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THE ANTIVIRAL ACTIVITY OF CERIUM AND LANTHANUM NANOOXIDES MODIFIED WITH SILVER

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Today, the antiviral activity of oxide nanomaterials can be used in the fight against the viral disease COVID-19. It is thought that Ag nanoparticles may bind to the surface glycoprotein of the virus and interfere with the virus's interaction with epithelial cells, and inhibit virus reproduction by releasing silver ions in the cell. The viruses' inhibition with RNA (ribonucleic acid) and DNA (deoxyribonucleic acid) genomes by oxide nanocomposites action was presented.

In this research, the surface structure of doped CeO_2 (La_2O_3) was studied by nitrogen adsorption-desorption based on BET method. The silver atom's existence in CeO_2 - Ag^0 can facilitate the transport of more holes to the surface and can enhance the optical, antivirus activity. The primary particle size of pure cerium dioxide is 7 nm, for CeO_2 - Ag composite at 2 and 4 wt. % of silver is 6.5 and 6.9 nm; for La_2O_3 - Ag 27 and 35 nm, respectively.

Cell viability was assessed using an MTT (3-(4,5-Dimethylthiazol 2-yl)-2,5-diphenyltetrazolium bromide) assay after NPs (nanoparticles) exposure, since only viable cells have functional mitochondrial dehydrogenase enzymes that can reduce MTT to formazan. Nanoparticles were non-toxic for BHK-21(Syrian hamster kidney), Hep-2 (Human larynx carcinoma), and MDCK (Canine kidney) cells in concentrations of 10 and 100 μg/ml, while cell viability was within 76÷100 %. La_2O_3 and CeO_2, which contained 4 wt. % of Ag at a concentration of 1000 μg/ml had a lower toxic effect: for BHK-21 cells 68 and 76 % of viable cells, respectively; for Hep-2 - 40 and 36 %, for MDCK - 42 and 48 %; La_2O_3 and CeO_2 with 2 and 5 wt. % of Ag at a concentration of 1000 μg/ml were highly toxic. The level of BHK-21, Hep-2, and MDCK cells viability was in a range of 7 to 37 %.

It has been stated that oxides of cerium and lanthanum have a pronounced virucidal action against the Herpes simplex virus and Influenza A virus by completely inhibiting the development of its cytopathic action. The lanthanum and cerium oxides with 2 and 5 wt. % of silver inhibited the development of the virus's CPE by more than 5.0 log_{10} compared to the virus control. The results show that lanthanum and cerium oxides with 2 and 5 wt. % silver have a high virucidal effect against herpes simplex virus type 1. A 1.0÷4.0 log_{10} reduction in the infectious titer of the Herpes virus synthesized "de novo" in the presence of lanthanum and cerium oxide nanocomposites has been shown.

Keywords: *cytotoxicity, adenovirus, Herpes simplex virus, Influenza A virus, antiviral activity, virucidal action, CeO_2-Ag, La_2O_3-Ag*

INTRODUCTION

Viral infections are one of the principal causes of mortality in the entire world that result in significant human, social, and economic costs. Today, omicron, the most recent SARS-CoV-2 variant of concern, harbors multiple mutations in the spike protein. Initial studies suggest that omicron substantially reduces the neutralizing capability of antibodies induced from COVID-19 vaccination or previous infection [1].

Currently, the attention of scientists is paid to modern research devoted to the development of a new generation of antimicrobial agents with low toxicity and antiviral prolonged action [2]. In this case, metal oxides doped with noble and rare earth elements are frequently used composite materials. As a rule, multicomponent systems demonstrate high antibacterial activity and synergistic effect compared to the individual oxides [3, 4]. The functional materials based on cerium and titanium oxides are widely used due to their photocatalytic properties for the destruction of various contaminants and wastewater treatment and biomedical aims because of their antiviral and bactericidal activity.

The different kinds of methods, including shape, size, and facet control, element doping have been developed to effectively enhance the photocatalytic performance through increasing

the broad absorption of sunlight, prolonging the lifetime of photo-induced carriers, and enhancing the optical activity and photocatalytic stability of CeO_2, TiO_2, and ZnO [4–8]. Noble metal nanoparticles (NPs) can show SPR (surface plasmonic resonance), which can be tailored by engineering the shape, size, and surroundings. Therefore, noble metal NPs can not only strongly absorb visible light but also can serve as an electron sink and source of active reaction sites [9–18, 20–23].

