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The Detrimental Effect of Titanium Dioxide Nanoparticles on Liver, Kidney and Lipid Profile of Albino Mice Intraperitoneal Exposure

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ABSTRACT: ***Background:*** *Titanium dioxide nanoparticles (TiO_2 NPs) have widespread use in industrial and biological fields owing to their distinctive physicochemical characteristics. Nonetheless, their growing prevalence raises concerns over their possible toxicological impacts, especially on the functionality of essential organs.* ***Objective:*** *The present work examines the subacute toxicity of TiO_2 nanoparticles on hepatic and renal function and modifications in the lipid profile in a mouse model.* ***Methods:*** *Forty-eight adult female albino mice were divided randomly into three groups (n=16 each). Two groups were treated intraperitoneally with TiO_2 NPs at 100 mg/kg and 400 mg/kg, respectively, while the control group was treated with distilled water. The animals were sacrificed after 7 and 21 days of treatment. Serum levels of urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), and lipid profile parameters (cholesterol, HDL, LDL) were estimated.* ***Results:*** *Both treated groups showed significant rises in urea, creatinine, AST, and ALT levels ($p<0.0001$) compared to the control. These were more pronounced at higher concentrations and longer exposure durations. Cholesterol level fell after 21 days, with significant drops in HDL and rises in LDL ($p<0.0001$).* ***Conclusions:*** *TiO_2 NPs induce dose- and time-related alteration of liver and kidney function, and lipid metabolism in mice. These findings highlight that further toxicological research on nanoparticle exposure in environmental and biomedical applications is needed.*

KEYWORDS: *Titanium dioxide nanoparticles; Nanotoxicology; Biochemical markers; Liver and kidney functions; Lipid profile alteration*

INTRODUCTION

Nanomaterials are minuscule particles composed of metals, metal oxides, nonmetallic substances, and ceramics, characterized by dimensions between 1 and 100 nanometers, or with at least one dimension less than 100 nanometers [1]. Nanotechnology rapidly spreads, and it is found in around 1,300 consumer products. However, the potential hazards of nanomaterial exposure should not be overlooked [2]. The behavior of nanoscale particles varies throughout chemical and biological reactions due to their small size and dimensions; these materials behave differently from their usual large-sized counterparts, which have dimensions more than 100 nanometers [3]. When bronchial endothelial cells are exposed to carbon nanotubes under glass in vitro, they break down the oxygen-containing DNA strand [4]. They also alter gene expression and mitochondrial function in vivo via the oxidative stress mechanism [5]. Nanoparticles also cause inflammation and inhibit the immune system in the body [6]. Titanium dioxide nanoparticles (TiO_2 NPs) are an odorless, non-flammable white powder that crystallize into three distinct polymorphs: brookite, rutile, and anatase, each with good chemical stability. According to studies, TiO_2 NP granules have a great capacity to absorb and saturate UV radiation, giving items containing these particles a luster [7]. Based on these characteristics, they are commonly used in cosmetics, salad dressings, confectionery, toothpaste, and sunscreens [8], [9].

The toxicity of titanium nanoparticles is governed by the pace at which they enter the body, followed by the rate at which they are absorbed, distributed, metabolized, and excreted [10]. It is

entered into the body by inhalation, ingestion, transdermal, intravenous, or intramuscular injections. According to studies, excessive doses of nanomaterials produce considerable tissue alterations and damage because nanoparticles migrate throughout the body regardless of the route of exposure [11]. Recent research has also shown that various pollutant nanoparticles, including titanium nanoparticles, can pass the placental barrier and enter the fetal liver and brain [12], [13]. To better understand the potential health risks associated with TiO_2 NPs in biological systems, the current study assessed the effects of TiO_2 NPs on kidney and liver function by measuring urea, creatinine, aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels, as well as their effect on lipid profile levels.

