the histopathological study, no pathological lesion was observed and the liver had a normal appearance. Liver tissue was normal in the groups receiving 10 (Figures 2-B) and 20 mg/kg of NPs, but lesions, such as hyperemia and dilation in central veins, were observed in the group receiving 50 mg/kg (Figures 2-C and D).

Jejunum Histopathology

Jejunum was completely normal in the control group (Figure 3-A) and in the groups that received 10 and 20 mg/kg of NPs. However, in the group that received 50 mg/kg of NPs, crypt structures were injured, the mucosa was eroded, and jejunum villi were loosened. Our results showed that in the TiO2 NP-treated groups, injured crypt structure, mucosal erosion, and the loosening of intestinal villi were present. The straight line shows the villus height (Figure 3-B). Absorptive cells were long and cylindrical. Basally located nuclei were in harmony with the shape of the cell. Microvilli were located on the luminal side of the cells (Figure 4-A).

Examining Histological Changes by Electron Microscopy

After 60 days of oral exposure to TiO2, the ultrastructure of the absorptive cells showed significant changes. The most striking histopathological findings

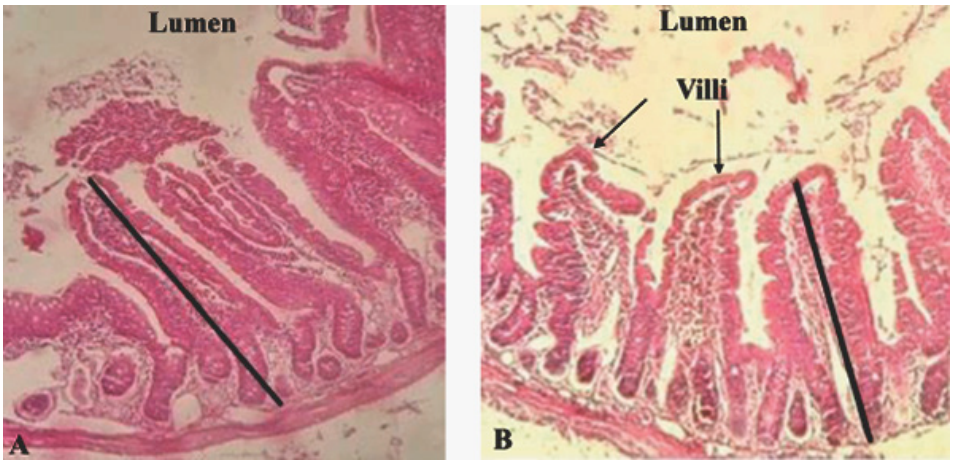

Figure 3.
A: Light micrograph of the jejunum of control rats demonstrating normal histological architecture. H & E stain (×400). B: Light micrograph of the intestine of rats exposed to 50 mg/kg TiO2 NPs. H & E stain (×400).

in the group of 50 mg/kg were distortion in microvilli and increased goblet cells and mast cells (Figure 5-A and B), mitochondrial elongation, along with excessive swelling of mitochondria and matrix dissolution (Figure 4-B).

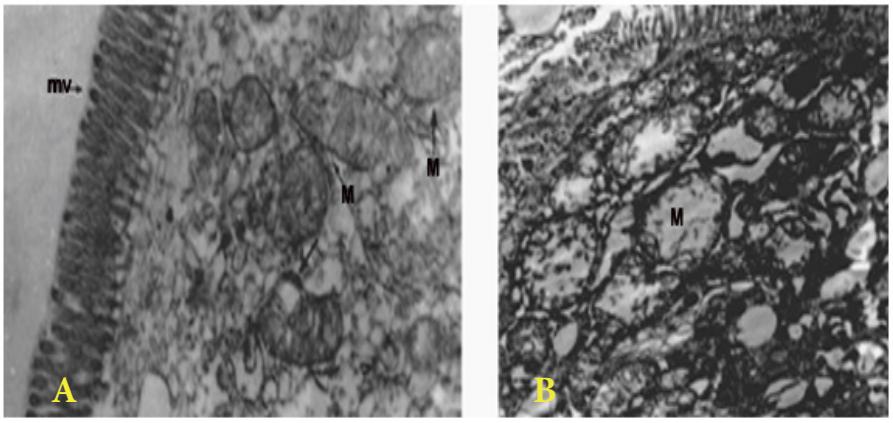

Figure 4.
A: Electron micrograph of the jejunum of control rats demonstrating normal histological architecture. Microvilli and apically located mitochondria in the control group. mitochondria (M) and microvilli (mv) (×20.000). B: Electron micrograph of the jejunum of rats exposed to 50 mg/kg TiO2 NPs. Mitochondrial cristae loss (M). Alterations in microvilli can be observed (×20.000).