The cytotoxicity determination of synthesized oxides with different percentages of Ag is an integral component of any drug development process. The research is carried out using an MTT assay [17, 23]. The cytotoxicity of CeO_2 and Ag NPs has been studied separately [22]. It was found that the effects on hepatocyte fish (primary) and human cell line (C3A) were 250 μg/ml of Ag NPs, while 1000 μg/ml of CeO_2 NPs did not cause cytotoxicity for both [23]. At the same time, the bactericidal, fungicidal, and antiviral properties of silver are well known and successfully used in practice.

On the other hand, nanosized cerium oxide (nanoceria) can take part into the membrane formation in biological processes, and the water purification [16, 18–20, 21–23], in particular, as a regulator of reactive oxygen species and a free radical scavenger. Moreover, the photocatalytic activity of CeO_2 nanotubes and nanoparticles is comparable to commercial TiO_2 (*P25*) [19]. A comparative study of the absorption and toxicity effect of silver and cerium dioxide nanoparticles from a contaminated environment proved a decrease in sensitivity in the series: nano-Ag > micro Ag > nano CeO_2 = micro CeO_2. As such, cerium dioxide nanoparticles increased the immunogenicity of the influenza vaccine [20].

The CeO_2, TiO_2, and La_2O_3 with concentration Ag of 4 wt. % inhibited the growth processes of prokaryotic cells of *E. coli, Bacillus sp*., and *S. aureus* [4, 25].

Inactivation efficiency of H1N1 (*Influenza virus*) by Cu, TiO_2, Ag and Au nanoparticles has been shown due to their interaction with nucleic acids or thiol groups of proteins. These proteins are essential for the admission of the virus into host cells, such as lymphocytes, by binding to CD4 receptors [18].

Cursten Weiss *et al.* [2] show that noble metal (Ag, Au, Pt) / oxide nanocomposites have a wide application to the SARS-COV2 antiviral photodynamic and thermal therapy due to surface plasmon resonance during heating or irradiation process (≥ 400 nm).

Thus, the potential of nanomaterials based on CeO_2 and La_2O_3 has attracted interest in approaches to viral infections since they can be designed to act directly against viruses. Various tests must take place *in vitro* and *in vivo* to apply these nanostructures in new therapies or vaccines with blocking active receptors of a virus by stopping the rapid action of its particles on the immune system and optimize better constructions and avoid toxic effects on the body. It is important to deepen our knowledge about antiviral mechanisms too.

The purpose of this work is a comparative study of cytotoxicity and antiviral activity on RNA and DNA models of genomic viruses of CeO_2-Ag and La_2O_3-Ag nanocomposites for biomedical application.

OBJECTS AND METHODS

Synthesis of the lanthanum and cerium oxides doped by silver with different concentrations was performed using the chemical precipitation method [3, 4, 25]. Results of the morphological study, surface characteristics and spectral analysis are present in [3, 25].

BET surface area of CeO_2-Ag and La_2O_3-Ag nanopowders were performed using a Micromeritics ASAP 2000 BET surface analyser. The values of surface area varied from 2.4 to 8.0 m^2/g.

Cell cultures MDCK, BHK-21 (clon 13) and Hep-2 were used in experiments [26]. The *Influenza A virus* (H1N1) (strain FM/1/47), *Herpes simplex virus* type 1 (HSV-1/US) were obtained from the collection of the Institute of Epidemiology and Infectious Diseases of the Academy of Medical Sciences of Ukraine and human adenovirus serotype 2 (HAdV2) was obtained from the Institute of Microbiology, Medical University of Budapest. Cells were cultured in 45 % Dulbecco's Modified Eagle's Medium (DMEM, Sigma, USA) and 45 % RPMI-1640 (Sigma, USA) with 10 % (v/v) fetal bovine serum (FBS, Sigma, USA) and 100 U/ml gentamycin.

Cell viability was assessed using an MTT (3-(4,5-Dimethylthiazol2-yl)-2,5-diphenyltetrazolium bromide) assay after NPs exposure, since only viable cells have functional mitochondrial dehydrogenase enzymes that can reduce MTT to

formazan. The viability (%) of the treated cells was defined as the percentage of absorbance compared to control untreated cells (100 % viability). The percentage of cell viability under the condition of NPs action was calculated as in work [17].