MATERIALS AND METHODS

Characterization of (TiO_2 NPs)

Titanium dioxide nanoparticles utilized in this investigation were acquired from Oma International Trading, an Authorized Partner of Sigma-Aldrich (Germany). The company supplied the material in a 100-g glass container with a particle size of <100 nm; the basis of mineral value is 99.9%; surface area 90±25 m^2/g; bp < 136 m°; and density (1.2±0.05) g/ml at 25 °C. It had a white powder appearance with nearly spherical morphology. The zeta potential of TiO_2 NPs in phosphate-buffered saline 122 was measured using a combined dynamic light scattering/particle 123 electrophoresis instrument. According to the manufacturer's datasheet, the TiO_2 NPs had a primary particle size of <100 nm with no surface coating, and no further characterization was carried out. The dosing solution was prepared by dissolving 1 gram of nano-titanium dioxide in a liter of distilled water and mixing it with the Ultra device at room temperature. Subsequently, it was diluted to concentrations of 100 and 400 mg/kg and administered via intraperitoneal injection volume 0.2 ml/kg into the peritoneal cavity of mice [14].

Experimental Animals and Study Design

Adult female albino mice, weighing 25±10 grams and aged four to six weeks, were supplied by the Iraqi Center for Genetics and Cancer Research (ICCMGR) / Mustansiriyah University. Healthy mice were maintained in polypropylene enclosures with a temperature of 25±5 °C, a relative humidity of 60±10 %, and a 12±3-hour light/dark cycle. There was an unlimited supply of food and beverages. The animals were housed and cared for at (ICCMGR). Three groups (n=16) were randomly assigned to forty-eight albino female mice. Groups were administered TiO_2 NPs intraperitoneally (IP): one of them was administered at a dose of 100 mg/kg, while the other was administered at a dose of 400 mg/kg. The final group was administered an intraperitoneal dose of distilled water as a control. The mice were sacrificed at varying time points (7 or 21 days after treatment). Serum was obtained by centrifuging blood from the orbital vein of each rodent at 3000 rpm for 15 minutes.

Biochemical Analysis

The biochemical parameters in mice's serum were assessed using the Cobas C111 Biochemical Analyzer, as follows: (1) Liver function marker: Alanine aminotransferase (ALT) and Aspartate aminotransferase (AST), (2) Renal function test: creatinine and urea, and (3) Lipid profile parameters: cholesterol, high-density lipoproteins, and low-density lipoproteins.

Statistical Analysis

The data were presented as the mean±standard error (mean±SE). Fisher's test was employed to analyze the data for numerous comparisons following one-way analysis of variance (ANOVA). A regression analysis was conducted using the analysis of combined variance (ANCOVA). The data analysis for all experiments was performed using Stat View 5.0. The differences were deemed significant when the P-value<0.05.

RESULTS AND DISCUSSION

These results show the effects of two different concentrations of TiO_2 NPs, high (400 mg/kg) and low (100 mg/kg), in different consumption duration points (7 and 21 days) on some body systems, the kidney function in Table 1, liver function in Table 2, and lipid profile changing in Table 3. The

results of urea and creatinine (mg/dL) of groups treated with high and low concentrations of TiO_2 NPs compared to the control for 7 and 21 days of consumption are shown in Table 1. The level of urea and creatinine significantly increased (P<0.0001) in both treated groups compared to the control for 7 and 21 days, and this was especially true for the group treated with a high dose of TiO_2 NPs concentration, as their concentration was significantly higher (P<0.0001) than that of the group treated with a low concentration. Moreover, it was found that the TiO_2 NPs concentration influences kidney function, as well as the consumption duration, since urea and creatinine levels were significantly higher (P<0.0001) for 21 days compared to 7 days of consumption in the treated groups, but not in the control group.

