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GREEN SYNTHESIS OF ANTIBACTERIAL CERIUM OXIDE NANOPARTICLES USING *MAGNOLIA KOBUS* LEAVES EXTRACT

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The aim of this work was to synthesize cerium oxide nanoparticles (CeO_2-NPs) using the Magnolia kobus leaves extract, to determine the composition of the extract and the participation of its components in the synthesis of NPs, to study the morphology and structure of the obtained NPs, to investigate their antibacterial activity. The composition of the plant extract and involving of its components in green synthesis of CeO_2-NPs was studied by high-performance liquid chromatography (HPLC) and matrix-assisted laser/desorption ionization mass spectrometry (MALDI MS). It has been shown that the extract contained phenolic compounds (derivatives of simple phenols, flavonoids, hydroxybenzoic and hydroxycinnamic acids, lignans, coumarins), as well as carotenoids, chlorophylls, terpenoids and sterols. The composition of the liquid phase from the reaction mixture (reaction liquid) after the NPs formation was studied to determine the components of the extract involved in the synthesis of CeO_2-NPs. According to the results of HPLC and MALDI MS studies, significant differences were found in the composition of the plant extract and the reaction liquid: hydroxybenzoic acids, flavonoids and terpenoids disappeared or their concentration was significantly decreased, the content of lignans changed to a lesser extent, and it was observed the appearance of hydrophilic low-molecular compounds probably formed as a result of synthesis and stabilization of NPs. Synthesized CeO_2-NPs were characterized by means of scanning electron microscopy (SEM) and X-ray diffraction (XRD). According to SEM and XRD, CeO_2-NPs had a crystalline structure and were of spherical shape; the average size of the crystallites was ~ 20 nm, and the diameter of the primary particles was 50 ± 10 nm. It has been found that hydroxybenzoic acids, flavonoids and terpenoids are active participants in the green synthesis of CeO_2-NPs in the presence of Magnolia kobus leaves extract, while lignans (fargesin/kobusin and eudesmin) are involved in less extent in the reduction/stabilization of CeO_2-NPs. The synthesized particles possess antibacterial properties and can be used in the preparation of materials for medical and biological purposes.

***Keywords**: plant extract, phenolic compounds, green synthesis, cerium oxide nanoparticles; MALDI MS, HPLC, antibacterial activity*

INTRODUCTION

Cerium is one of the most reactive metals that can oxidize readily. Due to the special electronic structure, the oxidized form of cerium varies between CeO_2 and Ce_2O_3. Ce_2O_3 is an unstable form and it turns into CeO_2 [1]. Cerium oxide nanoparticles (CeO_2-NPs) exhibit unique physical and chemical properties. The positive charge on the surface of CeO_2-NPs allows them to be functionalized, thus expanding their area of application (catalysis, medicine, electronics, *etc*.). CeO_2-NPs demonstrate antioxidant, antitumor, antibacterial and antiviral properties, reduce ischemic damage to the brain, inhibit the progression of some ophthalmic diseases, diabetes, Alzheimer's disease, atherosclerosis, *etc*., and can be used in the diagnosis of various diseases [2].

Traditional methods of nanoparticles (NPs) synthesis often involve the use of toxic chemicals harmful for the environment and human health. Therefore, there is a need for

simple, cost-effective and green methods that use natural sources containing biologically active compounds. These compounds are capable of both reducing metal ions and stabilizing NPs, with formation of coatings on their surface that ensure biocompatibility and specificity of their action. Various plant extracts, microorganisms, in particular bacteria, fungi, algae may serve as such sources [3–6]. Namely, CeO_2-NPs obtained via the green synthesis are the most promising for biomedical applications.

Magnolia kobus is a plant known for its medicinal properties. Its leaves contain various active compounds, including polyphenols, flavonoids, and alkaloids. The components of *Magnolia kobus* extracts exhibit antioxidant, anti-inflammatory, anti-allergic, immunomodulatory, neuroprotective, antiviral and antibacterial properties [7]. A number of studies have reported the use of *Magnolia kobus* leaves extract to synthesize NPs of such metals as gold, silver, copper, palladium [8–10].