The synthesized virus "*de novo*" is a virus obtained in the cells due to the presence of nanoparticles. The determination of infectious titres of viruses formed *"de novo"*. Infectious titers of viruses synthesized in the presence of silver-doped lanthanum and cerium oxides were determined by the endpoint of virus dilution causing 50 % cytopathogenic effect (CPE) on cells [27]. To determine the titres of viruses synthesized "*de novo*", cells were infected and, after adsorption, nanoparticles were introduced in dilutions of 1:10÷1:1000. After 3–4 days of cultivation, the cells were frozen three times, centrifuged for 20 min at 3000 rpm, and the cell sediment was removed, serial 10-fold dilutions were prepared and a monolayer of cells was infected with them. After 3–4 days of cultivation, MTT solution was added to the wells and the optical density of the samples was determined. The virus dilution that reduces the optical density of the sample compared to the optical density of the cell control by 50 % is the virus titre and is expressed as $\log_{10}$TCID50/ml (decimal logarithms of 50 % tissue cytopathic doses in ml). The index of inhibition of virus reproduction (IPR) was calculated according to the formula:

$$I = \textit{Virus titer control} - \textit{Virus titer experiment } (\log_{10}) \quad (1)$$

RESULTS AND DISCUSSION

Raman spectra. It is well known that Raman spectroscopy is sensitive to the short-range order, to the chemical bond itself, spectral modifications (wavenumber, width, intensity) of disordered materials, such as nanomaterials (La_2O_3, La_2O_3-Ag) can be used to characterize them. Therefore, Raman spectroscopy is widely used to characterize nanomaterials such as heterogeneous catalysts too. In this part, spectral modifications observed for nanocrystallized CeO_2 (CeO_2-Ag) are discussed [25].

CeO_2 crystallizes in the cubic fluorite structure with the major band at 458 cm^{-1} corresponding to the space group O_h^5 (Fm3m-cubic crystal system). Group theory predicts one triply degenerate Raman active optical phonon (F_{2g} symmetry) and one infrared-active optical phonon (F_{1u} symmetry), which presents either LO or TO character (with different wavenumbers) depending on the relative propagation/polarization directions of the mode [21]. So, one can notice, that each cerium(IV) ion (Ce^{4+}) is coordinated by eight oxygen (O^{2-}) ions.

We observed broadening and shift of a peak in the short-wave region to 449 cm^{-1} in doped CeO_2. The argentum can be a promoter of oxygen vacancies in CeO_2. As for TiO_2-Ag [17], when silver is contacting with CeO_2, electrons will transfer from CeO_2 to silver. So, these electrons transfer to silver and loads on the surface of silver will be scavenged by the electron acceptor, so decreases the recombination between electrons and holes, thereby silver atoms act as electron traps. Thus, the silver atom's existence in CeO_2-Ag^0 can facilitate the transport of more holes to the surface and can enhance the optical, antiviral and bactericidal activity [4, 25].

The possible silver-ceria interaction is connected with the morphology and size effects of both Ag and CeO_2 particles, concentrations of oxygen vacancies in their structures [25]. The Ce^{4+} oxidation state is regarded as more stable than Ce^{3+} due to Ce^{4+} electronic structure ($[Xe]4f^0$), which is more stable than that of Ce^{3+} ($[Xe]4f^1$). Moreover, the transition between Ce^{3+} and Ce^{4+} accompanies the process of oxygen vacancy formation. In the case of a cubic fluorite structure, atoms of oxygen can quickly diffuse since they are all in one plane [5, 25, 27, 28].

As such, defects created during the incorporation of La^{3+} can promote of formation of labile oxygen vacancies, connected to this relatively high mobility of bulk oxygen species within the lattice cell thereby enhancement in the ceria reducibility. However, since both CeO_2 and La_2O_3-CeO_2 samples exhibit the same reactivity of lattice oxygen (the same values of hydrogen consumption), it can be excluded formation of solid solution as a result of the diffusion of La^{3+} into ceria lattice. According to Xue *et al*. [29], the incorporation of La^{3+} into ceria lattice at Ce^{4+} sites led to the formation of solid solution because La^{3+} with a big radius of 0.11 nm can expand structure of ceria leading to the higher specific surface area.

Cytotoxicity test. Modern medicine is beginning to actively use nanotechnology in clinical diagnostics, targeted drug delivery, cancer treatment by hyperthermia and other fields. Biocompatibility, toxicity and ability to penetrate cells are the main criteria that determine the effectiveness of nanoparticles in medicine [2, 17, 21–23]. Nevertheless, the toxicity of nanostructured materials is an open issue due to several factors, such as high reactivity, intrinsic toxicity of the material, and non-specific interactions with biological objects, that are determined by particle shape, size and structure.

