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THE IMPACT OF SILVER NANOPARTICLE MODIFICATION ON THE STRUCTURE, PHOTOACTIVE, TOXICOLOGICAL, AND VIRUCIDAL PROPERTIES OF ANATASE FOR USE IN BIOLOGY AND MEDICINE

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The structural-morphological, toxicological, cytotoxic, and virucidal properties of photoelectronic TiO_2 and TiO_2-Ag were investigated to ascertain safety concerns related to their production and application. It was demonstrated that the TiO_2-Ag nanocomposite exhibits an anatase crystalline modification and is composed of TiO_2 nanoparticles ranging from 13 to 20 nm and Ag nanoparticles with sizes of 35–40 nm, with silver localized on the surface of titanium dioxide. LD_{50} values were established as 4783.30 mg/kg for nano-TiO_2 and 724.44 mg/kg for nano-TiO_2-Ag after acute intraperitoneal administration of nanopowders to mice. Accumulation of TiO_2 and TiO_2-Ag nanopowders was observed, causing damage to the livers, kidneys, and lungs of laboratory animals. TiO_2-Ag and TiO_2 nanomaterials could potentially induce chronic inflammation and allergic reactions in synthesis operators. These nanomaterials affected the activity of mitochondrial enzymes in testicular cells of boars, exerting a damaging effect on mitochondrial membranes and cells overall. Silver modification of nano-TiO_2 led to reduced toxicity of nanoparticles for BHK-21 and MDCK cells. Significant virucidal effects of TiO_2-Ag and TiO_2 nanoparticles were demonstrated.

Key words: titanium dioxide nanoparticles, toxicology, mechanism of action, cytokines, nanomaterials, oxidative enzymes, cytotoxicity, virucidal action.

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ВПЛИВ МОДИФІКУВАННЯ АНАТАЗУ НАНОЧАСТИНКАМИ СРІБЛА НА ЙОГО СТРУКТУРУ, ФОТОАКТИВНІ, ТОКСИКОЛОГІЧНІ ТА ВІРУЛІЦИДНІ ВЛАСТИВОСТІ ДЛЯ ВИКОРИСТАННЯ В БІОЛОГІЇ І МЕДИЦИНІ

Для розв'язання безпекових питань одержання і застосування фотоелектронних наноматеріалів TiO_2 і TiO_2-Ag вивчені їх структурно-морфологічні, токсикологічні, цитотоксичні та віруліцидні властивості. Показано, що нанокомпозит TiO_2-Ag має анатазну кристалічну модифікацію і складається з наночастинок TiO_2 розміром 13–20 нм і Ag – 35–40 нм, срібло локалізується на поверхні діоксиду титану. При гострому внутрішньоочеревинному введені нанопорошків мишам, встановлено, що LD_{50} для нано-TiO_2 дорівнює 4783,30 мг/кг, LD_{50} для нано-TiO_2-Ag – 724,44 мг/кг. Нанопорошки TiO_2 і TiO_2-Ag накопичуються і пошкоджують печінку, нирки і легені лабораторних тварин. Наноматеріали TiO_2-Ag і TiO_2 можуть потенційно викликати хронічне запалення та алергічні реакції у операторів синтезу. Наноматеріали TiO_2-Ag і TiO_2 впливають на активність мітохондріальних ензимів статевих клітин кнурів й справляють ушкоджуючу дію на мембрани мітохондрій й клітин загалом. Модифікування сріблом нано-TiO_2 призводило до зменшення токсичності наночастинок для клітин BHK-21 та MDCK. Показана значна віруліцидна дія наночастинок TiO_2-Ag і TiO_2.

Ключові слова: нанодіоксид титану, токсикологія, механізм дії, цитокіни, наноматеріали, окиснювальні ензими, цитотоксичність, віруліцидна дія.