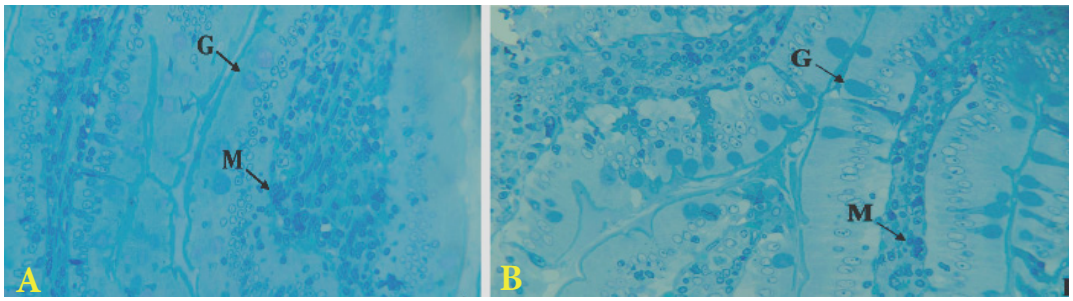

Figure 5.
A: Semi-thin micrograph of the jejunum of control rats demonstrating normal histological architecture. Goblet cells (G) and Mast cells (M) can be observed. B: Semi-thin micrograph of the jejunum of rats exposed to 50 mg/kg TiO2 NPs. An increase in Goblet cell (G) and Mast cell (M) numbers can be observed.

Discussion

It is very challenging to draw firm conclusions on the toxicity of TiO2. Recent toxicity studies on TiO2 raised concerns for liver effects (fibrosis, steatosis, and edema) [13-18], and the potential promotion of intestinal tumors [16, 19-21] after ingestion. On the other hand, there are also toxicity studies showing no effect on the liver and intestine despite prolonged exposure and high doses [22, 23]. We included information from in vivo studies using advanced techniques to assess specific adverse effects in the liver, jejunum, and kidney. The toxic effects associated with TiO2 NPs in humans are mainly long-term effects resulting from chronic exposure by different routes (inhalation, ingestion, and transcutaneous passage from sun cream or internal production from titanium prostheses). The exposure of humans to TiO2 via different consumer products is estimated at 5 mg per person per day in occidental countries. Once incorporated into tissues, TiO2 nanoparticles are not eliminated and accumulate over time, which can lead to very high doses of several grams after several tens of years of exposure It is very difficult to recreate such chronic exposures in rodent models that have a short lifespan of no more than two years. Thus, most animal toxicity studies carried out on these NPs use different doses administered at a single time or over a relatively limited period. Daily, humans are exposed orally to TiO2 via food, food supplements, toothpaste (for young children), and medicines [24, 25]. Analysis of postmortem tissues indicated that these particles are taken up by the jejunum and are subsequently transported to secondary organs, such as the liver and kidney [26, 27]. Current legislation of the food additive E171 is based on the lack of effects in the chronic study by NCI (1979), investigating only traditional toxicological endpoints (NCI 1979). The small size of particles

enables them to enter and damage the organism by penetrating the physiological barriers traveling with circulatory systems [5]. A study found that oral exposure to the nano-forms of diverse particles was more toxic than micro-counterparts [28]. This study investigates the effect of TiO2 NPs on the kidney, jejunum and liver tissues.Nanoparticles can spread more in blood, kidney, liver and other organs [29]. This study agrees with Dhawan A et al. [30] who showed that oral exposure to TiO2 NPs causes apoptosis in the rat liver cells and induces severe oxidative stress. We concluded that TiO2 NPs can induce changes in the kidney, jejunum, and liver of rats. Liver damage may result from excess oral TiO2 NPs, which is in line with another study in 2012 [31]. The histo-toxicity of TiO2 NPs in high doses (50 mg/kg BW/day) was more than in low doses (10 mg/kg BW/day) in the kidney, jejunum, and liver tissues. Dietary exposure to TiO2 NPs caused liver toxicity [32]. Other investigations have demonstrated that pathogenic mechanisms initiated by some NPs were dominated by inflammation-driven effects, which occurred due to oxidative stress or DNA damage [5]. This explains the role of oxidative stress in cellular death by necrosis or degeneration in the rat kidney, jejunum, and liver treated with TiO2 NPs.