Several methods of green synthesis of CeO_2-NPs with sizes from 2 to 75 nm using plant extracts are known [3]. Each of these techniques uses the reaction of the components of the green reagent (a solution of biological origin) with a cerium salt. The solution of reagents can be heated to a certain temperature and treated with high pressure, irradiated with microwave or ultraviolet radiation, subjected to ultrasonic treatment, boiling. In general, the temperature regimes in various methods of CeO_2-NPs synthesis vary from room temperature to temperatures over 200 °C. Usually, high temperatures are used to obtain more uniform and stable NPs with fewer impurities and higher crystallinity.

The nanoscale lattice of cerium oxide has a cubic structure of fluorite. Ce^{3+} and Ce^{4+} can coexist on its surface. The charge deficit due to the presence of Ce^{3+} is compensated by an oxygen vacancy in the lattice. Thus, CeO_2-NPs contain internal oxygen defects, which are the sites of catalytic reactions. The concentration of oxygen defects increases with decreasing particle size. The presence of a mixed valence state plays an important role in the absorption of reactive forms of oxygen and nitrogen. It is assumed that the ratio of surface Ce^{3+}/Ce^{4+} also correlates with the NPs toxicity [11]. Since little is known at the moment on the mechanism of NPs contact with bacteria and their toxicity for cells, the study of their antimicrobial activity is also of current importance.

The aim of this work was to synthesize CeO_2-NPs using the *Magnolia kobus* leaves extract, to determine the composition of the extract and the participation of its components in the NPs synthesis, to study the morphology and structure of the obtained NPs, to investigate their antibacterial activity.

MATERIALS AND METHODS

Magnolia kobus leaves served as raw material for obtaining plant extracts. The plant material was selected at the M.M. Gryshko National Botanical Garden of National Academy of Sciences of Ukraine; magnolia trees grew in natural conditions. 20 mL of ethanol (70 %) were added to 1 g of crushed fresh leaves and the mixture was treated with ultrasound at 60 °C for 30 min. Then, the extract was drained, and the extraction procedure was repeated 4 times more.

Analysis and determination of classes of biologically active substances was carried out using an automatic four-channel liquid chromatograph Agilent 1100 with a diode-matrix detector. Separations were carried out on a chromatographic column Poroshell 120 EC-C18 (2.1×150 mm 2.7 μm). The following gradient composition used for each analysis: 0÷3 min – 89 % A + 11 % B at the flow rate 0.12 mL/min, 30 min – 40 % A + 60 % B at the flow 0.12 mL/min, 53 min – 0 % A + 100 % B at the flow 0.12 mL/min, 70 min – 0 % A + 100 % B at the flow rate increased to 0.56 mL/min, where A is water (0.05 M H_3PO_4) and B is methanol. The injection volume was 2 μL, column temperature was 20 °C at 0 min and increased to 40 °C at 53 min. Detection was performed at the wavelengths of 206, 254, 300, 350 and 450 nm. The contents of simple phenols and hydroxybenzoic acids derivatives were expressed in mg equivalents of gallic acid, hydroxycinnamic acids derivatives were expressed in mg equivalents of chlorogenic acid, glycosides of quercetin and kaempferol were expressed in mg equivalents of rutin, coumarins were expressed in mg equivalents of 7-hydroxycoumarin. Monoterpenoids, sterols, carotenoids and catabolites of chlorophylls were identified based on their UV-Vis spectra and retention times.

Qualitative analysis of the samples was performed using matrix-assisted laser

desorption/ionization time-of-flight mass spectrometry (MALDI MS). Mass spectra were recorded in positive ion registration mode using an Autoflex II mass spectrometer (Bruker Daltonics Inc., Germany) equipped with a nitrogen laser (337 nm). Sample preparation for the analysis was carried out as follows. 1 μL of the extract solution was applied to the steel target, and after drying an additional 1 μL of the matrix solution was applied; α-cyano-4-hydroxycinnamic acid (HCCA, a saturated solution in a mixture of acetonitrile, deionized water, and trifluoroacetic acid in a volume ratio of 70 : 30 : 0.1) was used as a matrix. After drying the samples were subjected to laser desorption/ionization in the pulse mode: the duration of the laser pulse was 3 ns, and the frequency was 20 Hz. Spectra were recorded in linear mode with an ion extraction delay of 10 ns and an accelerating voltage of 20 kV. The resulting spectra were the sum of 20 individual spectra obtained as a result of irradiation with 25 pulses at each individual point with the deposited sample. The laser power was determined by the optimal signal-to-noise ratio and kept the same for different samples. Preliminary MALDI mass spectra processing (smoothing, baseline correction, and determination of major isotope peaks) was performed using FlexAnalysis software (Bruker Daltonics, Germany). Further processing of the mass spectra in the form of a list of individual analytically important peaks (m/z – intensity) of the main isotopes was carried out using the mMass program [12]. Within this program environment, the peaks belonging solely to the analyte were located and the so-called "derivatized" MALDI mass spectra were plotted. Then, using the public databases on polyphenols, carotenoids and other plant metabolites [13–15] as well as taking into account the results of HPLC analysis and the data from the literature [16–22], the most probable sample components were identified.