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Nanomaterials based on titanium dioxide with high photocatalytic activity are promising for organic pollutant degradation, disinfection, antimicrobial surfaces, and self-cleaning applications. It is known that photocatalytic activity can be enhanced by incorporating noble metals into titanium dioxide (anatase) [5, 10, 12]. Titanium dioxide actively generates oxygen-containing radicals that can damage biological molecules of pathogens (E. coli, Staphylococcus aureus, etc.) such as proteins, lipids, and nucleic acids [2–4, 6, 7, 9]. During UV irradiation, charge separation can occur on the surface of the catalyst. The reducing particle size to the nanoscale dimensions enhances light absorption throughout their volume, leading to increased antiviral activity of TiO_2 too [2, 4, 7]. Besides, TiO_2 and CeO_2 nanostructures [2, 6, 7] are promising candidates for antimicrobial applications due to low toxicity, band gap energy, superior efficacy, tunable structure, etc. Specifically, at the Institute for Problems of Materials Science (IPMS), photoactive nanopowders based on titanium dioxide are synthesized using an original method involving the thermal decomposition of metatitanic acid with silver addition. To address safety concerns related to the production and application of these nanomaterials, as well as to study their disinfection capabilities, it

is crucial to gather information about the structure, morphology, physicochemical properties, toxicological characteristics of nano-TiO_2 and nano-TiO_2-Ag, as well as their biological activity. Magnetite NPs have clinical applications due to their relative safety, and unique magnetic are responsible for a simple and controllable preparation [11]. In previous studies, *in vitro* cytotoxic, virucidal and anti-adenoviral effects of titanium oxide were determined, as well as its ability to photoactivate [8].

The purpose of the study was to investigate and evaluate the morphological, optical, photocatalytic, toxicological, cytotoxic, and virucidal properties of the synthesized nano-TiO_2 and nano-TiO_2-Ag in laboratory animals and in vitro.

Materials and methods. The morphology of nano-TiO_2 and nano-TiO_2-Ag with the surface structure were investigated using scanning electron microscopy (SEM) the Mira 3 Tescan microscope (Czech Republic) and a transmission electron microscope (TEM) JEM-1400 (JEOL, Japan).

Diffuse reflectance spectra in the ultraviolet and visible ranges (200–1000 nm) were recorded on a Perkin-Elmer Lambda Bio 35 UV-Vis spectrophotometer.

The photocatalytic activity of nanopowders (TiO_2, TiO_2-Ag) was evaluated based on phenol degradation (50 mg/l) using Xe-lamp 300 W (λ=365 nm).

The toxicity of titanium dioxide nanoparticles (nano-TiO_2) and a composite of titanium dioxide with nanosilver (nano-TiO_2-Ag) was studied in acute and subacute experiments on mice, guinea pigs, and rabbits using generally accepted toxicological methods. Research on the irritating effect on the mucous membrane of rabbit eyes and the skin of guinea pigs was conducted according to the relevant methodological guidelines (1980). Sensitizing action was studied using the methodology of Alekseeva O.G., Petkevich A.I. (1973). Acute toxic effects were studied under conditions of intraperitoneal administration with subsequent calculation of LD_{50} according to Prozorovsky (1962). Cumulative properties were investigated according to Lim et al. (1961).

The content of titanium and silver in the liver, kidneys, spleen, heart, lungs, and brain tissues of experimental mice was determined using inductively coupled plasma optical emission spectroscopy. Microsections of internal organs were examined using a light microscope (Olympus BX51).

The impact of nano-TiO_2 and nano-TiO_2-Ag on the immune system was investigated by assessing the functional activity of peripheral blood mononuclear cells from healthy donors in vitro. The production of cytokines including interleukin-1 (IL-1), interleukin-4 (IL-4), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) was measured.

The effects of nano-TiO_2 and nano-TiO_2-Ag on reproductive cells were evaluated through indicators such as oxygen consumption rate (ng-atom O2/0.1 ml per minute), succinate dehydrogenase (SDH) activity (U/g × 0.1 ml), cytochrome c oxidase activity (U/g × 0.1 ml), and sperm survival (hours). The study involving the effects of nanomaterials on boar reproductive cells was conducted under the guidance of Dr. D.D. Ostapiv at the Institute of Animal Biology NAAS [1].