In the present study, animals were exposed to TiO2 NPs at different doses (10, 20, and 50 mg/kg BW). The rats were euthanized after 60 days to observe the chronic toxicological effects of TiO2. The range of doses used in our study was in accordance with other toxicological studies [33-35]. Morphological damage was induced by oral exposure to TiO2 NPs. In order to observe morphological changes, we opted for a high dose (50 mg/kg BW). The two lower doses (10 and 20 mg/kg BW) were used to detect histopathological changes.

Liver

The liver is the major distribution site due to its high blood circulation and the phagocytosis of NPs by Kupffer cells. The other major target organs are the spleen, kidneys, and lungs [8, 33, 34]. The amount of TiO2 NPs in the mouse liver, spleen, lung, and kidneys reached high levels 14 days after intraperitoneal administration. Wang et al. in 2007 [7] also reported the accumulation of TiO2 NPs in the liver, kidneys, intestine, and lungs following oral administration. These alterations were correlated with oxidative stress localized in the same area of the liver. It may be the reason why hepatocytes present around the central vein are particularly sensitive to oxidative stress induced by TiO2. In conclusion, the present study highlighted the fact that TiO2 NPs caused detectable histological changes only in animals treated with high doses. In the liver, lesions affecting hepatocytes cells were related to oxidative stress.

Kidney

In the kidneys, morphological alterations entailed the swelling of the renal glomeruli and therefore, probably more exposure to oxidative stress induced by TiO2 [10]. Bowman's capsule was the most affected part following exposure to the high doses of TiO2 NPs. These alterations were accompanied by changes in renal and hepatic function parameters that persisted chronically. In contrast, animals treated with lower doses showed no histological changes by light microscopy or significant variation in renal and hepatic function parameters. However, the very sensitive metabolomics approach allowed us to demonstrate a very early change in metabolism, even in animals exposed to the lowest doses of TiO2.

Jejunum

At least four zones are distinguished in the intestinal tract, namely the duodenum, jejunum, ileum, and colon. The gut epithelium is composed of enterocytes and mucus-secreting cells (Goblet cells). The NPs are usually believed to be taken up by Goblet cells and M-cells, although this process is dependent on the particle size. In the current experiment, different doses of TiO2 were administered orally and electron microscopic assessments were carried out based on the control group to reveal the pathologic changes in the jejunum epithelium cells. Correlated with the exposure dose, the most significant changes were observed in mitochondria, goblet cells, and mast cells. Overall, the results of the present study showed that the gastrointestinal tract and enterocytes in particular may represent a target of TiO2 NPs toxicity following direct exposure. Ultrastructural changes in the intestine epithelial cells were observed using transmission electron microscopy, and severe structural damage was found in microvilli and mitochondria. It indicates that the possible site of the action of these TiO2 NPs is the cytoplasmic membrane and endomembrane system of the intestine epithelial cells. These findings provide a basis for the development of novel NPs active compounds with a novel mechanism of action. The intestinal compartment is highly chemically and physically complex. As a result, further studies are recommended to highlight the mechanism and mode of action for a reliable risk assessment of TiO2 NPs relevant to food safety.

Materials & Methods

Nanoparticles Characterization

The TiO2 NPs were purchased from Sigma-Aldrich, UK. The TiO2 NPs used in this study were titanium (IV) oxide and anatase with a purity of 99.7%. The TiO2 NPs were weighted and suspended in ultrapure water. In order to reduce the size of NP aggregates, NPs were sonicated in a probe sonicator for 3 runs of 30 min as detailed in the previous publications. Briefly, TiO2 NPs were characterized by a particle size analyzer and the titanium particle size was about 30 nm.

Animal and Treatment

Thirty-two adult male rats at 2 months of age weighing approximately 220 g were used in this study. The rats were housed in cages under a regulated light and dark schedule on a 12 h day/night cycle and controlled ventilation, humidity, and temperature of 24°C ± 3°C and were fed with standard laboratory rodent pelleted feed and water ad libitum. After 5 days of acclimatization, the rats were distributed in four experimental groups of eight animals each (n = 8).