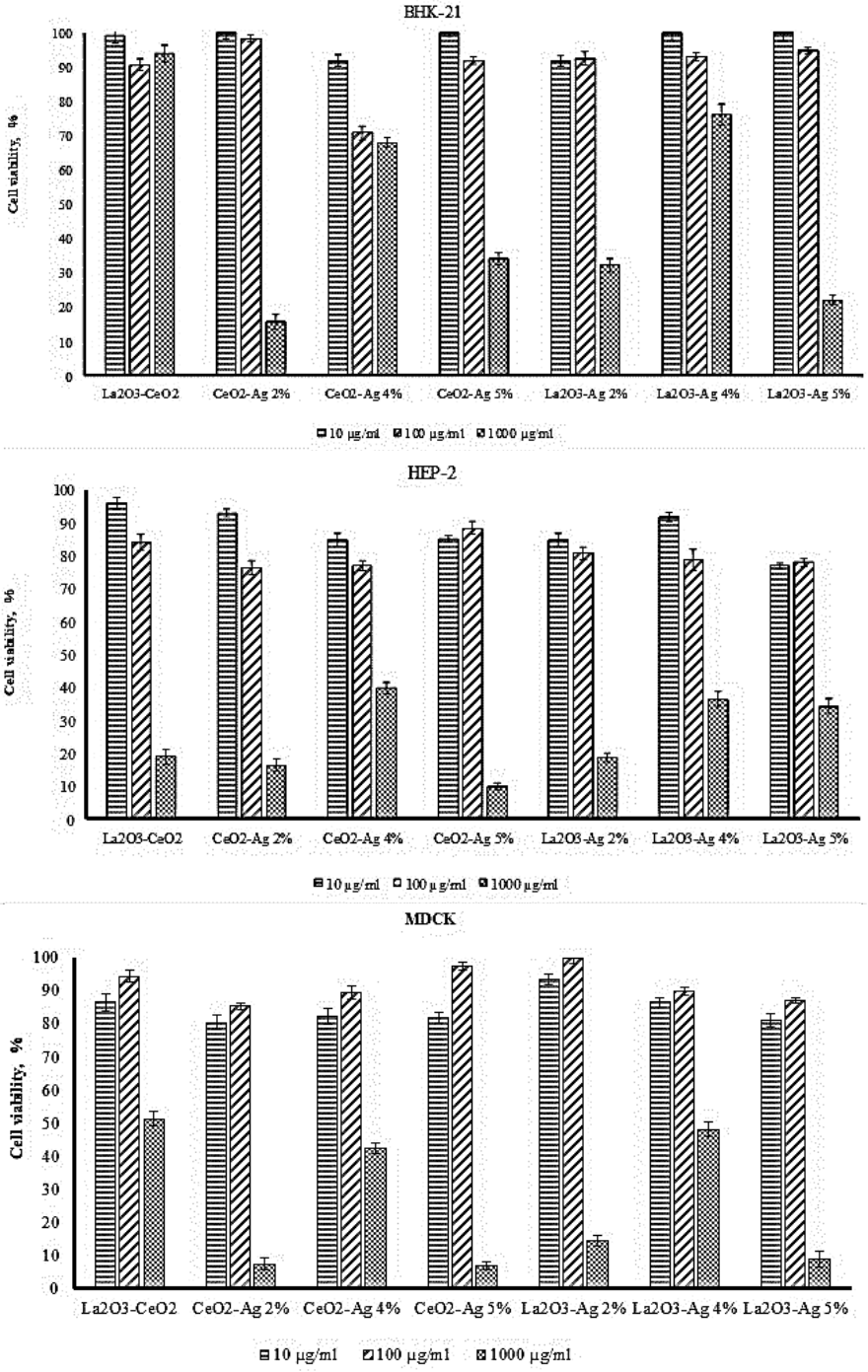

Fig. 1. Cytotoxicity of La_2O_3 and CeO_2 with different concentrations of Ag. Toxic effect evaluated by MTT assay after 72 h exposure of NPs on BHK-21, Hep-2 and MDCK cells. Values represent the mean ± S.D. for three independent experiments. Control untreated cells – 100 % viability

The MTT test is the most commonly used method for assessing the toxicity of substances *in vitro* [17, 23]. Fig. 1 shows the dose-dependent effect of silver-doped La_2O_3 and CeO_2 nanoparticles on cell viability. At the high concentration of 1000 μg/ml, quite different cell viability from 10 to 94 % was observed.

Nanoparticles were non-toxic for BHK-21, Hep-2, and MDCK cells in concentrations of 10 and 100 μg/ml, while cell viability was within 76÷100 %. La_2O_3 and CeO_2, which contained 4 wt. % of Ag at the concentration of 1000 μg/ml had a lower toxic effect: for BHK-21 cells 68 and 76 % of viable cells, respectively; for Hep-2 – 40 and 36 %, for MDCK – 42 and 48 %. On the other hand, La_2O_3 and CeO_2 with 2 and 5 wt. % of Ag at the concentration of 1000 μg/ml were highly toxic. The level of BHK-21, Hep-2, and MDCK cells viability was in the range from 7 to 37 %.