In biological activity studies of NPs, monolayer cell cultures were utilized: MDCK cells (canine kidney) and BHK-21 cells (kidney of Syrian hamsters). Influenza A virus subtype H1N1, strain A/FM/1/47 and Herpes simplex virus type 1, strain US were used as model viruses in this study.

Cell viability was assessed based on their mitochondrial activity using the 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide assay (NeoFroxx, Germany). The cytotoxicity concentration value (CC_{50}) for NPs was determined.

When determining the virucidal activity of NPs, equal volumes of virus suspension and NPs suspension were incubated at 37°C for 1 hour. A series of dilutions was prepared and cells were infected in a 96-well plate. The virus was adsorbed at 37°C for 1 hour, after which serum-free medium was added and incubated at 37°C with 5 % CO_2 until a pronounced cytopathic effect of the virus appeared. The results were analyzed spectrophotometrically using MTT analysis on a Multiskan FC microplate reader (Thermo Fisher Scientific, USA) at a wavelength of 538 nm [8].

Statistical analysis of the obtained results was performed considering the normal distribution of indicators using the Shapiro-Wilk test. Parametric statistical criteria were employed, including Student's t-test, analysis of variance (ANOVA), and the Scheffe multiple comparison method. Non-parametric tests included the Wilcoxon W test, the Kruskal-Wallis rank one-way analysis of variance, and multiple comparisons using the Dunn criterion. Statistically significant differences were considered at $p<0.05$. Data analysis was conducted using the MedStat v.5.2 software package (Copyright © 2003–2019).

Results of the study and their discussion. It was determined that the nano-TiO_2 powder contained nanoparticles predominantly with sizes ranging from 21 to 28 nm (Fig. 1A). The nano-TiO_2 powder exhibited a well-developed surface structure due to the presence of mesopores (pores of 2–50 nm) and a

specific surface area of 50.84 m²/g. SEM investigation of nano-TiO_2-Ag (Fig. 1B) revealed its dimensions to be in the range of 17–22 nm.

The results of TEM were presented in Fig. 1C, showing the surface of the TiO_2-Ag nanocomposite sample. The image depicts the deposition of silver on the oxide surface. "Bubble-like" silver particles are observed (highlighted in red). The silver particles have an average size of 35–40 nm, while the TiO_2 particles measure 13–20 nm. The specific surface area of nano-TiO_2-Ag is 50.11 m²/g.