Table 1. Serum urea and creatinine levels in control and TiO_2 nanoparticle-treated groups after 7 and 21 days

Group	Urea (mg/dL)		Creatinine (mg/dL)		P-value	
	Day 7	Day 21	Day 7	Day 21	Urea	Creatinine
Control	37.0 ± 0.2^c	37.2 ± 0.3^c	0.51 ± 0.06^c	0.55 ± 0.04^c	0.69	0.58
Treated Low (100 mg/kg)	43.5 ± 0.4^b	48.7 ± 0.3^b	1.46 ± 0.03^b	2.51 ± 0.12^b	0.0001	0.0001
Treated High (400 mg/kg)	48.2 ± 0.2^a	53.2 ± 0.5^a	2.25 ± 0.11^a	3.09 ± 0.04^a	0.0001	0.0001

Means (±SD) in each column with different superscript letters differ significantly ($P \leq 0.05$) by LSD test and exact P-values for pairwise comparisons are shown within the Table

Comparable results in AST and ALT (mg/dl) levels of groups treated with high and low concentrations of TiO_2 NPs compared to the control for 7 and 21 days of consumption were found (Table 2). AST and ALT levels significantly increased (P<0.0001) in both TiO_2 NPs treated groups compared to the control for 7 and 21 days, especially in the group treated with a high concentration of TiO_2 NPs, since their concentration was significantly higher (P<0.0001) than the group treated with a low concentration. Additionally, it was discovered that the TiO_2 NPs concentration was an influence on liver function and its consumption duration since the AST and ALT levels were significantly higher (P<0.0001) for 21 days compared to 7 days of consumption in treated groups but not in the control group.

Table 2. Serum AST and ALT levels in controls and TiO_2 nanoparticle-treated groups after 7 and 21 days

Group	AST (mg/dL) Day 7	AST (mg/dL) Day 21	ALT (mg/dL) Day 7	ALT (mg/dL) Day 21	P-value (AST)	P-value (ALT)
Control	21.4 ± 0.2^c	22.2 ± 0.4^c	15.3 ± 0.1^c	14.8 ± 0.3^c	0.13	0.12
Treated Low (100 mg/kg)	33.2 ± 0.5^b	39.8 ± 0.6^b	19.5 ± 0.2^b	24.96 ± 0.5^b	< 0.0001	< 0.0001
Treated High (400 mg/kg)	42.5 ± 0.5^a	50.6 ± 0.4^a	24.6 ± 0.3^a	30.3 ± 1.1^a	< 0.0001	< 0.0001

Means (±SD) in each column with different superscript letters differ significantly ($P \leq 0.05$) by LSD test and exact P-values for pairwise comparisons are shown within the Table

The results in Table 3 show a significant increase p<0.0001 in both cholesterol and LDL levels of the groups treated with (100/400) mg/kg TiO_2 NPs after (7/21) days compared with the control group. Conversely, HDL levels significantly decreased in the groups treated with 400 mg/kg TiO_2 NPs for 7 and 21 days compared to the control, while in the group treated with 100 mg/kg TiO_2 NPs its level significantly increased for 21 days but there was no difference after 7 days.

Table 4 shows the results of correlation between the kidney and liver enzymes (urea, creatinine, AST and ALT) with each other and with lipid profile parameters. There was significantly positive correlation between liver enzymes with kidney enzymes (P<0.0001) and with lipid profile parameters (P<0.01) and between kidney enzymes with lipid profile parameters (P<0.05).

Table 3. The effects of TiO_2 Nanoparticles on lipid profile parameters (LDL, HDL and Cholesterol) after 7 and 21 days of exposure

Group	Day	LDL (U/L)	HDL (U/L)	Cholesterol (U/L)	P-value
Control	Day 7	15.3 ± 0.5^{c}	76.1 ± 0.8^{b}	112.2 ± 0.5^{c}	0.15
Treated Low (100 mg/kg)	Day 7	26.1 ± 0.4^{b}	78.8 ± 1.4^{b}	117.6 ± 0.5^{b}	0.12
Treated High (400 mg/kg)	Day 7	28.2 ± 0.4^{a}	66.5 ± 0.8^{c}	123.8 ± 0.6^{a}	< 0.0001
Control	Day 21	16.8 ± 0.3^{c}	75.7 ± 0.6^{b}	102.5 ± 10.1^{c}	0.35
Treated Low (100 mg/kg)	Day 21	25.8 ± 0.8^{b}	80.3 ± 1.2^{a}	117.3 ± 0.6^{b}	0.73
Treated High (400 mg/kg)	Day 21	33.7 ± 1.0^{a}	68.5 ± 0.8^{c}	121.3 ± 1.5^{a}	0.13

