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The study of the antibacterial and antimycotic activity of nanostructures based on antibiotics, plant extracts and salts metals

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***Abstract*—The antibacterial activity of nanostructures based on antibiotics, plant extracts and metal salts against *Escherichia.coli, Staphylococcus sp.* and *Aspergillus niger* was shown. A statistically significant increase in the inhibition effect of ceftriaxone in the poludan was shown by 33,3%, copper sulfate in Na-CMC - by 121,5-562,7% depending on the ratio of core:shell and suspension concentration, birch leaf extract in Na-alginate - by 36,7-86,3%, in guar gum - by 110,0-484,5% compared with pure preparations.**

The inhibitory effect from nanostructured silver nitrate was not detected. The most effective ratios are core:shell - 1:1 and 1:2.

Keywords—nanostructured forms; antibiotics; plant extracts; metal salts; biocidal activity

I. INTRODUCTION

In continuation of our research on the properties of nanostructured biologically active compounds [1], this work summarizes the results of previous studies.

The current situation in medicine, associated with the active adaptation of pathogens to the active substance, leads to the fact that it is necessary to search and develop new ways to effectively influence the pathogens [2]. Among such methods is the modification of existing substances in order to increase their biocidal properties without loss of economically viable production cost. So, in the process of nanostructuring, the proportion of the active substance in the total mixture decreases relative to pure, acting as a control [3].

Modification of the active substance by surface-active substances in various mass ratios due to self-organization is characterized by the production of guest-host nanostructures, where the biocidal agent acts as the core, and the surfactant acts as a carrier or shell. Such a molecular ensemble has all the characteristics of its components, but at the same time, some of them can vary, including antibacterial or antimycotic activity due to changes in the reactivity of the agent in the nanostructure [3]. The aim of our research is to study the changes in the antimicrobial and antifungal properties of active substances during nanostructuring with polymers.

II. EXPERIMENTAL

The following cephalosporin antibiotics acted as research objects: cefazolin, cefotaxime, ceftriaxone, cefepime, their modified variants in albumin and interferon. As a representative of preparations based on plant extracts - warty birch leaf extract (*Betula pendula Roth.* (*Verrucosa Ehrn.*) - control and nanostructures of the extract in sodium alginate and guar gum in the active substance: polymer ratios (in grams) 1:1, 1:2, 1:3. Of the metal salts, silver nitrate ($AgNO_3$) is given as the control, its nanoforms in Na-carboxymethylcellulose (Na-CMC) and gellan gum (1:1, 1:2, 1:3) and copper sulfate ($CuSO_4$) - control with nanostructured variants in Na-CMC with a ratio of 1:1, 1:2 and 1:3.

As test-cultures used *Escherichia.coli, Staphylococcus sp.* and *Aspergillus niger*.

The nanostructure sizes were measured on a Nanosight LM0 multiparameter nanoparticle analyzer manufactured by Nanosight Ltd (Great Britain) in the HS-BF configuration (Andor Luca high-sensitivity video camera, 405 nm semiconductor laser with a power of 45 mW). The device is based on the method of analysis of trajectories of nanoparticles (Nanoparticle Tracking Analysis, NTA), described in ASTM E2834 [4]. For measurement, the device parameters were selected: Camera Level = 16, Detection

Threshold = 10 (multi), Min Track Length: Auto, Min Expected Size: Auto, the duration of a single measurement is 215 seconds, and the use of a syringe pump.

The antibacterial and antimycotic activity of nanostructures in the test cultures **were** studied by the disk-diffusion method, which is based on the ability of a substance to diffuse into the nutrient medium from paper disks impregnated with it (9 mm in diameter, made from blue ribbon filter paper). For this, a suspension of microbial cells was prepared (in the case of *Asp. niger*, a spore) of 0.5 optical density using a Microscan Turbidity Meter (manufactured by Siemens). Then, the prepared suspension was sown with a lawn (100 microliters each) in prepared sterile Petri dishes with 5 ml of GMF growth medium (for the fungus - Saburo). Sterile paper discs impregnated with the test sample were placed in seeded cups (four discs per one Petri dish). Repeatability - three cups for each test sample of the substance. Crops were incubated at 27 ° C (for *E. coli* - 36 ° C) for 24 hours. The radius of inhibition zones around the paper discs was used to judge the differences in the sensitivity of the test-cultures to the test samples. To calculate the significance of the difference with the control of antibacterial and antimycotic activity, statistical processing of the averaged radius of inhibition zones were used by the difference method [5].