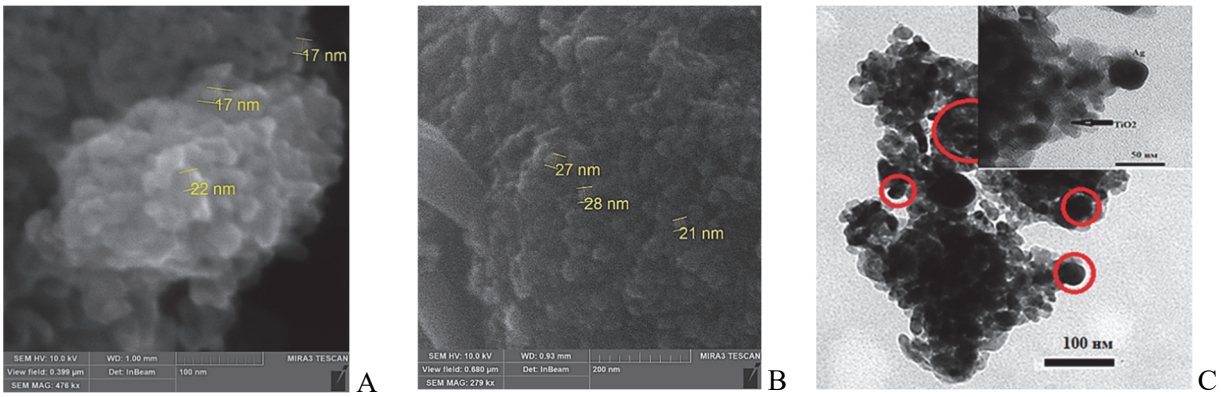

Fig. 1. Structure of TiO_2 and TiO_2-Ag nanomaterials: A – Structure of nano-TiO_2 determined by SEM using Tescan Mira 3 (at magnification 279.000, scale 200 nm), B – Structure of nano-TiO_2-Ag determined by SEM using Tescan Mira 3 (at magnification 476.000, scale 100 nm), C – Structure of nano-TiO_2-Ag determined by TEM using JEM-1400 (at magnifications ranging from 2000 to 100000, scale 100 nm and 50 nm)

The absorption spectrum of TiO_2 is limited to the UV range of radiation (Fig. 2, curve 3). In other words, nano-TiO_2 exhibits its activity only under UV irradiation ($\lambda < 400$ nm). This trend was also observed by other researchers [10]. Intense photon absorption in the range of 300–350 nm is observed for TiO_2 in the presence of nano-Ag in the UV range. This indicates efficient electronic heterojunctions at the metal oxide-metal interface, promoting the photocatalytic generation of electron-hole pairs (Fig. 3, curve 2).

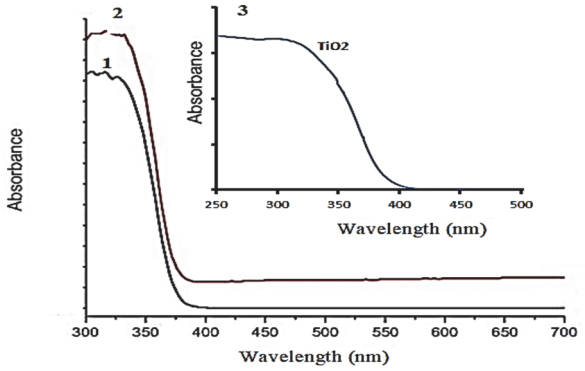

Fig. 2. UV absorption spectra of nanosystems with anatase: 1 – TiO_2 [10], 2 – TiO_2-Ag, 3 – TiO_2 (IPMS)

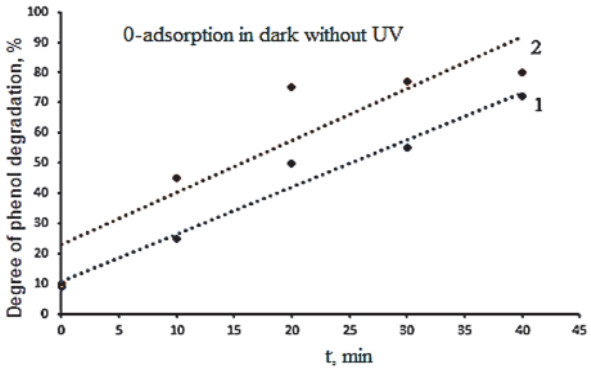

Fig. 3. Degree of phenol degradation after UV irradiation using nanosystems: 1 – TiO_2; 2 – TiO_2-Ag (4 %)

During photocatalysis (Fig. 3), oxygen serves as a source for generating reactive oxygen species (ROS) ($O_2^{\bullet -}$ and •OH). The results shown in Fig. 3 demonstrated the maximum phenol degradation effect upon contact with the TiO_2-Ag (4 %) system, attributed to its surface structure and photon absorption in the UV region of the spectrum.

Today, the issue of nanotoxicity is complex and multifaceted, requiring a holistic approach. One of the main problems in this field is the absence of standardized methodologies for *in vivo* and *in vitro,* studies in nanotoxicology at the current stage, and clear safety and acceptability criteria for nanomaterials have not been established.

Summarized data on the toxicological properties of TiO_2 and TiO_2-Ag nanopowders are provided in Table 1.

