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To the 80th Anniversary of B.I. Ionin

Nanocomposites of Silver with Arabinogalactan Sulfate: Preparation, Structure, and Antimicrobial Activity

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Abstract—Silver-containing nanocomposites based on sulfated arabinogalactan have been prepared under mild conditions. The products contain 2–12 nm silver nanoparticles stabilized by the polymer. The composites are readily water-soluble and reveal antimicrobial activity against a wide range of bacteria and fungi.

Keywords: arabinogalactan, sulfating, silver nanocomposite, antimicrobial activity

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Arabinogalactan is a major water-soluble polysaccharide of the widely spread Siberian Larch (*Larix sibirica Ledeb*.) wood. The polysaccharide content in wood is of 15–20%; therefore, larch is a reliable source of it [1]. The macromolecule structure allows arabinogalactan usage as a macromolecular carrier of pharmacologically active groups (thus enabling construction of novel low-toxicity and high biological availability drugs) and a scaffold for preparation and stabilization of nanostructures [2].

A modified natural polysaccharide, sulfated arabinogalactan AGS, has been recognized for remarkable but not yet implemented potential of application as a nanoparticles stabilizing scaffold [3]. Sulfated arabinogalactan combines solubility in water with a unique set of biological properties, including anticoagulant, hypolipidemic, immunomodulating, and membranotropic activity.

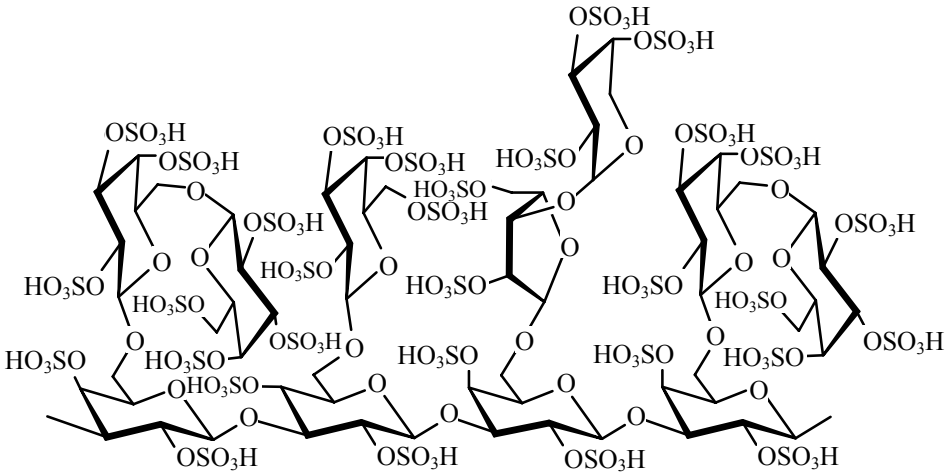
This study aimed to elaborate simple and efficient methods to prepare silver(0)-containing nanocomposites based on sulfated arabinogalactan scaffold and to determine their antimicrobial activity.

Ideally, polysaccharides should be sulfated in nonaqueous media (as polysaccharides are generally unstable towards hydrolysis) using the reagents excluding the possibility of side reactions other than sulfating. In this work, we performed sulfating of arabinogalactan isolated from *Larix sibirica Ledeb*. via interaction of a solution of the polysaccharide in DMSO with a sulfating mixture (SO_3–DMF complex) during 30 min at room temperature [3] (Scheme 1).

Development of the sulfating procedure, we accounted for a number of factors (temperature, reaction duration, and SO_3 concentration) aiming to maximize the product yield and sulfur content in the modified polymer.

For example, heterogeneous reaction during 3 h at room temperature afforded product containing 2.0–2.5% of sulfur. Heating of the mixture above ambient temperature or increasing the reaction time resulted in degradation of arabinogalactan. Varying of SO_3 content in the complex from 8 to 42% resulted in sulfur content in the product of 0.42 to 3.2%, the yield being of 53–94%.

Scheme 1.



Homogeneous reaction in DMSO medium during 3 h resulted in the sulfur content in the product up to 10%, however, the yield was down to 20%. Decreasing the reaction time to 15 min gave the product yield of 90% at the sulfur content of 7%.

The best result was achieved at the reaction time of 30 min. The product yield was of 120% with respect to mass of the starting polysaccharide. Precipitation titration of the product gave the sulfur content of 8–12 ± 0.4%.