Table 4. Correlation between liver and kidney enzymes and lipid profile parameters

Parameter 1	Parameter 2	r	P-value
Urea	AST	0.947	< 0.0001
Urea	ALT	0.888	< 0.0001
Creatinine	AST	0.912	< 0.0001
Creatinine	ALT	0.845	< 0.0001
LDL	Urea	0.581	< 0.0001
HDL	AST	0.120	0.007
Chol.	ALT	0.122	0.0062

As is well known, nanoparticles have entered many fields, including food, medicine, and cosmetics, including many types such as titanium nanoparticles. Many studies have focused on studying the risk of these nanoparticles, suggesting that TiO_2 NPs exposure could induce apoptosis in many cells or organs, such as the liver, spleen, and kidneys [13]–[15].

The arrival of nanoparticles into the living body can deliver them to the bloodstream and then move to various organs. Kidneys are considered one of the organs sensitive to foreign bodies due to their high blood supply and function in removing toxins and getting rid of xenobiotics [16]. The kidneys remove excess creatinine from the bloodstream; hence, measuring creatinine levels in the blood can reflect renal function [17]. As a result, if renal function fails, the serum creatinine level increases [18]. Nanoparticles diffuse into the kidney and reach the mesenchymal cells of the glomerulus, which affects kidney function after their accumulation [19]. Liu indicated an increase in creatinine levels of 50, 100, 200, and 300 mg/kg of body weight, which he attributed to the nanoparticles stimulating oxidative stress [19], [20]. The reason is their stimulation of oxidative stress, lipid peroxidation, and the production of inflammatory cytokines IL-12, TNF-α, and TNF-4 [21], [22]. When treating human kidney Glomerular IPIS cells line and mesenchymal HK-2 cells line with titanium nanoparticles, zinc oxide nanoparticles, and cadmium sulfide nanoparticles in vitro, the release of Reactive oxygen species, inhibition of glutathione levels, and activation of a type of protein NF-αb causes oxidative stress [23]. Urea is a by-product of protein metabolism that is eliminated through the kidneys. Therefore, any increase in urea concentration indicates significant damage to the kidney [24]. So, this evidence could explain the significant increase in urea and creatinine levels in groups treated with TiO_2 NPs.

The result of elevated AST and ALT, it is shown in this study, could reflect liver dysfunction because of the toxicant effects of TiO_2 NPs. The reason for this is the retention of nanoparticles in the liver, which is the organ for removing toxins from the body, including nanoparticles. These results agreed with Nouri's findings when injecting rats intraperitoneally at two concentrations [18]. Previous studies have shown the effect of TiO_2 NPs at various concentrations in causing pathological tissue changes represented by congestion and expansion of the hepatic cells with the infiltration of inflammatory cells [25]. The accumulation of nanoparticles in the liver likely triggered this response, as evidenced in other studies where it led to Kupffer cell activation, which make Kupffer cells perform their inflammatory function against foreign bodies, as the surface area of the nanoparticles helps them reach the cells or organs, either through passive diffusion in the liver, which causes the release of quantities of Reactive oxygen species and activates the inflammatory response and interferes with the defense mechanism of antioxidants [26].