III. RESULTS AND DISCUSSION

In the course of the study of nanostructures, the size distribution and other properties shown in Figure 1 and Table I were revealed.

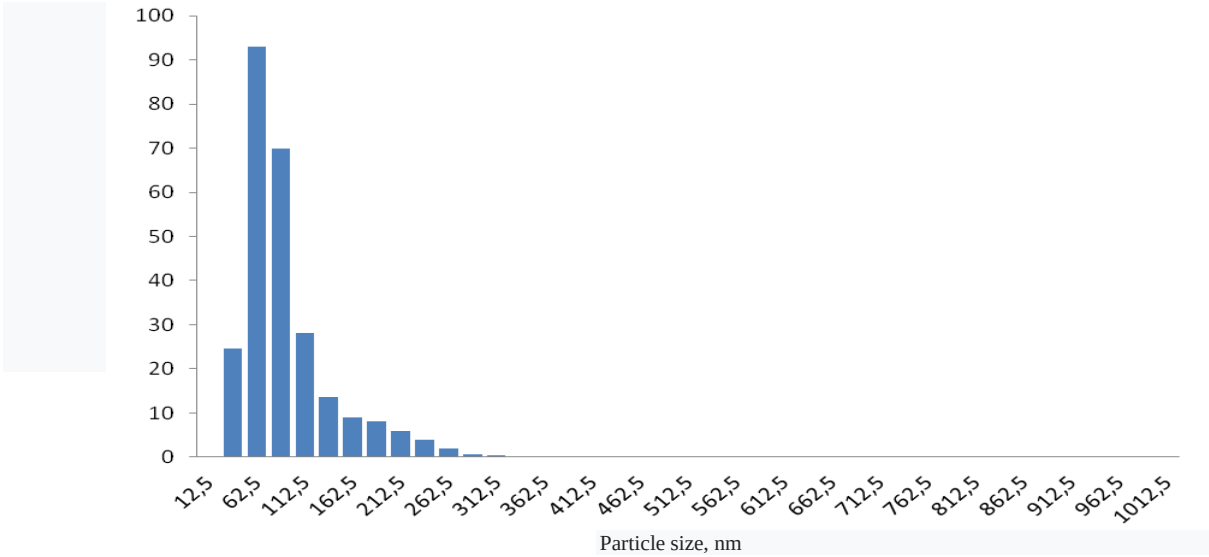

Fig. 1. Size distribution of cefepime nanostructures in sodium alginate in the sample (core:shell ratio 1:3).

TABLE I. STATISTICAL CHARACTERISTICS OF THE DISTRIBUTION OF CEFEPIME NANOSTRUCTURES IN SODIUM ALGINATE

Parameter	**Value**
The average size, nm	93
D10, nm	49
D50, nm	78
D90, nm	161
Polydispersity coefficient, (D90- D10)/D50	1.44
Total particle concentration, $\times 10^{12}$ particles / ml	2.60

Fig. 2. Inhibition zone of *E. coli* with the native form of cefotaxime.

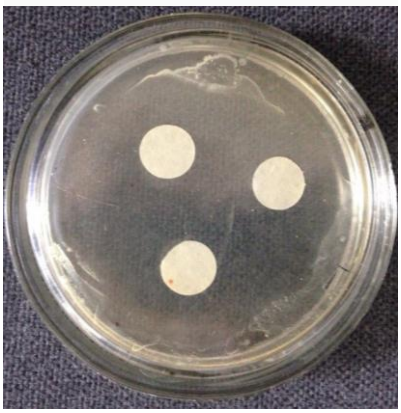

Fig. 3. Inhibition zone of *E. coli* with a nanostructured form of ceftriaxone in poludan

In continuation of our studies [2], the biological activity of cephalosporin antibiotics in native and nanostructured forms were determined. Various nanocapsule shells were used, which differently changed the effectiveness of antibiotics (Table II).