The maximum tolerable dose for nano-TiO_2 was 4000 mg/kg, whereas, for nano-TiO_2-Ag, the dose was below 1000 mg/kg. Based on the median lethal doses (LD_{50}) of the nanomaterials, nano-TiO_2 corresponds to hazard class 4 (slightly hazardous), while nano-TiO_2-Ag falls under hazard class 3 (moderately hazardous). Repeated (28-fold) intragastric administration of nano-TiO_2, resulting in a cumulative dose of 15.9 LD_{50} (76040 mg/kg), caused mild accumulation but did not lead to animal fatalities.

Table 1

Comparative Toxicological and Hygienic Assessment of TiO_2 and TiO_2-Ag Nanopowders

№	Parameter	Nano-TiO_2	Nano-TiO_2-Ag
1.	Maximum tolerable dose, mg/kg	4000	below 1000
2.	Intraperitoneal LD_{50}, mg/kg	4783.30	724.44
3.	Recalculated intragastric LD_{50}, mg/kg	14947.81	2263.87
4.	Hazard class of chemical substances	IV (slightly hazardous)	III (moderately hazardous)
5.	Local irritant effect on the skin	Does not cause	Does not cause
6.	Irritating effect on the mucous membrane of the eye	Mildly pronounced	Mildly pronounced
7.	Sensitizing effect	Mildly pronounced	Mildly pronounced
8.	Tentatively Safe Impact Levels (TSIL), mg/m³	0.2	0.3
9.	Cumulative properties	Mildly pronounced	Mildly pronounced
10.	Accumulation of Ti (and Ag for TiO_2-Ag nanopowders) in internal organs of laboratory animals after acute administration of TiO_2 or TiO_2-Ag nanopowders, respectively	Liver, kidneys, lungs, and spleen	Liver, kidneys, lungs, and spleen
11.	Characteristic microscopic signs of toxic effects on liver tissue	Mainly dystrophic histological changes (cytoplasmic vacuolization in hepatocytes)	Predominant initial necrotic changes (hepatocytes with pyknosis of nuclei)
12.	Characteristic microscopic signs of toxic effects on kidney tissue	Enlargement of the urinary space in renal corpuscles, dystrophic changes in tubular epithelium of varying degrees	
13.	Characteristic microscopic signs of toxic effects on lung tissue	Dystrophic, necrotic changes, and hemorrhagic infiltration of the tissue	
14.	Effect on the functional activity of mononuclear cells from donors under *in vitro* conditions	Increase in production IL-1	Increase in production IL-1, IL-6, TNF-α, IL-4
15.	Effect on testicular cells of boars *in vitro*	Decreased respiratory activity, increased succinate dehydrogenase activity, decreased sperm survival	Decreased respiratory activity, decreased sperm survival

Nano-TiO_2 and nano-TiO_2-Ag induce temporary, mildly pronounced inflammation of the ocular mucosa and a slightly pronounced sensitizing effect, with a slightly more pronounced effect observed with the TiO_2-Ag nanocomposite. Single and repeated application of nano-TiO_2 and nano-TiO_2-Ag do not cause skin irritation. Both nanopowders accumulate in the liver, kidneys, lungs, and spleen of laboratory animals following acute intraperitoneal administration. Histological analysis revealed that liver tissue predominantly exhibited dystrophic changes (67.7 %) under the influence of nano-TiO_2, while initial necrotic changes (70 %) predominated under the influence of nano-TiO_2-Ag. Histological signs of kidney and lung tissue damage were similar for both nanopowders.

Nano-TiO_2 and nano-TiO_2-Ag at concentrations of 30 μg/ml (equivalent to the dose that may accumulate in the bodies of synthesis operators over 20 years) increased the functional activity of peripheral blood mononuclear cells *in vitro*, as evidenced by cytokine production of IL-1, IL-6, and TNF-α ($p<0.05$). This suggests their potential to induce chronic inflammation, and they also increased IL-4 production ($p<0.05$), indicating possible allergic effects for synthesis operators. The functional activity of peripheral blood mononuclear cells was more significantly elevated under the influence of nano-TiO_2-Ag than nano-TiO_2. These nanomaterials exert damaging effects on boar reproductive cells, significantly altering indicators of oxygen consumption, mitochondrial enzyme activity, and sperm survival *in vitro* ($p<0.01$). The most sensitive marker was found to be sperm survival, which significantly decreased under the influence of nano-TiO_2 at a dose of 1/10 LD_{50}, reflecting disruption in mitochondrial enzyme activity and ATP resynthesis.