Synthesis of CeO_2-NPs was carried out as follows. Ammonium cerium(IV) nitrate salt was used as a source of metal ions. 10 mL of plant extract were added to 100 mL of 0.01 M aqueous salt solution. The reaction mixture was stirred using a magnetic stirrer for 5 hours at the temperature of 80 °C. After the sediment was formed, the aliquote of liquid phase was pipetted out for analysis by HPLC and MALDI MS. The sediment was dried at room temperature for 2 days and then annealed in a programmable muffle furnace for 2 hours at 600 °C.

The morphology of the obtained CeO_2-NPs was analyzed using a scanning electron microscope (SEM JSM6060LA, JEOL, Japan). The recording was carried out in the mode of secondary electrons with an accelerating voltage on the cathode of 30 kV. The samples were preliminary sputtered with gold. The size of primary particles was estimated from SEM image using the ImageJ program. The powder X-ray diffraction analysis was used to determine the phase composition of the samples and the average size of CeO_2 nanocrystallites. The diffractograms of the samples were recorded using a DRON-4-07 diffractometer with a Bragg-Brentano focusing geometry in Ni-filtered CuK_α radiation (λ = 1.5418 Å) in angular range of 10–80°. Phase identification was performed using the JCPDS database. The average size of CeO_2 crystallites, D_{cr}, was calculated for (111) peak using the Scherrer equation based on broadening of diffraction peaks of nanocrystalline substances [23]: $D_{cr} = k\lambda/(\beta\cos\theta)$, where D_{cr} is the crystalline size of CeO_2-NPs, θ is the diffraction angle, λ is the wavelength of X-ray source (0.15418 nm), β is the broadening of diffraction peak (the difference between the half-width at half maximum value of the peak of the studied CeO_2 sample (in the radians on 2θ scale) and the half-width of the same peak of the standard one, *i.e.* highly crystalline CeO_2 with an average crystallite size of more than 100 nm) and k is a Scherrer constant (~ 1).

The antagonistic activity of the CeO_2-NPs against the conditionally pathogenic *Escherichia coli* B-206 strain was investigated by the diffusion method in agar wells. 0.1 mL of a 24-hour suspension of a conditionally pathogenic strain of bacteria was applied to the surface of the meat-peptone agar and rubbed with a Drigalski spatula. Holes with a diameter of 8 mm were made with a sterile drill, into which 150 μL of NPs suspension was introduced with a sampler. A suspension of NPs (100 μg/mL) was prepared in a solution of dimethylsulfoxide (DMSO). The DMSO solution served as a negative control. Petri dishes were kept in a thermostat for 24 hours at a temperature of 37 °C. After the incubation period, the pathogen inhibition zone was calculated using the average value for three experiments [24].

RESULTS AND DISCUSSION

Water-ethanol extracts from magnolia leaves contain organic substances of various classes, such as phenolic acids, flavonoids, tannins, steroids, lignans, terpenoids, sugars, *etc*. [25, 26]. All of them, due to their functional groups, can participate in the green synthesis of NPs and in their stabilization. Certain compounds from this variety can serve as reducing and capping agents [9]. In order to evaluate the effect of individual components of the extract from the leaves of *Magnolia kobus* on the process of CeO_2-NPs formation, the composition of the original extract and of the liquid taken from the reaction mixture after the formation of a precipitate in the process of synthesis of NPs were investigated using HPLC and MALDI MS methods.

Chromatograms of the initial extract (Fig. 1 *a*) are characterized by the presence of a number of peaks corresponding to compounds of different classes. Among the signals present in the chromatograms, the peaks related to simple phenols, derivatives of carboxylic, hydroxycinnamic and hydroxybenzoic acids and flavonoids are of the most intensity; the latter are mainly represented by glycosides of quercetin and kaempferol. Also, in the chromatograms there are signals of coumarins, terpenoids and sterols, catabolites of chlorophylls and carotenoids.