Table. II data analysis shows that most of the nanostructured forms of all antibiotics with the exception of ceftriaxone reduced the primary effect and significantly reduced the inhibition zone of *E. coli*. Only ceftriaxone capsules, coated with a poludane, significantly increases antimicrobial activity on the first day of exposure. A further experiment with variants of antibiotic concentrations and exposure time showed that the initial effect of the capsules varies markedly with various antibiotics.

Cephalosporin antibiotics have low toxicity, high dose selectivity for antimicrobial effect, slow the development of drug resistance in

the process of application and are used parenterally, for intramuscular and intravenous administration. For other methods of administration, a new method of manufacturing antibiotics in microcapsules has been proposed. The most widely used in medicine are microcapsules range in size from 100 to 500 microns. A special type of microcapsules are nanocapsules, particles of medicinal substances with a size of 80-200 nm [1]. Micro- and nanocapsules are successfully used both for targeted drug delivery and for regulating their prolonged action in the body [2]. There are evidences of the use of sodium alginate, carboxymethyl cellulose and other natural polymers to form micro- and nanostructures containing antibiotics.

The antibacterial effect of cefazolin, cephalosporin antibiotics of the third generation cefotaxime and ceftriaxone in the native form, in poludan nano-shells (1:3) was manifested in separate variants, in others the effect was weakened with prolonged action of the antibiotic.

From other sources [4], it is known that antibiotics modified with mineral shells also influenced the simulated fragments of human skin, as well as microorganisms - objects of study [5].

TABLE II. SUMMARY TABLE OF ANTIBACTERIAL ACTIVITY OF NANOSTRUCTURED FORMS OF CEPHALOSPORIN ANTIBIOTICS

№	Antibiotic option	Shell	Zone of inhibition (mm)	Difference error, Sd	Student criterion, t_d
1	Cefepime (1)	-	16,0	-	-
		Poludane(1.1)	6,37	$Sd_{(1-1.1)}$= 0,18	$t_{d\,(1-1.1)}$= 43,8***
		Interferon (1.2)	9,5	$Sd_{(1-1.2)}$= 0,44	$t_{d\,(1-1.2)}$= 10,91***
				$Sd_{(1.1-1.2)}$= 0,39	$t_{d\,(1.1-1.2)}$= 7,9***
2	Cefazolin (2)	-	12,6	-	-
		Interferon (2.1)	11,75	$Sd_{(2-2.1)}$= 0,12	$t_{d\,(2-2.1)}$= 3,3*
3	Cefotaxime (3)	-	18,7	-	-
		Interferon (3.1)	10,62	$Sd_{(3-3.1)}$= 0,79	$t_{d\,(3-3.1)}$= 3,16*
		Poludane(3.2)	14	$Sd_{(3-3.2)}$= 0,64	$t_{d\,(3-3.2)}$= 9,38***
		-	…	$Sd_{(3.1-3.2)}$= 0,73	$t_{d\,(3.1-3.2)}$= 10,0***
4	Ceftriaxone (4)	-	19,5	-	-
		Poludane(4.1)	26	$Sd_{(4-4.1)}$= 0,44	$t_{d\,(4-4.1)}$= 17,77***
		Albumin (4.2)	17,37	$Sd_{(4-4.2)}$= 0,15	$t_{d\,(4-4.2)}$= 14,0***
		-	…	$Sd_{(4.1-4.2)}$= 1,22	$t_{d\,(4.1-4.2)}$= 7,04***

Note (hereinafter):
* - the difference is statistically significant at the level p => 0.05;
** - the difference is statistically significant at the level p => 0.01;
*** - the difference is statistically significant at the level p => 0.001.

A further experiment with variants of antibiotic concentrations and exposure time showed that the initial effect of the capsules varies markedly with various antibiotics.

In an experiment with nanostructured silver nitrate in Na-carboxymethylcellulose and gellan gum, (Table III) the inhibitory effect on *Staphylococcus sp.* (without conversion to the active substance) remained within the control (pure drug); statistically the difference is not significant.

The use of copper sulfate as an inhibitor in a nanostructure with Na-carboxymethylcellulose effect (Table IV, Fig. 4) turned out to be significantly higher than silver nitrate. In most variants with a core: shell ratio of 1:1 and 1:2, with the exception of 1% concentration, the inhibition zone exceeded the control by 2.2-4.5 times. The prolongation of the effect in this case was not investigated by us.