The findings of this study also agreed with Aboulhoda *et al.* (2020) when treating rats orally with different concentrations of nano zinc oxide, as histological and biochemical examination of the liver showed, when treated with concentrations of 400 mg/kg of body weight, an increase in liver enzymes [27]. The increase in the ALT and AST enzyme ratios in the groups treated was attributed to the effect of messenger nanoparticles in stimulating gene expression of ribonucleotide and ribonucleotide mRNA, and increasing the protein levels of a many inflammatory cytokines, respectively: L-10, IL-4, CRP, IL-1B, IL-6, TN-β, MIF, and NF-kB, which increases the level of inflammatory response, cell death, and the infiltration of enzymes into the bloodstream [28]. Titanium nanoparticles may stimulate oxidative stress in the liver since they are small in size and large surface area, which affects the cellular mechanism and stimulates inflammatory reactions and breakdown of hepatic cells [29]. The toxicity of nano titanium dioxide on the liver is due to the release of a high percentage of enzymes. The high activity of the two enzymes led to a decrease in the activity of antioxidant enzymes when exposed to nano titanium particles [30]. This was attributed to the effect of the particles in stimulating ROS, which affects the balance of oxidizing and non-oxidizing factors, stimulating lipid peroxidation, reducing the level of antioxidant enzymes, and causing cell death [26]. Kalas *et al.* indicated that liver dysfunction occurs due to the increase in enzyme levels due to the effect of nano-crystalline anatase titanium oxide particles in raising the level of Natural Killer cells, reducing the proliferation of B and T lymphocytes and the effectiveness of inflammatory cytokines, which causes liver dysfunction [31].

Our study revealed that TiO_2 NPs exposure (100,400 mg/kg) significant disorder in lipid profile due to induced the overproduction of reactive oxygen species (ROS) in the cytoplasm, which subsequently upregulated the expression of receptors for advanced glycation end products (AGEs) leading to lipid accumulation in the adipocytes and hepatocytes with a higher level of Reactive Oxidative Species [32]. The accumulation of TiO_2 NPs in the hepatocytes causes oxidative stress, liver inflammation, characterized by increased levels of enzymes. Many studies have shown that the accumulation of TiO_2 NPs activates intracellular oxidative stress, with a massive release of ROS and lipid peroxides [33]. Abnormal induction of ROS leads to dysregulation of other metabolic activities in cells, such as lipid metabolism and apoptosis [34]. Previous study reported that lipid overaccumulation in the primary adipocytes under exposure to TiO_2 NPs was impaired to the normal level with the application of the antioxidant at a concentration of 10 mM [35].

CONCLUSION

In the present study, we revealed that exposure to (100, 400 mg/kg) of TiO_2 NPs size <100 the crystalline form is a mixture of rutile and anatase; showed a significant increase in creatinine, urea, AST, and ALT levels not only in the groups treated with high concentrations but also with low concentrations of TiO_2 NPs compared to the control group, and for both periods of 7 and 21 days of titanium dioxide exposure. This could prove the high toxicity of these nanoparticles, resulting in an inability to manage accumulated waste products from metabolic processes. Moreover, an imbalance in the natural ratios of lipid profiles disrupts the normal lipid homeostasis in the body. Our research highlights the importance of reevaluating and comparing the effects of TiO_2 NPs, especially those used in foods.

SUPPLEMENTARY MATERIAL

No supplementary material is provided for this study.

AUTHOR CONTRIBUTIONS

Wasan A. Wahab Alsiadi: Conceptualization, Methodology, Investigation, Writing – original draft, software. Ban Talib Elhaboby: Data curation, Formal analysis, Visualization. Ali Ibrahim Alsamawi: Supervision, Writing – review & editing, Project administration, Visualization.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICAL APPROVAL

All animal experiments were conducted according to ethical policies and approved by the ethics committee of the University of Bilad Al-Rafidain (Approval no. CHMT/25100030M)

DECLARATION OF GENERATIVE AI USE

The authors declare that no generative Al or Al-assisted technologies were used in the preparation of this article.

REFERENCES

[1] T. A. Saleh, "Nanomaterials: Classification, properties, and environmental toxicities," *Environmental Technology & Innovation*, vol. 20, Art no. 101067, Nov. 2020, doi: 10.1016/j.eti.2020.101067.

[2] H.-R. Paur, F. R. Cassee, J. Teeguarden, H. Fissan, S. Diabate, M. Aufderheide, W. G. Kreyling, O. Hänninen, G. Kasper, M. Riediker, *et al.*, "In-vitro cell exposure studies for the assessment of nanoparticle toxicity in the lung—A dialog between aerosol science and biology," *Journal of Aerosol Science*, vol. 42, no. 10, pp. 668–692, 2011, doi: 10.1016/j.jaerosci.2011.06.005.