Infectious titer of different type viruses synthesized "de novo". The antiviral effect of nanoparticles was studied by determining the titer of the virus synthesized "*de novo*" [27]. *Herpes simplex virus* type I (HSV-1) is the causative agent of several pathologies ranging in severity from the common cold sore to life-threatening encephalitic infection. The virion of Herpes virus consists of an external membrane envelope, a protein aceous layer called the tegument, and an icosahedral capsid containing the double-stranded linear DNA genome [30].

It is well known that *Herpes simplex virus* 1 (HSV-1) has a double stranded linear DNA genome. As can be seen from the Table 1, lanthanum and cerium oxides without the addition of silver turned out to be the most effective against *Herpes simplex virus* type 1. At minimal dilution, complete suppression of CPE development was detected (by $4\log_{10}$). In a higher dilution, inhibition of CPE development decreased to $1.12\log_{10}$.

Table 1. Infectious titer of *Herpes simplex virus* type 1 (HSV 1 strain), synthesized *de novo* in the presence of nanocomposites

Virus titers and virus reproduction inhibition index (IPR) for a series dilutions of nanoparticles*						
Dilution	**100**		**1000**		**10000**	
Nanocomposites	**TCID50/ml, $\log_{10}$**	**IPR, $\log_{10}$**	**TCID50/ml, $\log_{10}$**	**IPR, $\log_{10}$**	**TCID50/ml, $\log_{10}$**	**IPR, $\log_{10}$**
La_2O_3-CeO_2	0	4	3.98	0.02	2.88	1.12
CeO_2-Ag 2 %	3.37	0.63	3.45	0.55	3.99	0.01
CeO_2-Ag 4 %	3.25	0.75	3.23	0.77	4.08	0
CeO_2-Ag >5 %	3.9	0.1	3.86	0.14	4.04	0
La_2O_3-Ag 2 %	4.26	0	4.46	0	3.94	0.06
La_2O_3-Ag 4 %	4.07	0	3.12	0.88	3.28	0.72
La_2O_3-Ag >5 %	4.21	0	3.84	0.16	3.58	0.42

*The titer of herpes virus in the control, without use of nanoparticles was 4 $\log_{10}$ TCID 50/ml

Cerium oxides with different silver content (2 and 4 wt. %) inhibited the development of the cytopathic effect of the virus by 0.55÷0.75 $\log_{10}$. Oxides based on lanthanum with different silver content did not have an inhibitory effect on the herpes virus.

The determination of the virucidal action was the interaction of the test sample with an extracellular virus. Equal volumes of virus and sample were kept for 1 h, and then the material was added to the cells. The efficiency of metal oxides was determined compared to the control of the virus. Metal oxides CeO_2-2 %Ag, CeO_2-Ag>5 %, La_2O_3-Ag>5 % and La_2O_3-2 %Ag had a pronounced virucidal effect against herpes simplex virus type 1 (Fig. 2). These samples completely inhibited the development of cytopathic action of the herpes virus, reducing the titer by $5.19\log_{10}$.

However, lanthanum and cerium oxides without silver and with 2 wt. % silver inhibited the development of CPE by only $0.75\div0.95\log_{10}$ compared to virus control. The obtained results show that lanthanum and cerium oxides of 4 and 5 wt. % are highly effective in the virucidal scheme of research, in the absence and reduction of silver content, this virucidal effect decreased.

The influenza virion is spherical or close to spherical in shape, 100–120 nm in diameter. Virus genome contains a segmented RNA with

eight segmented genes of different lengths such as PB2, PB1, PA, HA, NP, NA, *etc*. The genome is surrounded by a lipid bilayer containing two viral glycoproteins, hemagglutinin and neuraminidase [31]. The maximum reduction in infectious titer of influenza A virus (IAV) was observed with a minimum CeO_2-Ag>5 % dilution, and the value was 1.5log_{10} and no inhibition of virus reproduction was observed at higher dilutions (Table 2).

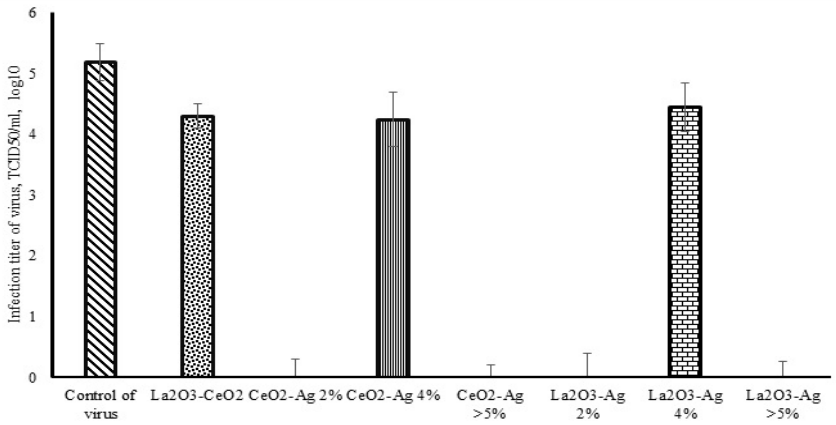

Fig. 2. Virucidal action of lanthanum and cerium oxides with silver content. Infectious titer of *Herpes simplex virus* of type 1 in the presence of NPs

