28-29 September 2023,
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# 2nd International Conference on Chemo and Bioinformatics
# ICCBIKG_2023

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International Conference on Chemo and BioInformatics

# BOOK OF PROCEEDINGS

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**ICCBIKG 2023**

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# $TiO_2$ nanoparticles and $TiO_2$ nanoparticles surface modified with salicylic acid affect neurological functions and oxidative stress markers in the eyes of adult rats

**K. Bobić[1*], A. Todorović[1], S. Pejić[1], F. Veljković[2], S. Veličković[2], S. Pajović[1], D. Drakulić[1]**

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**Abstract**: Titanium dioxide nanoparticles ($TiO_2$NPs) are widely used in pharmaceutics, food products and cosmetics. Besides numerous beneficial outcomes, they also induce toxic effects in different organs, including the eyes. The recent findings report that some surface modifications can attenuate $TiO_2$NPs toxicity. Thus, the aim of this study was to compare the effects of acute oral treatment with commercially available, bare $TiO_2$NPs and $TiO_2$NPs surface modified with salicylic acid (SA-$TiO_2$NPs) using adult Wistar rats as model organisms. Control animals were gastrically intubated with vehicle (0.01 M HCl), while others were treated with either $TiO_2$NPs or SA-TiO2NPs (1000mg/kg dissolved in vehicle). Afterward, the mortality rate as the acute toxicity parameter and parameters of neurological function were assessed. Animals were sacrificed on the 14th day following treatment. In the eye crude synaptosomal fraction, the effects of treatments on oxidative stress markers such as prooxidant/antioxidant balance (PAB) and lipid peroxidation (LPO) were compared. According to the obtained results, the mortality was 0 in all experimental groups. $TiO_2$NPs and SA-$TiO_2$NPs treatments displayed mild effects on spontaneous activity and pacing and had no impact on the visual placing reflex. Moreover, $TiO_2$NPs and SA-$TiO_2$NPs exposure significantly elevated PAB levels, when compared to controls. Animals treated with SA-$TiO_2$NPs had similar LPO levels as controls, while in $TiO_2$NPs group LPO levels were significantly increased. The presented data showed that both examined nanoparticles exerted similar outcomes referring to most of the investigated parameters, however, surface binding of SA decreased the level of LPO and thus, mitigated some of $TiO_2$NPs toxicity in the eyes.

**Keywords**: Titanium dioxide nanoparticles ($TiO_2$NPs) and surface modification with salicylic acid (SA-$TiO_2$NPs), neurological function, oxidative stress, eye, rat

## 1. Introduction

Titanium dioxide nanoparticles ($TiO_2$NPs) are widely used as a white pigment in daily consumer products, like food, toothpaste, sun cream, cosmetics, and plastics. They are also exploited in surgery, dentistry, and pharmacy; in antimicrobial and antibiotic therapies; as photosensitizers in photodynamic cancer therapy; and can potentially be used as a drug delivery system [1]. Unfortunately, toxic impacts of $TiO_2$NPs, provoked by oxidative stress (OS) and inflammation, are recognized in the brain, liver, kidneys, spleen, and eyes [2]. Their toxicity might be reduced by various modifications, including surface bounding of naturally occurring compounds with a wide range of biological activities and therapeutic applications. Since previous studies showed that some surface modifications can attenuate $TiO_2$NPs toxicity [3], we compared the effects of bare $TiO_2$NPs and SA-$TiO_2$NPs ($TiO_2$NPs surface modified with salicylic acid, SA) in the eyes of adult Wistar rats.

## 2. Materials and methods

For the purpose of the experiment, we used commercially available, bare $TiO_2$NPs (Sigma Aldrich Co., USA, sized 25 nm) with maximum absorption wavelength of 380 nm and SA-$TiO_2$NPs, synthesized and characterized at the Department for Radiation Chemistry and Physics, VINČA Institute of Nuclear Sciences - National Institute of the Republic of Serbia, University of Belgrade, with maximum absorption of 600 nm. The estimated concentration of SA bound to the surface of $TiO_2$NPs was 5 %.

All procedures were approved by the Ministry of Agriculture, Forestry and Water Management - Veterinary office of the Republic of Serbia (protocol 323-07-03626/2021-05). Adult Wistar rats, maintained under standard conditions, were randomly divided into 3 groups (n = 4 per group): controls treated with vehicle (2.5 ml, 0.01 M HCl) (V); animals treated with either $TiO_2$NPs or SA-$TiO_2$NPs (1000 mg/kg dissolved in 2.5 ml vehicle). All treatments were applied intragastrically in a single dose. During the 14-day rest period, the mortality rate as the acute toxicity parameter was monitored daily. On the last day, sensory-motor parameters, including spontaneous activity, pacing and visual placing reflex were assessed, as indicators of neurological function. Animals were then sacrificed, and their eyes were isolated on ice and stored at -80°C for further processing. Whole eyes were homogenized in 5 volumes of solvent (50 mM Tris-HCl, 0.25 M sucrose, 1 mM EDTA, pH 7.4) to isolate crude synaptosomal fraction [4]. Evaluation of eyes' oxidative status was conducted using modified spectrophotometrical methods for prooxidant/antioxidant balance (PAB) and lipid peroxidation (LPO) [5]. Obtained results are presented as a percentage of V and expressed as mean ± SEM. The GraphPad Prism 5 (GraphPad Software, Inc., USA) was used for statistical analysis, with one way analysis of variance (ANOVA) and Tukey's multiple-comparison post hoc test (statistical significance was $p < 0.05$).