Treatment Groups

Different doses of TiO2 were administered to experimental animals orally. The subjects were divided into four equal groups (n = 8). Doses were selected based on the available data on TiO2 NPs estimated human exposure and dispersibility of the test NPs in the selected medium, taking into account that the maximum volume administered by gavage to each rat cannot exceed 2 ml in aqueous solution. The TiO2 NPs were suspended in ultrapure water by sonication for 15 min and the dispersions were prepared daily. After 60 days, male rats were euthanized with CO2 gas (Code of Ethics: IR.UM.REC.1400.327). After dissecting the animals, tissue samples were taken from the liver, kidney, and intestine. The samples for LM were fixed in 10% buffered formalin. Next, the preparation of samples was performed by tissue processing. They were embedded in a paraffin dispenser, cut into 5-µm sections by semi-automatic microtome, and stained with Hematoxylin & Eosin. Briefly, the slides of tissues were examined by an image analysis system applied to an optical microscope. For electron microscopy, samples from jejunum were fixed in glutaraldehyde (3%) and osmium tetroxide. After the preparation of samples, they were blocked in Epon 812. Samples were cut by ultra-microtome and thin sections were double stained with saturated uranyl acetate (20 min) and lead citrate (10 min). Jeol JEM 100 CX-II electron microscope was used for examining the specimens.

Group I: Control animals received ultrapure water.
Group II: Received 10 mg/kg TiO2 NPs for 60 days.
Group III: Received 20 mg/kg TiO2 NPs for 60 days.
Group IV: Received 50 mg/kg TiO2 NPs for 60 days.

Ethics approval

This study has the code of ethics (Code of Ethics for Study IR UM.REC.1400.327).

Authors' Contributions

R J: Investigation; Writing-original draft; RJ , A R , A M J, H N:Conceptualization; Supervision; Writing-review & editing. All authors have been involved in writing the article, and accept responsibility for its content.

Acknowledgements

The excellent assistances of histology department in the preparation of this article is greatly appreciated.

Conflict of interest

The authors declare that they have no conflict of interest

References

1. Botelho MC, Costa C, Silva S, Costa S, Dhawan A, Oliveira PA, et al. Effects of titanium dioxide nanoparticles in human gastric epithelial cells in vitro. J Biomed Biotechnol. 2014;68(1):59-64. Doi: 10.1016/j.biopha.2013.08.006.

2. Chen Z, Wang Y, Ba T, Li Y, Pu J, Chen T, et al. Genotoxic evaluation of titanium dioxide nanoparticles in vivo and in vitro. Toxicol Lett. 2014;226(3):314-9. Doi: 10.1016/j.toxlet.2014.02.020.

3. Trouiller B, Reliene R, Westbrook A, Solaimani P, Schiestl RH. Titanium dioxide nanoparticles induce DNA damage and genetic instability in vivo in mice. Cancer Res. 2009;69(22):8784-9. Doi: 10.1158/0008-5472.CAN-09-2496.

4. Chen J, Dong X, Zhao J, Tang G. In vivo acute toxicity of titanium dioxide nanoparticles to mice after intraperitoneal injection . J Appl Toxicol. 2009;29(4):330-7. Doi: 10.1002/jat.1414.

5. Weir A, Westerhoff P, Fabricius L, Hristovski K, Von Goetz N. Titanium dioxide nanoparticles in food and personal care products. Environ Sci Technol. 2012;46(4):2242-50. Doi. org/10.1021/es204168d

6. Barlow S, Chesson A, Collins JD, Flynn A, Hardy A, Jany K-D, et al. The potential risks arising from nanoscience and nanotechnologies on food and feed safety. EFSA J. 2009;7(3).

7. Wang J, Zhou G, Chen C, Yu H, Wang T, Ma Y, et al. Acute toxicity and biodistribution of different sized titanium dioxide particles in mice after oral administration. Toxicol Lett. 2007;168(2):176-85. Doi: 10.1016/j.toxlet.2006.12.001.

8. Xie G, Wang C, Sun J, Zhong G. Tissue distribution and excretion of intravenously administered titanium dioxide nanoparticles. Toxicol Lett. 2011;205(1):55-61. Doi: 10.1016/j.toxlet.2011.04.034.