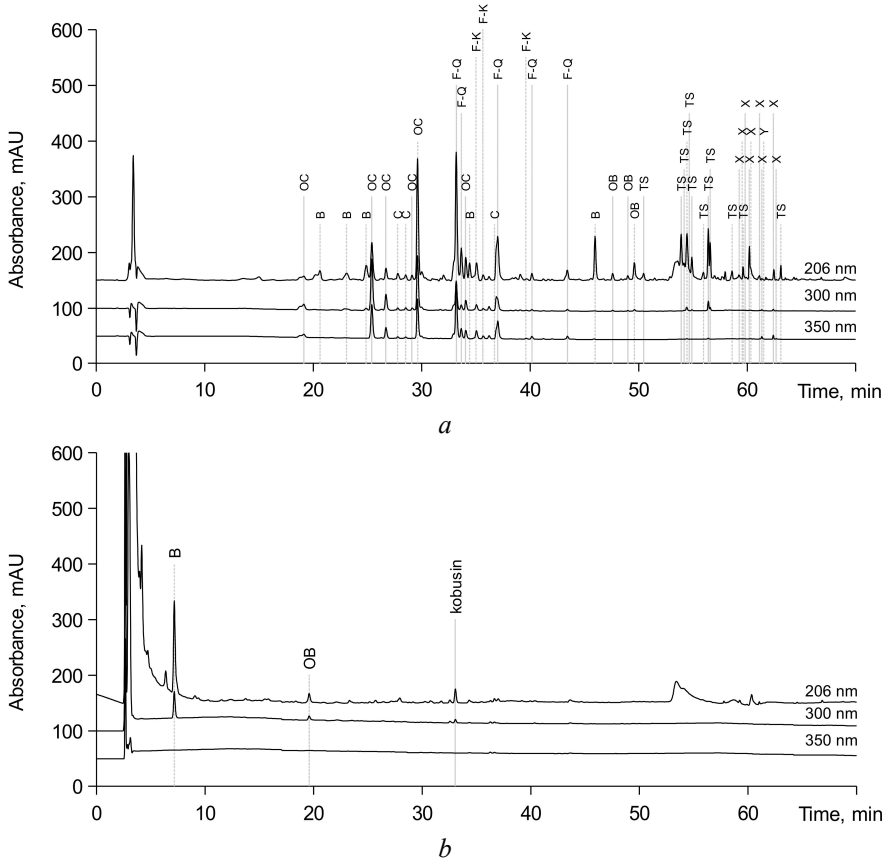

Fig. 1. Chromatograms of *Magnolia kobus* leaves extract (*a*) and of the liquid from the reaction mixture after green synthesis of CeO_2-NPs using *Magnolia kobus* leaves extract (*b*). Peak designations: B – simple phenols and derivatives of carboxylic acids; OB – hydroxybenzoic acid derivatives; OS – hydroxycinnamic acid derivatives; C – coumarin derivatives; F-Q – quercetin glycosides; F-K – kaempferol glycosides; TS – terpenoids and sterols; X – chlorophyll catabolites; Y – carotenoids

The chromatogram of the liquid taken from the reaction mixture after the formation of a precipitate in the process of CeO_2-NPs synthesis (Fig. 1 *b*) contains significantly fewer signals than the chromatogram of the original extract, while those signals that remain have a lower intensity. Comparison of Fig. 1 *a, b* shows that, as a result of the interaction of the extract

components with cerium salt and the NPs formation, the hydroxybenzoic acids, flavonoids and terpenoids disappear or their concentration significantly decreases, while the content of lignans decreases to a lesser extent. Instead, in the chromatogram of the liquid taken from the reaction mixture (Fig. 1 *b*), intense signals with a short retention time (up to 10 min) appear, which may be due to hydrophilic low-molecular compounds formed as a result of NPs synthesis and stabilization reactions.

The mass spectra of the studied samples are presented in Fig. 2.