## 3. Results and discussion

During the 14-day rest period, the mortality was 0 in all experimental groups, pointing to nonlethal effect of applied NPs (data not shown). As shown in Table 1., the investigated neurological parameters were unaffected by vehicle treatment. Both $TiO_2$NPs and SA-$TiO_2$NPs treatments caused noticeable, but mild effects on spontaneous activity and pacing, indicating neurological deficits that tempered animal behavior. The visual placing reflex was unchanged and showed no difference between groups, suggesting that the eye function probably remained intact following $TiO_2$NPs and SA-$TiO_2$NPs treatments.

**Table 1**. Assessment of neurological parameters of rats subjected to acute oral treatment with vehicle (V), bare titanium dioxide nanoparticles ($TiO_2$NPs) or titanium dioxide nanoparticles surface modified with salicylic acid (SA-$TiO_2$NPs).

| Neurological parameters/groups | V | $TiO_2$NPs | SA-$TiO_2$NPs |
|---|---|---|---|
| Spontaneous activity | – | + | + |
| Pacing | – | + | + |
| Visual placing reflex | – | – | – |

"–" no effect; "+" mild effect

In the eye crude synaptosomal fraction, the treatments' effect on OS markers: PAB and LPO were tested. As illustrated in Figure 1 both $TiO_2$NPs treatments significantly elevated PAB levels compared to V ($p < 0.05$), while the LPO level was significantly increased only in the $TiO_2$NPs group ($p < 0.001$). Animals treated with SA-$TiO_2$NPs had decreased LPO levels when compared to $TiO_2$NPs ($p < 0.001$).

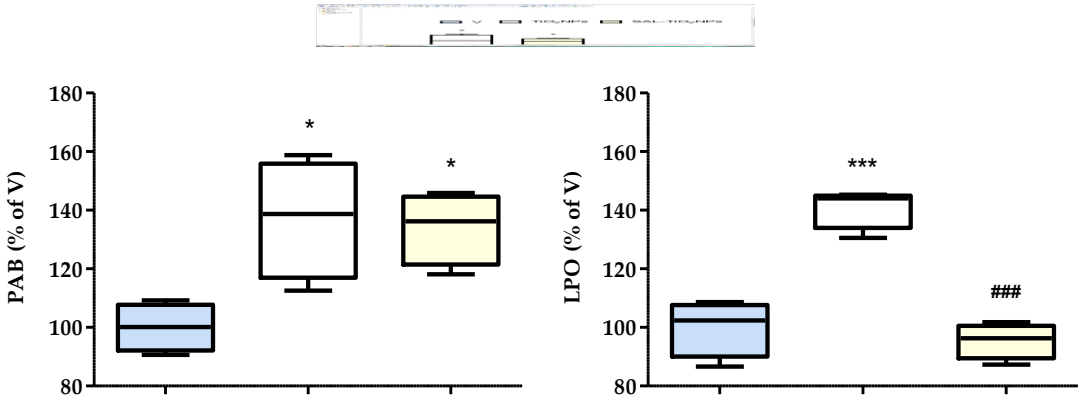


**Figure 1**. Levels of oxidative stress markers: prooxidant/antioxidant balance (PAB) (left) and end lipid peroxidation products (LPO) (right) in the eye crude synaptosomal fraction of rats, subjected to acute oral treatment with vehicle (V), bare titanium dioxide nanoparticles ($TiO_2$NPs) or surface modified with salicylic acid (SA-$TiO_2$NPs). Values are presented as percentage of V and expressed as mean ± SEM, with ANOVA and Tukey post hoc test statistical analysis. Statistically significant difference between V and other experimental groups is represented as * (* $p < 0.05$, *** $p < 0.001$) and between $TiO_2$NPs and SA-$TiO_2$NPs as # (### $p < 0.001$)

Based on presented results, it can be assumed that $TiO_2$NPs and SA-$TiO_2$NPs have different mechanisms of OS induction. $TiO_2$NPs-induced OS is associated with oxidative

changes of lipids, as also previously reported [6], while SA-$TiO_2$NPs in the eyes of rats do not affect lipids, but most likely their effects are accomplished through some other mechanisms of action.

## 3. Conclusions

Although $TiO_2$NPs and SA-$TiO_2$NPs exert similar outcomes referring to most of the investigated parameters, surface binding of SA reduces the level of lipid peroxidation and thus, at least partially, suppresses $TiO_2$NPs toxic effects in the eyes. Further research is needed to reveal unknown mechanisms of $TiO_2$NPs and SA-$TiO_2$NPs actions and to investigate the benefits associated with positive outcomes resulting from the implementation of other $TiO_2$NPs modifications.

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