Table 2. Infectious titer of *Influenza A* virus (strain A/FM/1/47), synthesized *de novo* in the presence of nanocomposites

Virus titers and virus reproduction inhibition index (IPR) for a series dilutions of nanoparticles*						
Dilution	**100**		**1000**		**10000**	
Nanocomposites	**TCID50/ml, log_{10}**	**IPR, log_{10}**	**TCID50/ml, log_{10}**	**IPR, log_{10}**	**TCID50/ml, log_{10}**	**IPR, log_{10}**
La_2O_3-CeO_2	7.56	0	7.27	0	7.44	0
CeO_2-Ag 2 %	6.50	0.26	7.37	0	7.71	0
CeO_2-Ag 4 %	7.48	0	7.79	0	6.26	0.5
CeO_2-Ag >5 %	5.24	1.52	7.52	0	7.09	0
La_2O_3-Ag 2 %	6.64	0.12	7.67	0	7.49	0
La_2O_3-Ag 4 %	7.68	0	7.62	0	7.41	0
La_2O_3-Ag >5 %	5.89	0.87	5.88	0.88	6.20	0.56

*The titer of *Influenza A virus* in the control without the use of nanoparticles was 6.76 log_{10} $TCID_{50}$/ml

It was shown, that the reduction of infectious titer of IAV in the experiment with La_2O_3-Ag > 5 wt. % ranged from 0.56 to 0.88log_{10}. Cerium and lanthanum oxides with lower silver content did not reduce the infectious titer of the IAV. All investigated metal oxides inhibited the development of CPE of the virus upon extra-clinical contact with the virus for 1 h (the virucidal effect, Fig. 3). Thus, cerium and lanthanum oxides of 2 and 5 % completely suppressed the reproduction of the virus and the infectious titer of the *Influenza virus* by 6.88log_{10}. This effect was observed regardless of the type of metal (cerium or lanthanum). The studied oxides without silver and 5wt. % of silver nanoparticles reduced the infectious titer of the virus by 2.01÷2.06log_{10} compared to the control virus.

Adenoviruses are medium-sized (90–100 nm), non-enveloped viruses with icosahedral nucleocapsid containing a double-stranded DNA genome. The viral capsid has the form of an icosahedron and is composed of 252 capsomers. Of these, 240 have a six-fold symmetry and are therefore called hexons. Twelve capsomers have five-fold symmetry, pentons and produce the particle corners. From every corner, an antenna-like fibre is protruding. This fibre is a glycoprotein that varies in length of adenoviruses belonging to different

subgroups. The fibre acts as the most important receptor-binding structure. Many of the other peptides function ascent and couple hexon and penton capsomers to a dense capsid [32].

The influence of nanoparticles on the reproduction of human adenovirus type 2 was investigated. As can be seen in Table 3, the nanoparticles La_2O_3-Ag > 5wt. % had the highest antiviral activity in the range of 0.83 to 1.0$\log_{10}$ for material dilutions of 1:100 and 1:1000, respectively (Table 3). The La_2O_3-CeO_2 nanoparticles inhibited virus infectivity (1:1000 and 1:10000 dilutions) by ≥ 0.86$\log_{10}$.

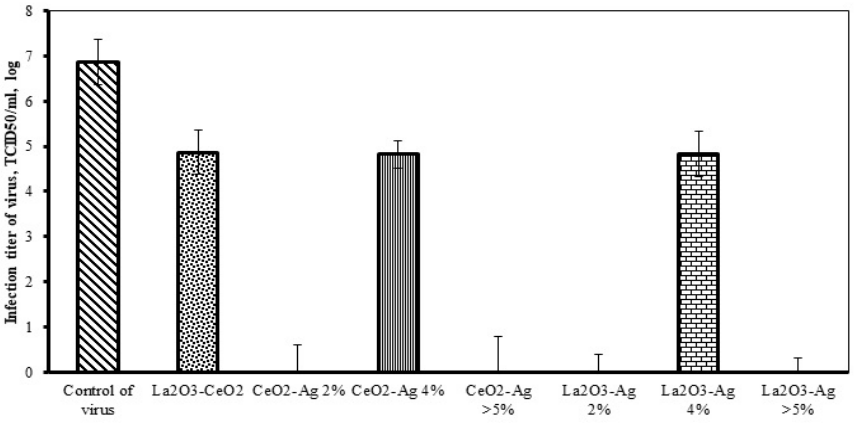

Fig. 3. Virucidal action of lanthanum and cerium oxides with silver content. Infectious titer of *Influenza A* virus in the presence of NPs