[3] I. Khan, K. Saeed, and I. Khan, "Nanoparticles: Properties, applications and toxicities," *Arabian Journal of Chemistry*, vol. 12, no. 7, pp. 908–931, 2019, doi: 10.1016/j.arabjc.2017.05.011.

[4] X. Li, W. Liu, L. Sun, K. E. Aifantis, B. Yu, Y. Fan, Q. Feng, F. Cui, and F. Watari, "Effects of physicochemical properties of nanomaterials on their toxicity: Effects of physicochemical properties of nanomaterials on their toxicity," *Journal of Biomedical Materials Research Part A*, vol. 103, no. 7, pp. 2499–2507, 2014, doi: 10.1002/jbm.a.35384.

[5] H. Zhao, L. Chen, G. Zhong, Y. Huang, X. Zhang, C. Chu, L. Chen, and M. Wang, "Titanium Dioxide Nanoparticles Induce Mitochondrial Dynamic Imbalance and Damage in HT22 Cells," *Journal of Nanomaterials*, vol. 2019, pp. 1–16, Apr. 2019, doi: 10.1155/2019/4607531.

[6] F. Zhao, C. Wang, Q. Yang, S. Han, Q. Hu, and Z. Fu, "Titanium dioxide nanoparticle stimulating pro-inflammatory responses in vitro and in vivo for inhibited cancer metastasis," *Life Sciences*, vol. 202, pp. 44–51, Jun. 2018, doi: 10.1016/j.lfs.2018.03.058.

[7] H. Shi, R. Magaye, V. Castranova, and J. Zhao, "Titanium dioxide nanoparticles: A review of current toxicological data," *Particle and Fibre Toxicology*, vol. 10, no. 1, Art no. 15, 2013, doi: 10.1186/1743-8977-10-15.

[8] V. Gupta, S. Mohapatra, H. Mishra, U. Farooq, K. Kumar, M. Ansari, M. Aldawsari, A. Alalaiwe, M. Mirza, and Z. Iqbal, "Nanotechnology in cosmetics and cosmeceuticals-a review of latest advancements," *Gels*, vol. 8, no. 3, Art no. 173, 2022, doi: 10.3390/gels8030173.

[9] M. Montazer and E. Pakdel, "Functionality of nano titanium dioxide on textiles with future aspects: Focus on wool," *Journal of Photochemistry and Photobiology C: Photochemistry Reviews*, vol. 12, no. 4, pp. 293–303, 2011, doi: 10.1016/j.jphotochemrev.2011.08.005.

[10] W. Yang, L. Wang, E. M. Mettenbrink, P. L. DeAngelis, and S. Wilhelm, "Nanoparticle toxicology," *Annual Review of Pharmacology and Toxicology*, vol. 61, no. 1, pp. 269–289, 2021, doi: 10.1146/annurev-pharmtox-032320-110338.

[11] A. Nastulyavichus, E. Tolordava, A. Rudenko, D. Zazymkina, P. Shakhov, N. Busleev, Y. Romanova, A. Ionin, and S. Kudryashov, "In vitro destruction of pathogenic bacterial biofilms by bactericidal metallic nanoparticles via laser-induced forward transfer," *Nanomaterials*, vol. 10, no. 11, Art no. 2259, 2020, doi: 10.3390/nano10112259.

[12] H. Hantoosh and H. Ismail, "Teratogenic effects of titanium dioxid nanoparticles on albion mice fetus Mus musculus," *Egyptian Academic Journal of Biological Sciences, D. Histology & Histochemistry*, vol. 8, no. 1, pp. 35–46, 2016, doi: 10.21608/eajbsd.2016.14106.

[13] F. Minghui, S. Ran, J. Yuxue, and S. Minjia, "Toxic effects of titanium dioxide nanoparticles on reproduction in mammals," *Frontiers in Bioengineering and Biotechnology*, vol. 11, Art no. 1183592, May 2023, doi: 10.3389/fbioe.2023.1183592.