Structure of sulfated arabinogalactan was determined from data of elemental analysis, molecular mass analysis as well as IR and ^{13}C NMR spectroscopy.

Electron microscopy study revealed that AGS material was a nanostructured polymer consisting of 200–600 nm agglomerated spherical particles.

Molecular mass of the polymer as determined by gel permeation chromatography on a column filled with Sefadex G-100 gel was of 22.8 kDa, the polydispersity degree being of 1.07.

Broad absorption bands in the IR spectrum of the sulfating product were typical of polymer materials. Besides the bands common of the parent polysaccharide and the sulfating product, the spectrum of AGS contained a strong band at 1235 cm^{-1} assigned to S=O stretching and confirming the presence of sulfate groups in the product. The characteristic bands at 817 and 849 cm^{-1} pointed at the presence of primary and secondary axial sulfate fragments in the AGS macromolecules [4].

The presence and location of sulfate groups in AGS was additionally confirmed by ^{13}C NMR data. In particular, the 6.0 ppm downfield shift of the signals of the C^2 and C^4 atoms of the polysaccharide main chain and of the C^6 atoms of the side and end groups bearing sulfate groups was observed. Signals of the C^3 and C^5 atoms geminal with respect to the sulfate-substituted carbon atoms revealed the upfield shift by 2–4 ppm.

Hence, the AGS was a functionalized biopolymer containing sulfate groups at the C^2 and C^4 atoms of the main chain and at the C^6 atoms of the end groups of the polysaccharide [5].

Using the prepared sulfated polymer to prepare novel functional nanocomposites with Ag(0) is promising as compared with inorganic and synthetic polymers as the polysaccharide is low-toxic and reveals excellent bioavailability. Besides that, the AGS inherited the nanostructured morphology of the parent arabinogalactan; thus, likely, it should have retained its immunomodulating and membranotropic properties [3]. Introduction of sulfate groups makes it a potential heparinoid and antimicrobial agent [6, 7].

We tried different procedures to incorporate metal silver in the polymer matrix of sulfated arabinogalactan: chemical dispersing of metal silver particles using DMSO as a reducing agent, microwave irradiation, and mechanical activation. The effect of the preparation method on the composite properties were elucidated (Table 1).

Moreover, we used different silver salts as precursors: $AgNO_3$, CH_3COOAg, and Ag_2O. Water and DMSO were used as solvents. The process of silver nanoparticles formation was monitored with UV spectroscopy.

Table 1. Preparation conditions and properties of the composites sulfated arabinogalactan–Ag^0

Exp. no.	AGS, mmol	Salt, mmol	Solvent, mL	Preparation method	*T*, °C	Time, min	Ag, %	$[\alpha]_D^{21}$	Size of the major fraction of particles, nm	Phase composition	Size of the coherent scattering region, nm
1	0.5	CH_3COOAg, 1.0	DMSO, 2	Chemical	20	720	6.3	–30.1	30	Ag	15
2[a]	0.5	$AgNO_3$, 1.0	DMSO, 2	Chemical	50	10	8.1	–29.4	2	Ag + Ag_2SO_4	19
3	0.5	Ag_2O, 0.6	H_2O, 3	Chemical	20	180	8.6	–43.5	96	Ag + Ag_2SO_4	36
4	0.25	$AgNO_3$, 1.0	DMSO, 2	Microwave activation	120	1	6.2	–84.3	12	X-ray amorphous	–
5[b]	0.3	$AgNO_3$, 0.15	No solvent	Mechanical activation	20	15	3.6	–34.8	8	Ag	9

[a] Addition of 0.02 mL of 30 wt % NH_4OH solution. [b] Addition of 0.25 mmol of NaOH.

Our attempts to prepare silver nanocomposite based on AGS using a procedure described in Ref. [8] failed. Performing the reaction in the basic medium (pH 10–11) upon heating to 90°C resulted in cleavage of sulfate groups off the AGS molecules.

Mixing of aqueous solutions of the sulfated polysaccharide and $AgNO_3$ resulted in formation of silver salt of AGS and Ag_2SO_4. However, using DMSO as solvent in the presence of CH_3COOAg without alkali addition and at room temperature gave a product containing 6.3% of silver (Table 1, Exp. 1). Addition of 0.02 mL of ammonia (pH 8–9) to the reaction mixture containing $AgNO_3$ and heating to 50°C yielded a composite containing 8.1% of silver within 10 min (Table 1, Exp. 2).