TABLE III. INHIBITION ZONES OF *STAPHYLOCOCCUS SP.* AS AN INDICATOR OF THE ANTIBACTERIAL ACTIVITY OF A SILVER NITRATE NANOSTRUCTURE IN NA-CARBOXYMETHYLCELLULOSE AND GELLAN GUM

Ratio	Na-carboxymethylcellulose			Gellanic gum			%
	Averaged radii of inhibition zones, X (мм)	***Difference error, Sd***	***Student criterion, t_d***	***Averaged radii of inhibition zones, X (мм)***	***Difference error, Sd***	***Student criterion, t_d***	
Clean (1.1)	3,81	$Sd_{(1.1-2.1)}$ = 0,21; $Sd_{(1.1-3.1)}$ = 0,20; $Sd_{(1.1-4.1)}$ =0,19;	$t_{d(1.1-2.1)}$ =7,095***; $t_{d(1.1-3.1)}$=13,097***; $t_{d(1.1-4.1)}$=10,536***	4,41	$Sd_{(1.1-2.1)}$ = 0,17; $Sd_{(1.1-3.1)}$ = 0,21;	$t_{d.\ (1.1-2.1)}$ =4,146***; $t_{d.\ (1.1-3.1)}$=7,785***	0,15
1:1 (2.1)	2,30			3,69			
1:2 (3.1)	1,13			2,76			
1:3 (4.1)	1,8			-			
Clean (1.2)	3,75	$Sd_{(1.2-2.2)}$ = 0,11; $Sd_{(1.2-3.2)}$ = 0,14; $Sd_{(1.2-4.2)}$ =0,12;	$t_{d.\ (1.2-2.2)}$ =4,448***; $t_{d.\ (1.2-3.2)}$=9,976***; $t_{d.\ (1.2-4.2)}$=3,472**	4,19	$Sd_{(1.2-2.2)}$ = 0,17; $Sd_{(1.2-3.2)}$ = 0,18; $Sd_{(1.2-4.2)}$ =0,15;	$t_{d.\ (1.2-2.2)}$ =7,154***; $t_{d.\ (1.2-3.2)}$=2,677*; $t_{d.\ (1.2-4.2)}$=6,540***	0,2
1:1 (2.2)	3,25			3,00			
1:2 (3.2)	2,34			3,72			
1:3 (4.2)	3,31			3,22			
Clean (1.3)	4,04	$Sd_{(1.3-2.3)}$ = 0,15; $Sd_{(1.3-3.3)}$ = 0,17; $Sd_{(1.3-4.3)}$ =0,2	$t_{d\ (1.3-2.3)}$ =4,363***; $t_{d.\ (1.3-3.3)}$=6,226***; $t_{d.\ (1.3-4.3)}$=6,295***	4,24	$Sd_{(1.3-2.3)}$ = 0,15; $Sd_{(1.3-3.3)}$ = 0,14; $Sd_{(1.3-4.3)}$ =0,12	$t_{d.\ (1.3-2.3)}$ =1,231; $t_{d\ (1.3-3.3)}$=7,081***; $t_{d.\ (1.3-4.3)}$=10,011***	0,25
1:1 (2.3)	3,37			4,05			
1:2 (3.3)	2,97			3,27			
1:3 (4.3)	2,76			2,96			

TABLE IV. INHIBITION ZONES OF *ESHERICHIA COLI* AS AN INDICATOR OF THE ANTIBACTERIAL ACTIVITY OF COPPER SULFATE NANOSTRUCTURES IN NA-CARBOXYMETHYLCELLULOSE.