The cytotoxic effect of nanoparticles (derived from metatitanic acid and dispersed in propanediol-alcohol) was investigated in cells. At a concentration of 100 μg/ml, the studied nanoparticles were toxic to the cells. In subsequent dilutions, the nanoparticles exhibited no toxicity. The cytotoxic concentration values, which inhibit cell viability by 50 % (CC_{50}), were determined. For example, the CC_{50} of nano-TiO_2 and TiO_2-Ag 4wt % for MDCK cells were 50 μg/ml and 52 μg/ml, respectively, while for BHK-21 cells, they were 81 μg/ml and 62 μg/ml.

The impact of substances on an extracellular virus, their virucidal effect, and the ability to deactivate its infectivity were assessed. In the experiments, NPs were used at concentrations of 50 μg/ml,

and the influenza virus with a titer of 9.5 $\log_{10}$ $TCID_{50}$/ml and herpes simplex virus with a titer of 5.0 $\log_{10}$ $TCID_{50}$/ml were employed. The reduction in herpes virus infectivity titer upon contact with both types of nanoparticles for 1 hour was 5.0 $\log_{10}$ $TCID_{50}$/ml (Table 2).

Table 2

Virucidal action of nanoparticles TiO_2 and TiO_2-Ag 4wt % against influenza type A virus (IAV) and herpes simplex virus type 1(HSV-1/US)

Samples	Infectious virus titer after 1 hour of contact, $\log_{10}$ $TCID_{50}$/ml	Reduction in infectious virus titer, $\log_{10}$ $TCID_{50}$/ml
TiO_2 + IAV	2.0	7.5
TiO_2 + HSV-1/US	0	5.0
TiO_2-Ag 4wt % +IAV	1.6	7.9
TiO_2-Ag 4wt % + HSV-1/US	0	5.0
Control IAV	9.5	-
Control HSV-1/US	5.0	-

Nano-TiO_2 and TiO_2-Ag 4wt % also substantially inactivated the influenza virus, reducing its titer by 7.5 and 7.9 $\log_{10}$ $TCID_{50}$/ml, respectively.

The obtained results suggest that both titanium dioxide and silver-modified titanium dioxide exhibit equally pronounced virucidal effects on influenza type A virus and herpes simplex virus type 1.

Therefore, upon contact of nanoparticles with herpes simplex virus type 1 for 1 h, they completely inactivated its infectivity. Nanoparticles had a pronounced virucidal effect against influenza type A virus, reducing its infectious titer by 7.5–7.9 $\log_{10}TCID_{50}$/ml. It is characteristic that the severity of the effect did not depend on the doping of titanium oxide with silver.

Summing up the obtained results, it can be concluded that besides photoactive, the nanocomposites with also possess biological activity because of Ag nanoparticles and silver ions, in addition to oxygen-containing radicals, exhibit antibacterial activity by replacing Mg^{2+} or Ca^{2+} ions in the bacterial membrane with Ag^{+} ions, forming a complex with thiol groups of the cell membrane. This leads to bacterial death and complete disruption of their cellular structure [2, 6, 7, 9].