The salt change did not result in increase of silver content in the composite. Starting from AGS and silver oxide afforded a product with 8.6% of silver (Table 1, Exp. 3). Hence, we could prepare the nanocomposites containing 3.6–8.6% of silver without using alkali or using minimal amount of ammonia. All the products were water-soluble and could be isolated from the aqueous solutions via precipitating in ethanol or acetone. The prepared composites could be converted back in the form of aqueous solutions stable upon prolonged storage.

A composite with comparable silver content of 6.2% was prepared upon microwave initiation of the process during 1 min [9]; that turned the fastest and the most efficient method to prepare the nanocomposite (Table 1, Exp. 4).

Mechanical activation method [10] was successfully used to prepare silver nanoparticles via mixing of AGS and silver chloride using a ball mill. The mechanical activation approach afforded the target product with addition of a small amount of alkali; without the additive, the yield of water-soluble fraction was significantly decreased (Table 1, Exp. 5). Evidently, the alkali addition favored the interaction of AGS with silver ions and prevented further aggregation of the reduced silver nanoparticles.

Formation of silver nanoparticles was confirmed by appearance of absorption band at λ 424–445 nm in the UV spectrum, coinciding with data of studies on plasmon absorption of silver nanoclusters [11, 12].

According to IR spectroscopy data, formation of the nanocomposites based on AGS was not accompanied with structural changes of the polysaccharide.

The formed nanocomposite samples were studied by means of X-ray diffraction analysis. One of the samples was X-ray amorphous, whereas diffraction patterns of other samples contained the lines assigned to Ag and (in some cases) to Ag_2SO_4.

Only the strongest line (111) of Ag(0) was reliably registered in the diffraction patterns. Processing of the

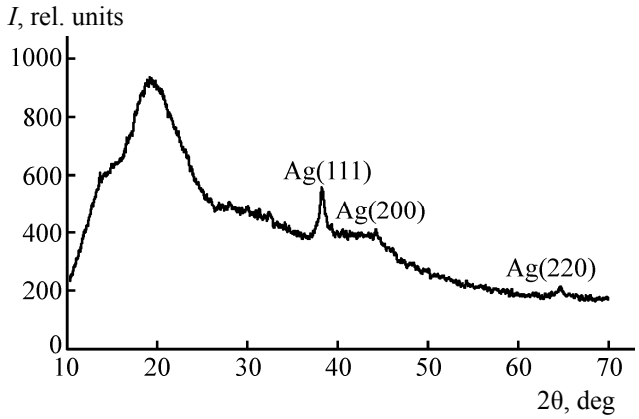


Fig. 1. X-ray diffraction pattern of silver-containing nanocomposite (6.3% of Ag).

data with EVA software allowed calculation of the size of coherent scattering regions from the line broadening (Fig. 1 and Table 1).

Size of silver nanoparticles as determined from TEM data was of 2–96 nm (Fig. 2 and Table 1). Size of the major fraction (52%) of silver particles was within 2–12 nm, 18% of the particles were of 15–30 nm, and the rest of the particles (30%) were of 31–96 nm.

All the composites were characterized in terms of specific optical activity; the starting polymers were dextrorotatory whereas the derived silver-containing nanocomposites were levorotatory.

ESR study of the prepared composites revealed the presence of a broad (about 50 mT) signal, a signal of six equidistant components, and a narrow singlet at *g*-factor range typical of free electron in the spectra of all the samples. On top of that, spectra of samples 2 and 4 contained a signal assigned to Fe^{3+} ions, whereas spectra of samples 3 and 4 contained an anisotropic signal of axial symmetry with doublet splitting in the parallel orientation, the Hamiltonian parameters being of $g_{\|}$ 2.400, $g_{\perp}$ 2.063, A 16.5 mT and $g_{\|}$ 2.400, $g_{\perp}$ 2.083, A 15.0 mT, respectively. Analysis of ESR parameters allowed the following signals assignment. The broad signal seemingly was of the same nature as the similar signals in natural [13] as well as synthetic [14] polymer materials, originating likely from specific specimen ordering and collective spin interactions (antiferromagnetism) causing the positive magnetic susceptibility. Formation of Fe^{3+} and Mn^{2+} ions has been earlier assigned to the presence of tiny amounts of the corresponding admixtures [15, 16].