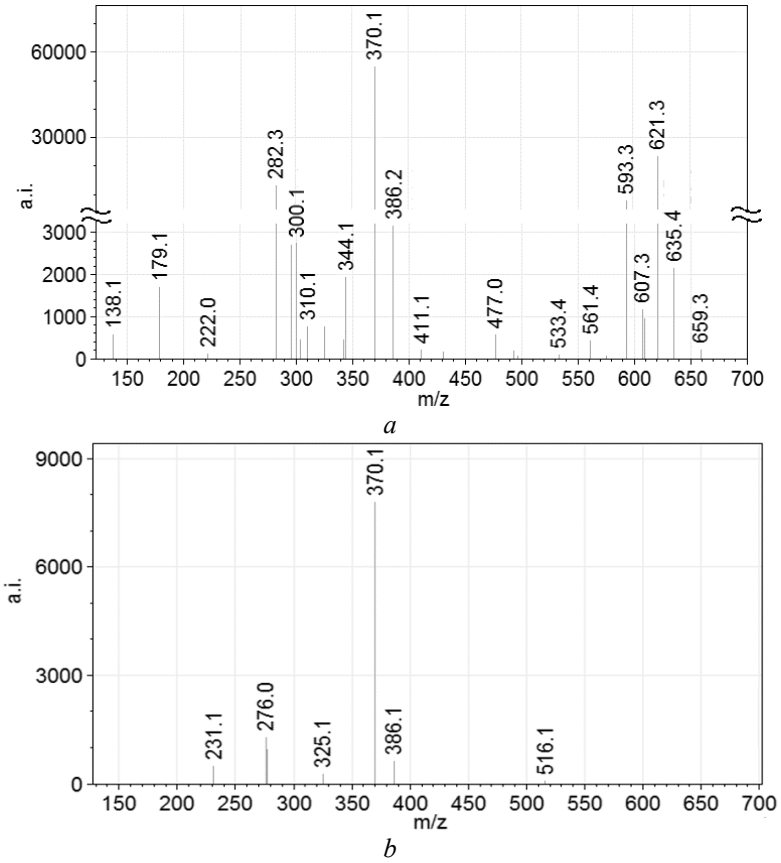

Fig. 2. Derivatized MALDI mass spectra of *Magnolia kobus* leaves extract (*a*) and of the liquid from the reaction mixture after green synthesis of CeO_2-NPs using *Magnolia kobus* leaves extract (*b*)

Analysis of the mass spectra shows that the spectrum of the original extract (Fig. 2 *a*) contains the signals related to such phenolic compounds as hydroxybenzoic acid (*m*/*z* 138), coniferaldehyde (*m*/*z* 179), quercetin (*m*/*z* 325), flavones (*m*/*z* 344), sulfate-derivatives of quercetin (*m*/*z* 477). The extract also contains such lignans as randainol/obovatol (*m*/*z* 282), magnolignan (*m*/*z* 300), fargesin/cobusin (*m*/*z* 370) and eudesmin (*m*/*z* 386), as well as terpenes (*m*/*z* 222), carotenoids (*m*/*z* 533, 561, 635, 659), chlorophylls (*m*/*z* 593, 621). Some signals may be attributed to different classes of compounds. Thus, for example, the *m*/*z* 296 signal can be attributed to a lignan, alkaloid, steroid, or carboxylic acid derivative (Table).

In the case of the liquid taken from the reaction mixture after the formation of the precipitate, most of these signals have a much lower intensity (peaks with *m*/*z* 325, 371, 386) or do not appear at all in the mass spectrum (Fig. 2 *b*). Thus, given in Table and in Fig. 2 data show that the spectrum does not contain signals corresponding to such phenolic compounds as hydroxybenzoic acids (*m*/*z* 138), flavones (*m*/*z* 344), sulfate derivatives of quercetin (*m*/*z* 477); these compounds are apparently involved in the synthesis/stabilization of CeO_2-NPs. Among the signals registered in the mass spectrum of the liquid from the reaction mixture, the signal corresponding to the lignan fargesin/cobusin (*m*/*z* 370) is of the most

intensity. For peaks with *m/z* 325, 370, 386, a decrease in relative intensity by approximately 2.5-6.5 times is observed. These observations indicate that the corresponding compounds are probably involved in less extent in the reduction and stabilization of CeO_2-NPs. New signals with *m/z* 231, 276, 516 also appear in the mass spectrum of the liquid from the reaction mixture (Fig. 2 *b*). It is possible that these peaks are associated with a group of hydrophilic compounds of unidentified structure that were formed as a result of the reactions between the extract components and the precursors of CeO_2-NPs.