9. Cho W-S, Kang B-C, Lee JK, Jeong J, Che J-H, Seok SH. Comparative absorption, distribution, and excretion of titanium dioxide and zinc oxide nanoparticles after repeated oral administration. Part Fibre Toxicol. 2013;10(1):1-9. Doi: 10.1186/1743-8977-10-9.

10. Geraets L, Oomen AG, Krystek P, Jacobsen NR, Wallin H, Laurentie M, et al. Tissue distribution and elimination after oral and intravenous administration of different titanium dioxide nanoparticles in rats. Part Fibre Toxicol. 2014;11(1):1-

21. Doi: 10.1186/1743-8977-11-30.

11. Jones K, Morton J, Smith I, Jurkschat K, Harding A-H, Evans G. Human in vivo and in vitro studies on gastrointestinal absorption of titanium dioxide nanoparticles. Toxicol Lett. 2015;233(2):95-101. Doi: 10.1016/j.toxlet.2014.12.005.

12. Chen J, Dong X, Zhao J, Tang G. In vivo acute toxicity of titanium dioxide nanoparticles to mice after intraperitioneal injection. J Appl Toxicol. 2009;29(4):330-7. Doi: 10.1002/jat.1414.

13. Fabian E, Landsiedel R, Ma-Hock L, Wiench K, Wohlleben W, Van Ravenzwaay B. Tissue distribution and toxicity of intravenously administered titanium dioxide nanoparticles in rats. Arch Toxicol. 2008;82(3):151-7. Doi: 10.1007/s00204-007-0253-y.

14. Bergin IL, Witzmann FA. Nanoparticle toxicity by the gastrointestinal route: evidence and knowledge gaps. IJBNN. 2013;3(1-2). Doi: 10.1504/IJBNN.2013.054515.

15. Azim SAA, Darwish HA, Rizk MZ, Ali SA, Kadry MO. Amelioration of titanium dioxide nanoparticles-induced liver injury in mice: possible role of some antioxidants. Exp Toxicol Pathol. 2015;67(4):305-14. Doi: 10.1016/j.etp.2015.02.001.

16. Cui Y, Liu H, Zhou M, Duan Y, Li N, Gong X, et al. Signaling pathway of inflammatory responses in the mouse liver caused by TiO2 nanoparticles. J Biomed Mater Res A. 2011;96(1):221-9. Doi: 10.1002/jbm.a.32976.

17. Shukla RK, Kumar A, Vallabani NVS, Pandey AK, Dhawan A. Titanium dioxide nanoparticle-induced oxidative stress triggers DNA damage and hepatic injury in mice. Nanomedicine. 2014;9(9):1423-34. Doi: 10.2217/nnm.13.100.

18. Talamini L, Gimondi S, Violatto MB, Fiordaliso F, Pedica F, Tran NL, et al. Repeated administration of the food additive E171 to mice results in accumulation in intestine and liver and promotes an inflammatory status. Nanotoxicology. 2019;13(8):1087-101. Doi: 10.1080/17435390.2019.1640910.

19. Valentini X, Deneufbourg P, Paci P, Rugira P, Laurent S, Frau A, et al. Morphological alterations induced by the exposure to TiO2 nanoparticles in primary cortical neuron cultures and in the brain of rats. Toxicol Rep. 2018;5:878-89. Doi: 10.1016/j.toxrep.2018.08.006.

20. Wang Y, Chen Z, Ba T, Pu J, Chen T, Song Y, et al. Susceptibility of young and adult rats to the oral toxicity of titanium dioxide nanoparticles. Small. 2013;9(9-10):1742-52. Doi: 10.1002/smll.201201185.

21. Bettini S, Boutet-Robinet E, Cartier C, Coméra C, Gaultier E, Dupuy J, et al. Food-grade TiO2 impairs intestinal and systemic immune homeostasis, initiates preneoplastic lesions and promotes aberrant crypt development in the rat colon. Sci Rep. 2017;7(1):40373. Doi:10.1038/srep40373.

22. Proquin H, Jetten MJ, Jonkhout MC, Garduno-Balderas LG, Briede JJ, de Kok TM, et al. Gene expression profiling in colon of mice exposed to food additive titanium dioxide (E171). Food Chem Toxicol. 2018;111:153-65. Doi: 10.1016/j.fct.2017.11.011.