A narrow signal in the region typical of the free electron recorded at room temperature could be assigned either to the oxygen vacancies having captured electron [17] or to Ag(0) [18, 19]. The latter assignment seemed more probable in view of the signal weakening being correlated with the nanoparticles agglomeration upon the nanocomposite storage. The anisotropic signal was likely due to the complex of Ag(II) with the electron configuration of $4d^9$ [19, 20].

Hence, ESR results confirmed the presence of silver nanoparticles in the samples of all the studied nanocomposites.

Antimicrobial activity of silver nanoparticles was estimated using the composite 3 (Table 1, Exp. 3) as an example, in comparison with silver salt of AGS, following the recommendations in Refs. [21, 22]. In total, 38 microorganism strains were probed (Table 2). The results revealed that the nanostructured silver-containing composites showed a pronounced antimicrobial action. A solution of ultradisperse AGS–Ag^0 system at concentration of >3% suppressed the growth of Gram-positive as well as Gram-negative strains including the *Candida* fungi; at concentration of 1% the composite affected the growth of Gram-negative strains only, whereas the suppressive action vanished at lower concentration of <0.5%. The nanostructured silver salt of sulfated arabinogalactan ($AGSO_3Ag$) revealed antimicrobial activity against Gram-positive and Gram-negative microorganisms including the *Candida* fungi at the solution concentration of 1% or above, whereas at concentra-tion of 0.5% the antifungal activity vanished, and at concentration of 0.1% the antimicrobial activity was retained only against some of the tested Gram-negative strains.

Hence, the data revealed the prospects of development of a new field of sulfated arabinogalactan chemistry, preparation of functional nanosized materials. It was demonstrated that the nanostructures could be successfully formed and stabilized via very simple synthetic methods.

A definite advantage of the sulfated arabinogalactan and its silver-containing composites revealing antimicrobial and antithrombotic activity is a combination of properties of the modified natural scaffold and a nanosized particles, allowing for implementation of new approaches towards development of water-soluble antimicrobial and antiseptic biomaterials. The prepared materials may be used in practical medicine

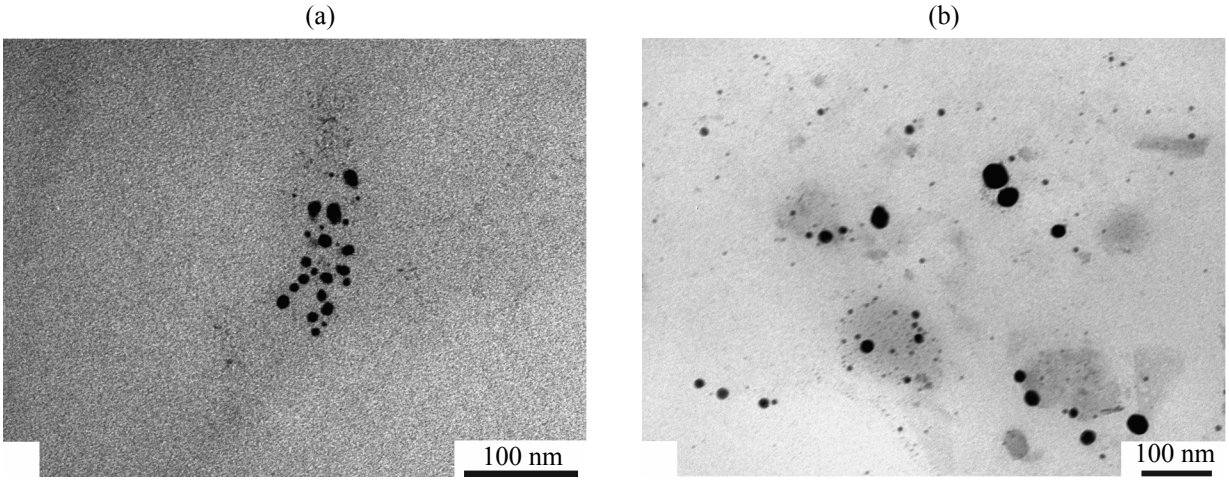


Fig. 2. TEM images of silver nanoparticles in the sulfated arabinogalactan matrix. (a) the sample prepared using mechanical activation; (b) the sample prepared using microwave activation.

as highly efficient low-toxic antibacterial drugs and wound dressings with broad range of activity. In combination with the antithrombotic action such materials may be promising as special implant coatings in neuro- and cardiosurgery.