Table 3. Infectious titer of human adenovirus type 2 (HAdV2), synthesized *de novo* in the presence of nanocomposites

Virus titers and virus reproduction inhibition index (IPR) for a series dilutions of nanoparticles*						
Dilution	**100**		**1000**		**10000**	
Nanocomposites	**TCID50/ml, $\log_{10}$**	**IPR, $\log_{10}$**	**TCID50/ml, $\log_{10}$**	**IPR, $\log_{10}$**	**TCID50/ml, $\log_{10}$**	**IPR, $\log_{10}$**
La_2O_3-CeO_2	6.12	0	5.12	0.87	5.13	0.86
CeO_2-Ag 2 %	6.21	0	5.36	0.63	6.18	0
CeO_2-Ag 4 %	6.11	0	6.1	0	6.02	0
CeO_2-Ag >5 %	6.19	0	6.04	0	6.04	0
La_2O_3-Ag 2 %	6.04	0	5.23	0.76	5.19	0.8
La_2O_3-Ag 4 %	6.09	0	5.16	0.83	6.1	0
La_2O_3-Ag >5 %	5.16	0.83	4.99	1.0	5.96	0.03

*The titer of HAdV2 in the control, without use of nanoparticles was 5.99 $\log_{10}$ $TCID_{50}$ / ml

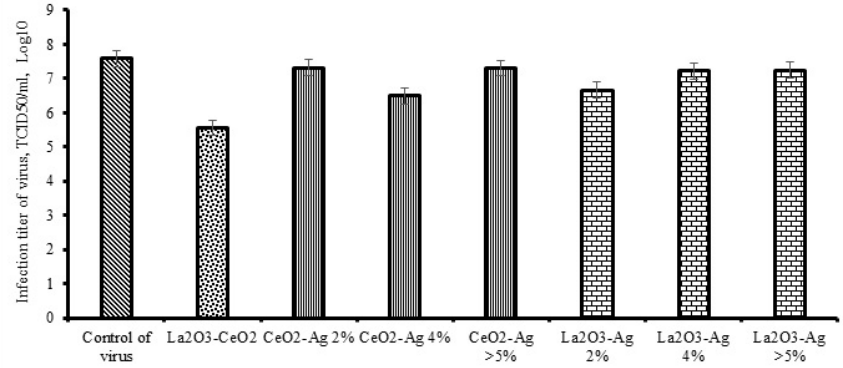

Fig. 4. Virucidal action of lanthanum and cerium oxides with silver content. Infectious titer of human adenovirus type 2 in the presence NPs

All doped nanoparticles had very low virucidal activity against HAdV2 (Fig. 4); only La_2O_3-CeO_2 reduced the virus titer by $2\log_{10}$, which is considered sufficient to consider the substance virucidal. La_2O_3 with 2 wt. % of silver reduced the virus titer by $0.9\log_{10}$, and CeO_2-Ag 4% by $1.1\log_{10}$.

CONCLUSIONS

Thus, nanosized powders of pure cerium, lanthanum oxides and composites based on them doped with silver were chosen to perform the antiviral activity study. The features of the silver-ceria interaction is connected with the morphology and size effects of both Ag and CeO_2 particles, concentrations of oxygen vacancies in the ceria structure, and possible redox properties that are caused by the interplay between Ag^+/Ag^0 and Ce^{3+}/Ce^{4+} pair.

All studied nanocomposites were non-toxic for BHK-21, Hep-2 and MDCK cells, as concentrations of 10 and 100 μg/mL inhibited cell viability maximum of 28 %.

It was stated that oxides of lanthanum and cerium with a silver content of 2÷4 wt. % have pronounced virucidal action against *Herpes simplex virus* type 1 (US strain) and completely inhibit development of its cytopathic action without UV action. The anti-herpetic effect of lanthanum and cerium oxides, which reduce the infectious titers of the "*de novo*" synthesized virus by $1.0\div4.0\ \log_{10}$, is shown, which indicates their high efficiency. Metal oxides CeO_2-2 % Ag, CeO_2-Ag > 5 %, La_2O_3-Ag > 5 % and La_2O_3-2 % Ag had a pronounced virucidal effect against *Herpes simplex virus* type 1, they inhibited the development of cytopathic action of the herpes virus, reducing the titer by $5.19\ \log_{10}$.