Ratio	Na-carboxymethylcellulose			%
	Averaged radii of inhibition zones, X (мм)	***Difference error, Sd***	***Student criterion, $t_{расч.}$***	
Clean (1.1)	1,64	$Sd_{(1.1-2.1)}$ = 0,4; $Sd_{(1.1-3.1)}$ =0,9; $Sd_{(1.1-4.1)}$ =0,2	$t_{d.\ (1.1-2.1)}$ =11,433***; $t_{d.\ (1.1-3.1\ )}$ =6,117***; $t_{d.\ (1.1-4.1)}$ =0,2	0,5
1:1 (2.1)	6,91			
1:2 (3.1)	7,7			
1:3 (4.1)	1,68			
Clean (1.2)	1,58	$Sd_{(1.2-2.2)}$ = 0,2; $Sd_{(1.2-3.2)}$ = 0,6; $Sd_{(1.2-4.2)}$ =0,1	$t_{d\ (1.2-2.2)}$ =7,718***; $t_{d\ (1.2-3.2)}$ =13,252***; $t_{d.\ (1.2-4.2)}$ =0,417	0,75
1:1 (2.2)	3,5			
1:2 (3.2)	10,47			
1:3 (4.2)	1,6			
Clean (1.3)	2,3	$Sd_{(1.3-2.3)}$ = 0,1; $Sd_{(1.3-3.3)}$ = 0,9; $Sd_{(1.3-4.3)}$ =0,2	$t_{d.\ (1.3-2.3)}$ =2,842; $t_{d.\ (1.3-3.3)}$ =8,989***; $t_{d.\ (1.3-4.3)}$ =0,312	1
1:1 (2.3)	1,79			
1:2 (3.3)	10,39			
1:3 (4.3)	2,37			

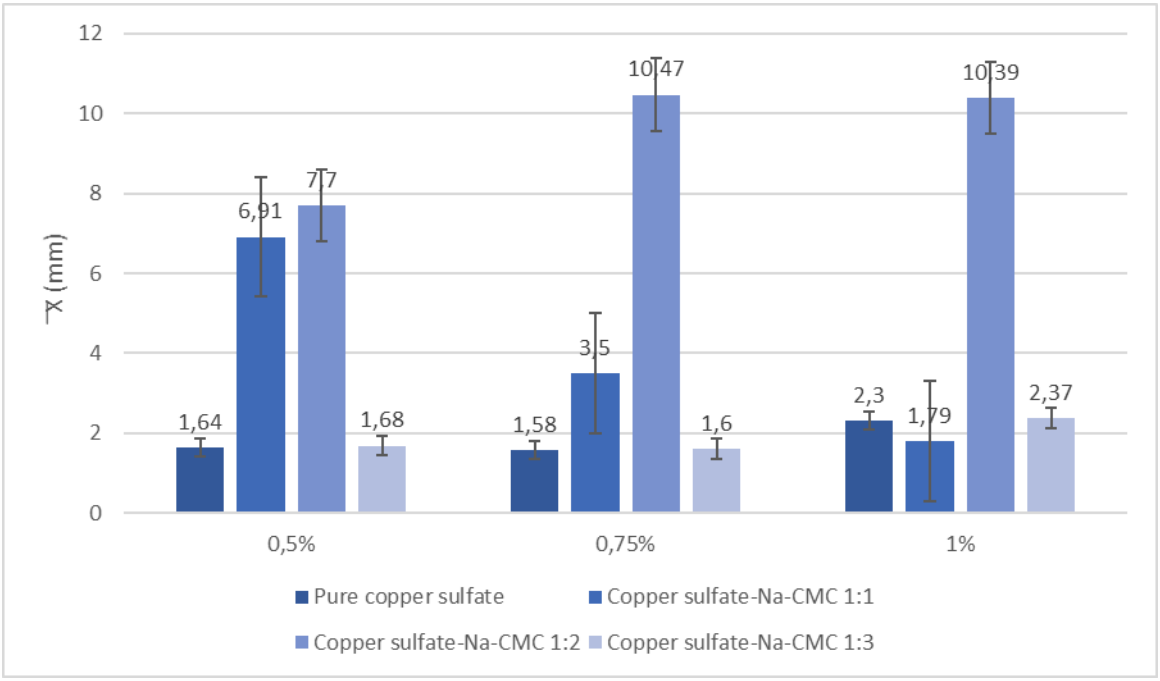

Fig. 4. Averaged zones of growth inhibition of *E. coli* as an indicator of the antibacterial activity of copper sulfate nanostructures in Na-carboxymethylcellulose.