EXPERIMENTAL

IR spectra were recorded using a Bruker Vertex 70 instrument (KBr pellets). ^{1}H and ^{13}C spectra were registered using a Bruker DPX-400 instrument at 400.1 and 100.6 MHz, respectively. UV spectra were measured using a Perkin Elmer Lambda 35 spectrophotometer at 200–700 nm. Elemental analysis was performed using a Flash EA 1112 analyzer. Optical rotation angle was determined using a Polamat A Carl Zeiss–Jena polarimeter. Microscopy images were obtained using a Leo 906 E transmission electron microscope at accelerating voltage of 80 kV. Microwave treatment was performed using an Anton Paar Monowave 300 single-mode microwave reactor (peak power of 850 W). Mechanical activation was performed in a ML-1 bell mill in a titanium reactor. X-ray diffraction analysis was carried out using a Bruker D8 ADVANCE diffractometer (monochromatic CuK_{α} radiation in a step-scan mode). The crystal phases were identified via comparison of the experimental values of interplanar spacing and relative intensities with reference ones. ESR spectra were recorded in an X-range using a Bruker ELEXSYS E 580 spectrometer. Accuracy of *g*-factor measurement for narrow and broad signals was of ±0.0002 and ±0.01, respectively. Sulfur content was determined by titration.

Molecular mass of sulfated arabinogalactan was determined by means of gel permeation chromatography using a Sephadex G-100-filled column (24 × 350 mm). Dextran (20, 40, and 2000 kDa) and D-galactose standards were used for calibration. Isotonic solution was used as eluent. Content of AGS in aqueous fractions was determined by means of phenol–sulfuric acid method [23].

Heterogeneous sulfating of arabinogalactan. 1 g of arabinogalactan was stirred with 10 mL of a sulfating mixture (preparation of the latter see in [3]) during 3 h at room temperature. After addition of 50 mL of acetone the reaction product was filtered off, washed with acetone, and dried under reduced pressure. Yield 1.12 g. Found, %: C 41.2; H 6.2; S 2.1.

Sulfating of arabinogalactan in DMSO medium. 10 mL of a sulfating mixture (SO_3 in DMF, 18 of SO_3) was added to a solution of 1 g of arabinogalactan in 3 mL of DMSO upon stirring. After 30 min of stirring, the product was precipitated with five-fold volume of ethanol, filtered off, washed with ethanol and diethyl ether, and dried under reduced pressure. Yield 1.2 g. Found, %: C 31.6; H 5.5; S 12.0.

Preparation of silver nanocomposites stabilized with sulfating arabinogalactan. *a*. 0.17 g (1.0 mmol) of silver acetate was added to a solution of 0.2 g (0.5 mmol) of AGS in 2 mL of DMSO. The solution was stirred during 14 h at room temperature. The product was precipitated with five-fold volume of ethanol, filtered off, dissolved in water, and dialyzed during 2 days. The purified product was precipitated

Table 2. Antimicrobial activity of the silver-containing composite (sample 3) and the $AGSO_3Ag$ salt

Microorganism	Sample 3				$AGSO_3Ag$			
	3%	1%	0.5%	0.1%	3%	1%	0.5%	0.1%
E. coli ATCC 25922	–	–	+	+	–	–	–	+
E. coli BLRS 1224	–	–	+	+	–	–	–	+
E. coli BLRS 2320	–	–	+	+	–	–	–	+
Shigella Zonnei	–	–	+	+	–	–	–	–
Shigella Flexsner 2a	–	–	+	+	–	–	–	–
Salmonella enteritidis	–	–	+	+	–	–	–	+
Salmonella typhimurium	–	–	+	+	–	–	–	+
Salmonella C1	–	–	+	+	–	–	–	+
Morganella morgannii	–	–	+	+	–	–	–	–
Serratia marcescens	–	–	+	+	–	–	–	+
Serratia marcescens BLRS 4601	–	–	+	+	–	–	–	+
Enterobacter cloacae	–	–	+	+	–	–	–	+
Yersinia pseudotuberculosis	–	–	+	+	–	–	–	+
Klebsiella pneumonia BLRS	–	–	+	+	–	–	–	+
Pseudomonas aeruginosa hospital culture	–	–	+	+	–	–	–	–
Pseudomonas aeruginosa ATCC 27853	–	–	+	+	–	–	–	–
Acinetobacter baumannii	–	–	+	+	–	–	–	–
Acinetobacter baumannii hospital culture	–	–	+	+	–	–	–	–
Staphylococcus aureus ATCC 25923	–	+	+	+	–	–	–	+
Staphylococcus aureus MRSA 34R	–	+	+	+	–	–	+	+
Staphylococcus aureus MRSA 798	–	+	+	+	–	–	+	+
Staphylococcus aureus ATCC 29213	–	+	+	+	–	–	–	+
Staphylococcus aureus MRSA 67	–	+	+	+	–	–	+	+
Micrococcus luteus	–	+	+	+	–	–	–	+
Listeria monocytogenes	–	+	+	+	–	–	–	+
Enterococcus faecalis	–	+	+	+	–	–	–	+
Enterococcus faecium	–	+	+	+	–	–	–	+
Streptococcus pneumonia	–	+	+	+	–	–	–	+
Streptococcus pyogenes	–	+	+	+	–	–	–	+
Bacillus subtillis	–	+	+	+	–	–	–	+
Candida albicans	–	+	+	+	–	–	+	+
Candida glabrata	–	+	+	+	–	–	+	+
Candida tropicalis	–	+	+	+	–	–	+	+
Candida krusei	–	+	+	+	–	–	+	+
Candida krusei hospital culture	–	+	+	+	–	–	+	+
Cryptococcus neoformans	–	+	+	+	–	–	+	+