The maximum reduction in infectious titer of *Influenza A* virus (strain A/FM/1/47) was observed with a minimum CeO_2-Ag > 5 % dilution, and the value was $1.5\log_{10}$. The reduction of infectious titer IAV with La_2O_3-Ag > 5 wt. % ranged from 0.56 to $0.88\log_{10}$. All investigated metal oxides inhibited the development of CPE of the virus upon extra-clinical contact with the virus for 1h (virucidal effect). Cerium and lanthanum oxides of 2 % and 5 % completely suppressed the reproduction of the virus and the infectious titer of the influenza virus by $6.88\ \log_{10}$.

The nanoparticles of La_2O_3-Ag > 5 wt. % had the highest anti-adenoviral activity *Human Adenovirus* type 2 in the range of 0.83 to $1.0\log_{10}$ for material dilutions of 1:100 and 1:1000, respectively. Other nanoparticles, except CeO_2-Ag 4 wt. % and CeO_2-Ag > 5 wt. %, showed insignificant anti-adenoviral activity. All doped nanoparticles had very law virucidal activity against HAdV2; only La_2O_3-CeO_2 reduced the virus titer by $2.0\ \log_{10}$.

The ability of the investigated nanostructures CeO_2-Ag and La_2O_3-Ag to destroy the lipid envelope of *Herpes simplex* virus type 1 and *Influenza A* viruses without irradiation can be the prospect of antiviral action against viruses with a supercapsid such as the SARS-Cov-2 strain.

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Сьогодні противірусну активність оксидних наноматеріалів можна використовувати в боротьбі з вірусним захворюванням COVID-19. Вважається, що наночастинки Ag можуть зв'язуватися з поверхневим глікопротеїном вірусу та перешкоджати взаємодії вірусу з епітеліальними клітинами, а також пригнічувати репродукцію вірусу шляхом вивільнення іонів срібла в клітині. Показано інгібування вірусів геномами РНК (рибонуклеїнова кислота) і ДНК (дезоксирибонуклеїнова кислота) дією оксидних нанокомпозитів.

У цьому дослідженні структуру поверхні легованого CeO_2 (La_2O_3) вивчали методом адсорбції-десорбції азоту на основі методу БЕТ. Наявність атомів срібла в CeO_2-Ag^0 може сприяти транспортуванню більшої кількості дірок на поверхню та посилювати оптичну й антивірусну активність. Первинний розмір частинок чистого діоксиду церію становить 7 нм, для композиту CeO_2-Ag при 2 і 4 мас. % срібла 6.5 і 6.9 нм; для La_2O_3-Ag 27 і 35 нм відповідно.

Життєздатність клітин оцінювали за допомогою аналізу МТТ (3-(4,5-диметилтіазол-2-іл)-2,5-дифенілтетразолію бромід) після експозиції НЧ (наночастинок), оскільки лише життєздатні клітини мають функціональні ферменти мітохондріальної дегідрогенази, які можуть відновлювати МТТ до формазану. Наночастинки були нетоксичними для клітин ВНК-21 (нирка сирійського хом'яка), Нер-2 (карцинома гортані людини) та MDCK (нирка собаки) у концентраціях 10 та 100 мкг/мл, а життєздатність клітин була в межах 76÷100 %. Меншу токсичну дію мають La_2O_3 та CeO_2, які містять 4 мас. % Ag у концентрації 1000 мкг/мл: для клітин ВНК-21 68 та 76 % життєздатних клітин відповідно; для Нер-2 - 40 і 36 %, для MDCK - 42 і 48 %; La_2O_3 та CeO_2 з 2 та 5 мас. % Ag у концентрації 1000 мкг/мл були високотоксичними. Рівень життєздатності клітин ВНК-21, Нер-2 та MDCK знаходився в діапазоні від 7 до 37 %.

Встановлено, що оксиди церію та лантану мають виражену віруліцидну дію щодо вірусу простого герпесу та вірусу грипу А шляхом повного пригнічення розвитку його цитопатичної дії. Оксиди лантану та церію з 2 та 5 мас. % срібла пригнічували розвиток CPE (цитопатичний ефект) вірусу більш ніж на 5.0 log_{10} у порівнянні з контролем вірусу. Результати показують, що оксиди лантану та церію з 2 та 5 мас. % срібла мають високу віруліцидну дію проти вірусу простого герпесу типу 1. Зменшення інфекційного титру вірусу герпесу, синтезованого "de novo" на 1.0÷4.0 log_{10}, відбувається у присутності нанокомпозитів лантану та церію.

Ключові слова: *цитотоксичність, аденовірус, герпес вірус, вірус грипу А, антивірусна активність, віруліцидна дія, CeO_2-Ag, La_2O_3-Ag*

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