The extract of warty birch leaves, having a complex composition, is used in phototherapy as a diuretic, anti-inflammatory agent for bacterial diseases of the liver and kidneys, as well as vitamin deficiency. We studied the antibacterial effect of a nanostructured leaf extract in sodium alginate and guar gum (table V, Fig. 5, 6)

TABLE V. INHIBITION ZONES OF *ESHERICHIA COLI* AS AN INDICATOR OF THE ANTIBACTERIAL ACTIVITY OF NANOSTRUCTURES OF WARTY BIRCH LEAF EXTRACT IN SODIUM ALGINATE AND GUAR GUM

Ratio	**Sodium Alginate**			**Gellanic gum**			**%**
	***Averaged radii of inhibition zones,* X (мм)**	***Difference error,* Sd**	***Student criterion,* t_d**	***Averaged radii of inhibition zones,* X (мм)**	***Difference error,* Sd**	***Student criterion,* t_d**	
Clean (1.1)	2,04	$Sd_{(1.1\text{-}2.1)}$ = 0,15; $Sd_{(1.1\text{-}3.1)}$ = 0,21; $Sd_{(1.1\text{-}4.1)}$ =0,23;	$t_{d\,(1.1\text{-}2.1)}$ =7,549***; $t_{d\,(1.1\text{-}3.1)}$ =7,533***; $t_{d\,(1.1\text{-}4.1)}$ =7,274***	2,04	$Sd_{(1.1\text{-}2.1)}$ = 0,29; $Sd_{(1.1\text{-}3.1)}$ = 0,30; $Sd_{(1.1\text{-}4.1)}$ =0,11;	$t_{d\,(1.1\text{-}2.1)}$ =1,55; $t_{d\,(1.1\text{-}3.1)}$ =14,6***; $t_{d\,(1.1\text{-}4.1)}$ =1,10	1
1:1 (2.1)	3,18			2,5			
1:2 (3.1)	3,625			6,375			
1:3 (4.1)	3,8			2,17			
Clean (1.2)	1,28	$Sd_{(1.2\text{-}2.2)}$ = 0,09; $Sd_{(1.2\text{-}3.2)}$ = 0,11; $Sd_{(1.2\text{-}4.2)}$ =0,09;	$t_{d\,(1.2\text{-}2.2)}$ =1,832; $t_{d\,(1.2\text{-}3.2)}$ =4,276**; $t_{d\,(1.2\text{-}4.2)}$ =0,684	1,29	$Sd_{(1.2\text{-}2.2)}$ = 0,39; $Sd_{(1.2\text{-}3.2)}$ = 0,29; $Sd_{(1.2\text{-}4.2)}$ =0,15;	$t_{d\,(1.2\text{-}2.2)}$ =3,86***; $t_{d\,(1.2\text{-}3.2)}$ =21,59***; $t_{d\,(1.2\text{-}4.2)}$ =9,19***	3
1:1 (2.2)	1,125			2,81			
1:2 (3.2)	1,75			7,54			
1:3 (4.2)	1,29			2,71			
Clean (1.3)	1,625	$Sd_{(1.3\text{-}2.3)}$ = 0,12; $Sd_{(1.3\text{-}3.3)}$ = 0,12; $Sd_{(1.3\text{-}4.3)}$ =0,10	$t_{d\,(1.3\text{-}2.3)}$ =2,844***; $t_{d.\,(1.3\text{-}3.3)}$ =2,223**; $t_{d\,(1.3\text{-}4.3)}$ =6,157***	1,625	$Sd_{(1.3\text{-}2.3)}$ = 0,57; $Sd_{(1.3\text{-}3.3)}$ = 0,19; $Sd_{(1.3\text{-}4.3)}$ =0,10	$t_{d\,(1.3\text{-}2.3)}$ =8,82***; $t_{d\,(1.3\text{-}3.3)}$ =40,54***; $t_{d\,(1.3\text{-}4.3)}$ =6,16***	5
1:1 (2.3)	1,27			6,67			
1:2 (3.3)	1,6			9,29			
1:3 (4.3)	1,62			1,625			