Thus, in our work together with photocatalytic and biological activity we presented comparative toxicological and hygienic assessment of TiO_2 and TiO_2-Ag nanophotocatalyst compared to authors [2–4, 6, 7, 9]. Based on the conducted hygiene and experimental research, the preventive recommendations were developed to prevent the adverse effects of TiO_2 and TiO_2-Ag nanopowders on the bodies of synthesis operators working in the production of TiO_2 and TiO_2-Ag nanopowders using a multi-section rotary kiln. The calculated maximum permissible concentration (MPC) for nano-TiO_2 is 0.3 mg/m^3, and for nano-TiO_2-Ag, it is 0.2 mg/m^3. The level of risk from the harmful effects of TiO_2 and TiO_2-Ag nanopowders on the synthesis operator's workplace, assessed as average, was determined based on the toxicity of the nanoaerosol and the exposure to nanoaerosol at the synthesis operator's workplace. The conducted experimental toxicological, virucidal and production hygiene studies allowed for the scientific justification and implementation of a range of health measures, including medical-biological, organizational, sanitary-technological, individual, and other measures. Moreover, the obtained parameters of MPC, CC_{50}, LD_{50} and hazard class of chemical substances can be basis of certification synthesized nanomaterials for biosafety.

Due to their structural-morphological, physicochemical, toxicological properties, and biological activity, the synthesized nano-TiO_2 and nano-TiO_2-Ag are promising nanomaterials for use in biology and medicine.

Conclusions

1. It has been stated that the nano-composite TiO_2-Ag exhibited distinct physicochemical characteristics. Spectral methods confirmed the modification of anatase during the synthesis of TiO_2, TiO_2-Ag. Defects (Ti^{4+}, OH, oxygen vacancies, etc.) detected on the surface of nano-TiO_2 could act as active centers, allowing for modification with Ag nanoparticles to enhance virucidal and biocompatible properties. A comparison of the optical and photocatalytic properties of Ag-modified TiO_2 (with a 4 % concentration of Ag on the anatase surface) suggests the prospective use of TiO_2-Ag nanomaterial in biology and medicine due to its morphology and surface structure.

2. On the condition of acute intraperitoneal administration of nanopowders, LD_{50} for nano-TiO_2 was 4783.30 mg/kg, while LD_{50} for nano-TiO_2-Ag was 724.44 mg/kg. Toxicity and hazardousness were higher for the nano-TiO_2-Ag composite compared to nano-TiO_2. Based on LD_{50} values, nano-TiO_2

corresponds to hazard class 4 (slightly hazardous), while nano-TiO_2-Ag belongs to hazard class 3 (moderately hazardous). Upon repeated (28-fold) intragastric administration of nano-TiO_2, a weakly pronounced accumulation was noted. Nano-TiO_2 and nano-TiO_2-Ag do not cause skin irritation, evoke mild conjunctival irritation, and may induce a slightly pronounced sensitizing effect. These nanoparticles accumulate in the tissues of internal organs and damage the liver, kidneys, and lungs upon intraperitoneal administration. In in vitro conditions, nano-TiO_2 and nano-TiO_2-Ag enhance the functional activity of peripheral blood mononuclear cells, inducing the production of cytokines IL-1, IL-6, and TNF-α ($p<0.05$), indicating their potential influence on chronic inflammation formation, as well as increasing IL-4 production ($p<0.05$), suggesting a potential allergenic effect for synthesis operators. Nano-TiO_2 and nano-TiO_2-Ag exert damaging effects on male rat reproductive cells, with sperm survival being the most sensitive marker.

3. It was demonstrated that nano-TiO_2 and nano-TiO_2-4 %Ag at a concentration of 100 μg/ml were toxic to MDCK and BHK-21 cells. The cytotoxic concentration that inhibits cell viability by 50 % (CC_{50}) in MDCK cells was 50 μg/ml for nano-TiO_2 and 52 μg/ml for nano-TiO_2-4 %Ag. In BHK-21, these values were 81 μg/ml and 62 μg/ml, respectively.

4. The virucidal action of nanoparticles was investigated. A reduction in the infectious herpes virus titer by 5.0 $\log_{10}$ $TCID_{50}$/ml was observed after 1 h of contact, and a decrease of 7.5 and 7.9 $\log_{10}$ $TCID_{50}$/ml titer for influenza type A virus was achieved for nano-TiO_2 and nano-TiO_2-Ag, respectively.

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