[14] A. AL-Baker, A. AlKshab, and H. Ismail, "Effect of silver nanoparticles on some blood parameters in rats," *Iraqi Journal of Veterinary Sciences*, vol. 34, no. 2, pp. 389–395, 2020, doi: 10.33899/ijvs.2020.165812.

[15] A. M. B. Elnagar, A. Ibrahim, and A. M. Soliman, "Histopathological effects of titanium dioxide nanoparticles and the possible protective role of N-Acetylcysteine on the testes of male albino rats," *International Journal of Fertility and Sterility*, vol. 12, no. 3, pp. 249–256, 2018, doi: 10.22074/ijfs.2018.5389.

[16] E. Huerta-García, J. A. Pérez-Arizti, S. G. Márquez-Ramírez, N. L. Delgado-Buenrostro, Y. I. Chirino, G. G. Iglesias, and R. López-Marure, "Titanium dioxide nanoparticles induce strong oxidative stress and mitochondrial damage in glial cells," *Free Radical Biology and Medicine*, vol. 73, pp. 84–94, Aug. 2014, doi: 10.1016/j.freeradbiomed.2014.04.026.

[17] M. Ávila, M. G. Mora Sánchez, A. S. Bernal Amador, and R. Paniagua, "The metabolism of creatinine and its usefulness to evaluate kidney function and body composition in clinical practice," *Biomolecules*, vol. 15, no. 1, Art no. 41, 2025, doi: 10.3390/biom15010041.

[18] J. E. Hall and M. E. Hall, *Guyton and Hall textbook of medical physiology*. Elsevier, 2020, Online availiable: https://shop.elsevier.com/books/guyton-and-hall-textbook-of-medical-physiology/hall/978-0-323-59712-8.

[19] G. W. Liu, J. W. Pippin, D. G. Eng, S. Lv, S. J. Shankland, and S. H. Pun, "Nanoparticles exhibit greater accumulation in kidney glomeruli during experimental glomerular kidney disease," *Physiological Reports*, vol. 8, no. 15, Art no. e14545, 2020, doi: 10.14814/phy2.14545.

[20] M. H. Hazelhoff, R. P. Bulacio, and A. M. Torres, "Renal tubular response to titanium dioxide nanoparticles exposure," *Drug and Chemical Toxicology*, vol. 46, no. 6, pp. 1130–1137, 2022, doi: 10.1080/01480545.2022.2134889.

[21] K. Y. Abdel-Halim, S. R. Osman, M. A. Abuzeid, H. T. El-Danasoury, and A. M. Khozimy, "Apoptotic and histopathological defects enhanced by titanium dioxide nanoparticles in male mice after short-term exposure," *Toxicology Reports*, vol. 9, pp. 1331–1346, 2022, doi: 10.1016/j.toxrep.2022.06.003.

[22] W. A. W. Alsiadi, A. M. Albayati, and B. T. Elhaboby, "Detection levels of cytokines (IL-6 and IL-18) and microbial parameters in patients with renal failure in Diyala province," *Indian Journal of Forensic Medicine & Toxicology*, vol. 15, no. 2, pp. 1470–1475, 2021, doi: 10.37506/ijfmt.v15i2.14546.

[23] S. Gui, Z. Zhang, L. Zheng, Y. Cui, X. Liu, N. Li, X. Sang, Q. Sun, G. Gao, Z. Cheng, *et al.*, "Molecular mechanism of kidney injury of mice caused by exposure to titanium dioxide nanoparticles," *Journal of Hazardous Materials*, vol. 195, pp. 365–370, Nov. 2011, doi: 10.1016/j.jhazmat.2011.08.055.

[24] N. Alqurashy, "Evaluated the effect of titanium dioxide nanoparticles on the activity of creatinine and urea levels in Dialysis patients," *Wasit Journal for Pure sciences*, vol. 2, no. 3, pp. 248–256, 2023, doi: 10.31185/wjps.184.