23. Urrutia-Ortega IM, Garduño-Balderas LG, Delgado-Buenrostro NL, Freyre-Fonseca V, Flores-Flores JO, González-Robles A, Pedraza-Chaverri J, Hernández-Pando R, Rodríguez-Sosa M, León-Cabrera S, Terrazas LI, van Loveren H, Chirino YI. Food-grade titanium dioxide exposure exacerbates tumor formation in colitis associated cancer model. Food Chem Toxicol. 2016 Jul;93:20-31. Doi: 10.1016/j.fct.2016.04.014.

24. Blevins LK, Crawford RB, Bach A, Rizzo MD, Zhou J, Henriquez JE, et al. Evaluation of immunologic and intestinal effects in rats administered an E 171-containing diet, a food grade titanium dioxide (TiO2). Food Chem Toxicol. 2019;133:110793. Doi: 10.1016/j.fct.2019.110793.

25. Warheit D, Brown S, Donner E. Acute and subchronic oral toxicity studies in rats with nanoscale and pigment grade titanium dioxide particles. Food Chem Toxicol. 2015;84:208-24. Doi: 10.1016/j.fct.2015.08.026 .

26. Bachler G, von Goetz N, Hungerbuhler K. Using physiologically based pharmacokinetic (PBPK) modeling for dietary risk assessment of titanium dioxide (TiO2) nanoparticles. Nanotoxicology. 2015;9(3):373-80. Doi: 10.3109/17435390.2014.940404.

27. Rompelberg C, Heringa MB, van Donkersgoed G, Drijvers J, Roos A, Westenbrink S, et al. Oral intake of added titanium dioxide and its nanofraction from food products, food supplements and toothpaste by the Dutch population. Nanotoxicology. 2016;10(10):1404-14. Doi: 10.1080/17435390.2016.1222457.

28. Heringa MB, Geraets L, van Eijkeren JC, Vandebriel RJ, de Jong WH, Oomen AG. Risk assessment of titanium dioxide nanoparticles via oral exposure, including toxicokinetic considerations. Nanotoxicology. 2016;10(10):1515-25. Doi: 10.1080/17435390.2016.1238113.

29. Peters RJ, Oomen AG, van Bemmel G, van Vliet L, Undas AK, Munniks S, et al. Silicon dioxide and titanium dioxide particles found in human tissues. Nanotoxicology. 2020;14(3):420-32.Doi: 10.1080/17435390.2020.1718232.

30. Dhawan A, Sharma V. Toxicity assessment of nanomaterials: methods and challenges. Anal Bioanal Chem. 2010;398(2):589-605. Doi: 10.1007/s00216-010-3996-x.

31. Hillyer JF, Albrecht RM. Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles. J Pharm Sci. 2001;90(12):1927-36. Doi: 10.1002/jps.1143.

32. Sharma V, Singh P, Pandey AK, Dhawan A. Induction of oxidative stress, DNA damage and apoptosis in mouse liver after sub-acute oral exposure to zinc oxide nanoparticles. Mutat Res Genet Toxicol Environ Mutagen. 2012;745(1-2):84-91. Doi: 10.1016/j.mrgentox.2011.12.009.

33. Sanaa A, Maha Z, Samy A, Hebatallah A, Mai O. Roll of potent antioxidants in regulation of SMAD-2 transcription and TGF-B1 signaling in nano sized titanium dioxide-induced oxidative injury in mice liver. Inter. J Pharma. 2015;5:17-26.

34. Xiong D, Fang T, Yu L, Sima X, Zhu W. Effects of nano-scale TiO2, ZnO and their bulk counterparts on zebrafish: acute toxicity, oxidative stress and oxidative damage. Sci Total Environ. 2011;409(8):1444-52. Doi: 10.1016/j.scitotenv.2011.01.015.

35. Olmedo DG, Tasat D, Guglielmotti MB, Cabrini RL. Titanium transport through the blood stream. An experimental study on rats. J Mater Sci Mater Med. 2003;14(12):1099-103. Doi: 10.1023/b:jmsm.0000004007.26938.67.

How to cite this article
Javaheri R, Raji AH, Moghaddam Jafari A, Nourani H. Effects of Oral Exposure to Titanium Dioxide Nanoparticles on the Liver, Small Intestine, and Kidney of Rats assessed by light microscopy and Transmission Electron Microscopy. Iran J Vet Sci Technol.2023; 15(1): 41-48.
DOI: https://doi.org/10.22067/ijvst.2023.78900.1194
URL: https://ijvst.um.ac.ir/article_43705.html