Table. List of some compounds in the *Magnolia kobus* leaves extract, identified by MALDI MS

m/z	Attributed ion, assigned compound	Class of compounds	Extract	Reaction liquid
138.1	$M^{+\bullet}$, hydroxybenzoic acid(s)	Hydroxybenzoic acids	+	–
179.1	$[M+H]^+$, melein / ferulaldehyde / coniferaldehyde [18]	Coumarins / Hydroxy-cinnamic acids	+	–
222.0	$M^{+\bullet}$, eudesmol [19] / cadinol	Terpenoids	+	–
282.3	$M^{+\bullet}$, randainol [20] / obovatol [18]	Lignans	+	–
296.1	$M^{+\bullet}$, 4-methoxyl-honokiol X [20] $M^{+\bullet}$, obovatal [20] $[M+H]^+$, caffeoyl aspartic acid $[M+H]^+$, puterine [20] $M^{+\bullet}$, hydroxyoctadecadienoic acid [19] $M^{+\bullet}$, exemestane [21]	Lignans Lignans Carboxylic acids Alkaloids Carboxylic acids Steroids	+	–
300.1	$M^{+\bullet}$, magnolignan [20]	Lignans	+	–
325.1	$[M+Na]^+$, quercetin	Flavonoids	+	+
344.1	$M^{+\bullet}$, cirsilineol / eupatorin / pebrellin	Flavonoids	+	–
370.1	$M^{+\bullet}$, fargesin / kobusin [22]	Lignans	+	+
386.1	$M^{+\bullet}$, eudesmin [22]	Lignans	+	+
477.0	$[M+H]^+$, sulfato-derivatives of isorhamnetin/quercetin	Flavonoids	+	–
533.4	$[M+Na]^+$, β-Apo-2'-carotenol [14]	Carotenoids	+	–
561.4	$[M+H]^+$, C_{40}-carotenoids [14]	Carotenoids	+	–
593.3	$[M+H]^+$, Pheophorbide *a* [17, 21]	Chlorophylls	+	–
621.3	$[M+H]^+$, methyl pheophorbide *b* [17]	Chlorophylls	+	–
635.4	$[M+K]^+$, C_{42}-carotenoids [14]	Carotenoids	+	–
659.3	$[M+K]^+$, C_{42}-carotenoids [14]	Carotenoids	+	–

"+" – present peak in the mass spectra, "–" – peak is absent or with relative abundance less than 0.1 %

Figures 3 and 4 show the X-ray diffraction pattern and SEM image of the obtained CeO_2-NPs, respectively. The formation of CeO_2 cubic symmetry (JCPDS N 75-120) with the average crystallite size of 20 nm occurs. The SEM image indicate that nearly spherical NPs were formed. Their size is 50 ± 10 nm; particles of this size is known to be used for medical and biological purposes [3].

Fig. 5 presents the results of the test on the antibacterial properties of the obtained CeO_2-NPs with respect to the strain of conditionally pathogenic bacteria *Escherichia coli* B-206.

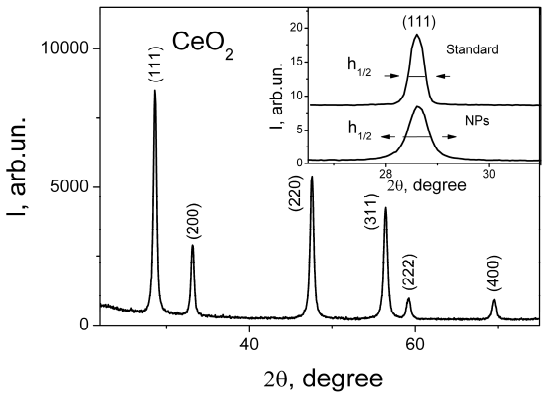

Fig. 3. X-Ray diffractogram of the obtained CeO_2-NPs

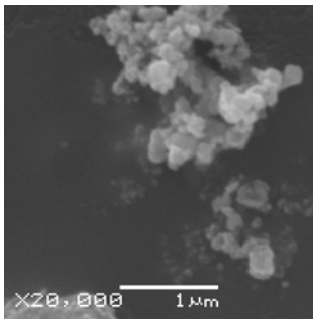

Fig. 4. SEM image of the obtained CeO_2-NPs

The given data show that around the well with NPs suspension (lower part of Fig. 5) a bacterial inhibition zone is formed, the diameter of which is 15.00 ± 0.07 mm. Thus, the obtained NPs indeed exhibit antibacterial activity and can be used to prepare materials for medical, biological, and pharmaceutical purposes.