with five-fold excess of ethanol, filtered off, washed with 20 mL of ethanol, and dried under reduced pressure. Yield 0.14 g; brown powder (nanocomposite sample 1) (λ_{max} 421 nm). Found, %: C 34.20; H 6.30; S 5.80; Ag 6.30.

Sample 2 (Table 1) was prepared similarly.

0.15 g (0.6 mmol) of Ag_2O was added to a solution of 0.2 g (0.5 mmol) of AGS in 3 mL of water. the reaction mixture was stirred during 3 h at room temperature, unreacted silver oxide was filtered off, and the product was dialyzed during 2 days. The product was precipitated with five-fold excess of ethanol, filtered off, washed with ethanol, and dried under reduced pressure. Yield 0.15 g; brown powder (nanocomposite sample 3) (λ_{max} 420 nm). Found, %: C 36.0; H 6.0; S 3.84; Ag 8.6.

b. *Microwave-assisted preparation.* 0.17 g (1.0 mmol) of $AgNO_3$ and 0.02 mL of aqueous ammonia was added to a solution of 0.2 g (0.5 mmol) of AGS in 2 mL of water. The solution was placed to a microwave oven chamber and heated during 2 min at 120°C. The product was precipitated with five-fold excess of ethanol, filtered off, washed with ethanol, and dried under reduced pressure. Yield 0.18 g; brown powder (nanocomposite sample 4) (λ_{max} 428 nm). Found, %: C 38.6; H 6.3; Ag 13.1.

c. *Mechanical activation.* 0.1 g (0.25 mmol) of AGS, 0.025 g (0.15 mmol) of $AgNO_3$, and 0.01 g (0.25 mmol) of NaOH were placed in a titanium vessel. The mixture was crushed during 10 min, dissolved in water, and dialyzed during 1 day. The product was precipitated with five-fold excess of ethanol, fileterd off, washed with 20 mL of ethanol, and dried under reduced pressure. Yield 0.08 g; light-pink powder (nanocomposite sample 5) (λ_{max} 424 nm). Found, %: C 41.97; H 5.79; Ag 3.7.

Antimicrobial activity was tested via a replication method recommended for colored strains using a test set of microorganisms obtained from State Collection of Pathogenic Microorganisms of Tarasevich State Research Institute of Standardization and Control of Medical Biological Specimens and strains set isolated from patients of Scientific Center of Reconstructive and Regenerative Surgery, Siberian Branch, Russian Academy of Medical Sciences [21].

In detail, 1 mL of the tested silver-containing solutions (0.1–3%) prepared using a pH 7.6 phosphate buffer was introduced into a sterile Petri dish; 15 mL of molten and cooled meat-peptone agar or the Saburo culture medium was added. After the agar setting, inoculate of a 1 day culture of the microorganism strain was applied onto the medium surface (10^3–10^4 KOE/mL). The specimens containing 1 mL of phosphate buffer instead of the tested compound served as reference. The dishes were incubated at 32–34°C during 48 h (the agar) or at 22–24°C during 72 h (the Saburo medium). The test result was determined accounting for the presence and growth of the microorganism colony: "+" growth observed and "–" no growth.

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