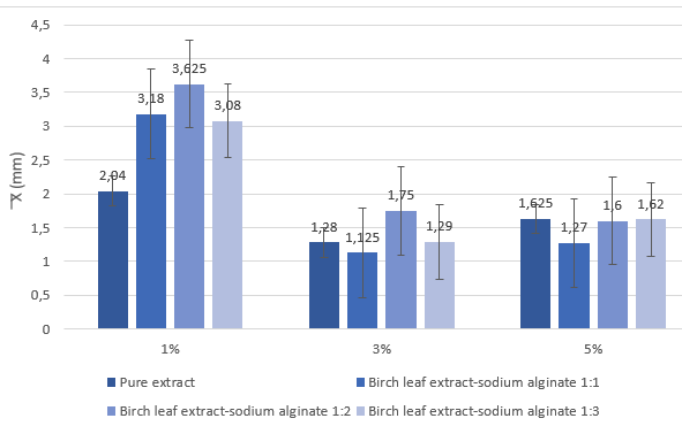

Fig. 5. Averaged zones of growth inhibition of *E. coli* as an indicator of the antibacterial activity of nanostructures of warty birch leaf extract in sodium alginate.

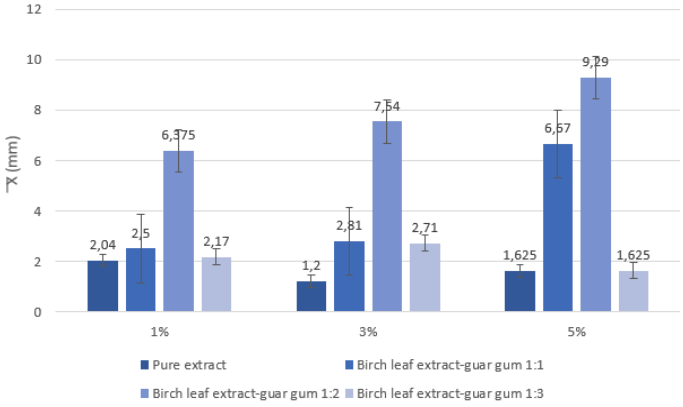

Fig. 6 Averaged zones of growth inhibition of *E. coli* as an indicator of the antibacterial activity of nanostructures of the extract of warty birch leaves in guar gum.

The data presented in the table V indicate a 1.4-fold increase in the inhibition effect on Esherichia coli in sodium alginate, up to 5.7-fold in guar gum as compared to the pure extract. Almost all variants of nanostructures with this shell had a high positive effect, which confirms the universality of this extract.

Aspergillus niger was used as a test object to study the inhibition activity of silver nitrate nanostructures in Na-carboxymethylcellulose and gellan gum (table VI, Fig. 7, 8). As it can be seen from the data in the table and figures, the effectiveness of the nanostructured silver salt was statistically insignificant in all the studied variants.

The properties of the shell did not affect the biocidal activity of the active substance.

TABLE VI. ININHIBITION ZONES OF *ASPERGILLUS NIGER* AS AN INDICATOR OF THE ANTIMYCOTIC ACTIVITY OF SILVER NITRATE NANOSTRUCTURES IN NA-CARBOXYMETHYLCELLULOSE AND GELLAN GUM