[25] M. Lehotska Mikusova, M. Busova, J. Tulinska, V. Masanova, A. Liskova, I. Uhnakova, M. Dusinska, Z. Krivosikova, E. Rollerova, R. Alacova, *et al.*, "Titanium dioxide nanoparticles modulate systemic immune response and increase levels of reduced glutathione in mice after seven-week inhalation," *Nanomaterials*, vol. 13, no. 4, Art no. 767, 2023, doi: 10.3390/nano13040767.

[26] J. J. Wang, B. J. Sanderson, and H. Wang, "Cyto- and genotoxicity of ultrafine TiO_2 particles in cultured human lymphoblastoid cells," *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*, vol. 628, no. 2, pp. 99–106, 2007, doi: 10.1016/j.mrgentox.2006.12.003.

[27] Z. Chen, D. Zhou, S. Han, S. Zhou, and G. Jia, "Hepatotoxicity and the role of the gut-liver axis in rats after oral administration of titanium dioxide nanoparticles," *Particle and Fibre Toxicology*, vol. 16, no. 1, Art no. 48, 2019, doi: 10.1186/s12989-019-0332-2.

[28] M. Z. Rizk, S. A. Ali, M. A. Hamed, N. S. El-Rigal, H. F. Aly, and H. H. Salah, "Toxicity of titanium dioxide nanoparticles: Effect of dose and time on biochemical disturbance, oxidative stress and genotoxicity in mice," *Biomedicine & Pharmacotherapy*, vol. 90, pp. 466–472, Jun. 2017, doi: 10.1016/j.biopha.2017.03.089.

[29] J. Khan, N. D. Kim, C. Bromhead, P. Truman, M. C. Kruger, and B. L. Mallard, "Hepatotoxicity of titanium dioxide nanoparticles," *Journal of Applied Toxicology*, vol. 45, no. 1, pp. 23–46, 2024, doi: 10.1002/jat.4626.

[30] Y. Duan, Y. Yang, Z. Zhang, Y. Xing, and H. Li, "Toxicity of titanium dioxide nanoparticles on the histology, liver physiological and metabolism, and intestinal microbiota of grouper," *Marine Pollution Bulletin*, vol. 187, Art no. 114600, Feb. 2023, doi: 10.1016/j.marpolbul.2023.114600.

[31] M. A. Kalas, L. Chavez, M. Leon, P. T. Taweesedt, and S. Surani, "Abnormal liver enzymes: A review for clinicians," *World Journal of Hepatology*, vol. 13, no. 11, pp. 1688–1698, 2021, doi: 10.4254/wjh.v13.i11.1688.

[32] J. Liu, L. Zhong, T. Yuan, J. Sun, Y. Wang, J. Chen, G. Yang, and T. Yu, "Exposure to titanium dioxide nanoparticles accelerates abnormal fat deposition through the mediation of the ROS via the AGE-RAGE signaling pathway in mice," Aug. 2023, doi: 10.1101/2023.08.24.554746.

[33] L. Kong, T. Barber, J. Aldinger, L. Bowman, S. Leonard, J. Zhao, and M. Ding, "ROS generation is involved in titanium dioxide nanoparticle-induced AP-1 activation through p38 MAPK and ERK pathways in JB6 cells," *Environmental Toxicology*, vol. 37, no. 2, pp. 237–244, 2021, doi: 10.1002/tox.23393.

[34] M. Monden, H. Koyama, Y. Otsuka, T. Morioka, K. Mori, T. Shoji, Y. Mima, K. Motoyama, S. Fukumoto, A. Shioi, *et al.*, "Receptor for advanced glycation end products regulates adipocyte hypertrophy and insulin sensitivity in mice," *Diabetes*, vol. 62, no. 2, pp. 478–489, 2013, doi: 10.2337/db11-1116.

[35] H. Lee, Y. J. Lee, H. Choi, E. H. Ko, and J.-w. Kim, "Reactive oxygen species facilitate adipocyte differentiation by accelerating mitotic clonal expansion," *Journal of Biological Chemistry*, vol. 284, no. 16, pp. 10 601–10 609, 2009, doi: 10.1074/jbc.m808742200.