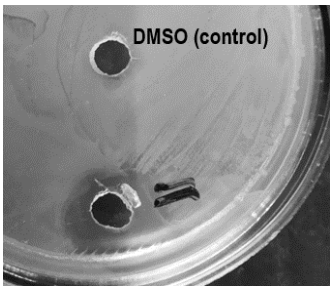

Fig. 5. Antagonistic activity of the obtained CeO_2-NPs against *E. coli* B-206

CONCLUSIONS

The results obtained show that the components of *Magnolia kobus* leaves extract are effective reagents for the green synthesis of crystalline CeO_2-NPs. The extract contains a large number of phenolic compounds (simple phenols, carboxylic and phenolic acids, flavonoids, lignans, coumarins), as well as carotenoids, chlorophylls, terpenoids and sterols, which can act as reducing agents and as stabilizing substances. A comparison of the composition of the original extract and the reaction liquid shows that the main participants in the synthesis of NPs are such components of the extract as hydroxybenzoic acids, flavonoids and terpenoids; lignans (fargesin/cobusin and eudesmin) are involved in less extent in the reduction/stabilization of CeO_2-NPs. According to SEM and X-ray diffraction data, the synthesized CeO_2-NPs have a crystalline structure and a spherical shape; the average size of the crystallites is ~ 20 nm, and the diameter of the primary particles is 50 ± 10 nm. The synthesized particles possess antibacterial properties and can be used in the preparation of materials for medical and biological purposes.

«Зелений» синтез антибактеріальних наночастинок оксиду церію з використанням екстракту з листя *Magnolia kobus*

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Метою роботи було синтезувати наночастинки оксиду церію (CeO_2-НЧ) з використанням екстракту з листків Magnolia kobus, визначити склад екстракту та участь його компонентів у синтезі наночастинок, вивчити морфологію та структуру одержаних наночастинок, дослідити їхню антибактеріальну активність. Склад рослинного екстракту та участь його компонентів у «зеленому» синтезі CeO_2-НЧ

вивчали за допомогою методів високоефективної рідинної хроматографії (ВЕРХ) та мас-спектрометрії з матрично-активованою лазерною/десорбцією іонізацією (МАЛДІ МС). Показано, що екстракт містив фенольні сполуки (похідні простих фенолів, флавоноїдів, гідроксибензойних і гідроксикоричних кислот, лігнани, кумарини), а також каротиноїди, хлорофіли, терпеноїди та стероли. Для встановлення компонентів екстракту, які беруть участь у синтезі CeO_2-НЧ, досліджували склад рідкої фази реакційної суміші (реакційної рідини) після формування наночастинок. За результатами ВЕРХ та МАЛДІ МС досліджень виявлено значні відмінності у складі рослинного екстракту та реакційної рідини: відбулося зникнення або суттєве зменшення концентрації гідроксибензойних кислот, флавоноїдів і терпеноїдів, меншою мірою змінився вміст лігнанів, спостерігалася поява гідрофільних низькомолекулярних сполук, що, ймовірно, утворилися внаслідок реакцій синтезу та стабілізації НЧ. Синтезовані CeO_2-НЧ було охарактеризовано методами скануючої електронної мікроскопії (СЕМ) та рентгеноструктурного аналізу (РСА). Згідно з даними СЕМ та РСА, CeO_2-НЧ мали кристалічну структуру та сферичну форму; середній розмір кристалітів становив ~ 20 нм, а діаметр первинних частинок склав 50±10 нм. Виявлено, що активними учасниками в «зеленому» синтезі CeO_2-НЧ у присутності екстракту з листків Magnolia kobus є гідроксибензойні кислоти, флавоноїди і терпеноїди, тоді як лігнани (фаргесин/кобусин та еудесмін) відіграють меншу роль у відновленні/стабілізації CeO_2-НЧ. Синтезовані частинки мають антибактеріальні властивості і можуть використовуватися при створенні матеріалів медико-біологічного призначення.

***Ключові слова**: рослинний екстракт, фенольні сполуки, «зелений» синтез, наночастинки оксиду церію, МАЛДІ МС, ВЕРХ, антибактеріальна активність*

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