Ratio	Na-carboxymethylcellulose			Gellanic gum			%
	Averaged radii of inhibition zones, X (мм)	*Difference error, Sd*	*Student criterion, t_d*	*Averaged radii of inhibition zones, X (мм)*	*Difference error, Sd*	*Student criterion, t_d*	
Clean (1.1)	6,12	$Sd_{(1.1-2.1)}$ = 0,37; $Sd_{(1.1-3.1)}$ = 0,42; $Sd_{(1.1-4.1)}$ =0,39;	$t_{d\,(1.1-2.1)}$ =0,113; $t_{d.\,(1.1-3.1\,)}$ =1,032; $t_{d.\,(1.1-4.1)}$ =6,055***	5,15	$Sd_{(1.1-2.1)}$ = 0,24; $Sd_{(1.1-3.1)}$ = 0,18; $Sd_{(1.1-4.1)}$ =0,21;	$t_{d..\,(1.1-2.1)}$ =4,775***; $t_{d.\,(1.1-3.1)}$ =21,793***; $t_{d..\,(1.1-4.1)}$ =11,899***	0,15
1:1 (2.1)	6,08			4,02			
1:2 (3.1)	5,69			1,15			
1:3 (4.1)	3,77			2,66			
Clean (1.2)	7	$Sd_{(1.2-2.2)}$ = 0,5; $Sd_{(1.2-3.2)}$ = 0,46; $Sd_{(1.2-4.2)}$ =0,38;	$t_{d.\,(1.2-2.2)}$ =0,547; $t_{d.\,(1.2-3.2)}$ =1,144; $t_{d.(1.2-4.2)}$ =5,419**	4,92	$Sd_{(1.2-2.2)}$ = 0,19; $Sd_{(1.2-3.2)}$ = 0,23; $Sd_{(1.2-4.2)}$ =0,22;	$t_{d.\,(1.2-2.2)}$ =1,677; $t_{d.\,(1.2-3.2)}$ =7,663***; $t_{d..\,(1.2-4.2\,)}$ =1,689	0,2
1:1 (2.2)	7,27			4,6			
1:2 (3.2)	6,48			3,15			
1:3 (4.2)	4,94			4,54			
Clean (1.3)	7,83	$Sd_{(1.3-2.3)}$ = 0,46; $Sd_{(1.3-3.3)}$ = 0,35; $Sd_{(1.3-4.3)}$ =0,32	$t_{d.\,(1.3-2.3)}$ =5,511***; $t_{d.\,(1.3-3.3)}$ =6,736***; $t_{d.\,(1.3-4.3)}$ =14,093***	5,42	$Sd_{(1.3-2.3)}$ = 0,26; $Sd_{(1.3-3.3)}$ = 0,18; $Sd_{(1.3-4.3)}$ =0,21	$t_{d.\,(1.3-2.3)}$ =0,978; $t_{d\,(1.3-3.3\,)}$ =22,894***; $t_{d.\,(1.3-4.3)}$ =1,691	0,25
1:1 (2.3)	5,29			5,67			
1:2 (3.3)	5,5			1,27			
1:3 (4.3)	3,33			5,06			

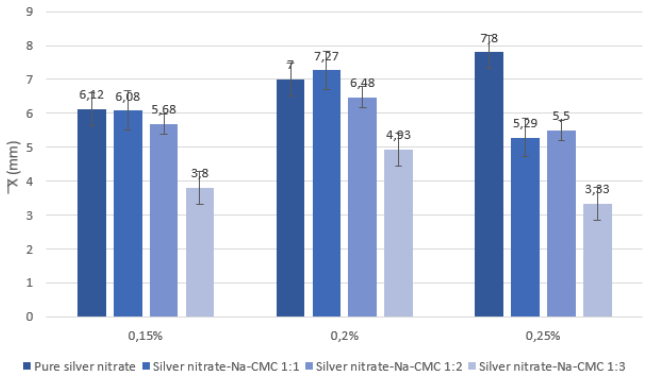

Fig. 7. Averaged zones of growth inhibition of *Aspergillus niger* as an indicator of the antimycotic activity of silver nitrate nanoconstructions in Na-carboxymethylcellulose.

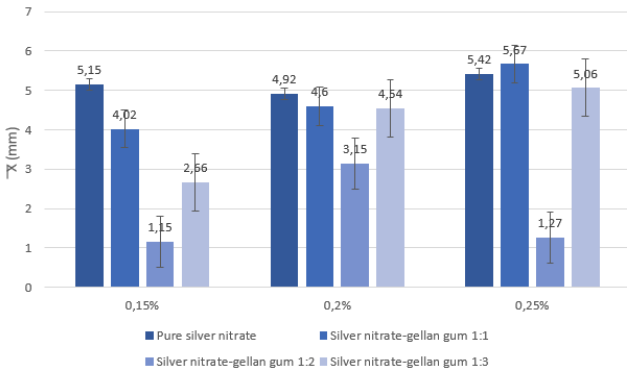

Fig. 8. Averaged zones of growth inhibition of *Aspergillus niger* as an indicator of antimycotic activity of silver nitrate nanoconstructions in gellan gum.

IV. CONCLUSION

The data presented indication of diversity of the reaction of test objects depending on the properties of the active substance and the carrier, and the concentration of nanostructures.

The influence of nanostructured complexes is manifested in some cases by an increase in the inhibition effect of a pure substance; in others, this effect is absent, but its manifestation in prolongation of action is possible.

Additional studies are needed to confirm this effect.

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