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Adjuvant Properties of Silver and Dimethyl Sulfoxide Nanoparticles in Studying Antibacterial Activity of Antibiotics against E. Coli

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ABBREVIATION

DMSO	*Dimethyl Sulfoxide*
CFU	*Colony-Forming Units*
WHO	*World Health Organization*
MIC	*Minimum inhibitory concentration*
DNA	*Deoxyribonucleic acid*
E. coli	*(Escherichia coli)*

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Abstract

The research results showed that silver nanoparticles have adjuvant properties that increase the bactericidal performance of antibiotics, more than when mono-use with dimethyl sulfoxide (DMSO) and when they are co-cultured. The bactericidal activity of silver nanoparticles against E. coli (Escherichia coli) ATCC 25922 was 0.08, and the E. coli isolate was 0.32 μg / ml. The study of the bactericidal activity with dimethyl sulfoxide for E. coli ATCC 25922 made it possible to establish it at the level of 9.75, and for the E. coli isolate is 4.86 μg / ml. The reference E. coli strain ATCC 25922 had the highest sensitivity of both AgNPs and their combination with antibiotics in comparison with the E. coli isolate, which was isolated from an animal with clinical manifestation of an infectious disease.

The combination of AgNPs and the antibiotic enrofloxacin, gentamicin, ceftimag, cypromag, oxytetracycline, ampicillin showed the greatest increase in bactericidal activity against both E. coli ATCC 25922 and E. coli isolate than AgNPs + antibiotic + DMSO, except for cloxacillin's in the study with isolate E. coli.

Keywords: *Antibiotic, Argovit, Bactericidal Activity, Enrofloxacin, Silver Nanoparticles,*

INTRODUCTION

In 2001, on the decision of the UN World Health Organization (WHO), it was established that in the treatment of infectious diseases, the main issue is the problem of antibiotic resistance and the program "Global strategy for the containment of antimicrobial resistance" is aimed at its prevention, formation and spread. The countries of the European Union and North America have developed national programs to combat the spread of this dangerous phenomenon. In 2004, the United Nations World Health Organization proposed to consider the phenomenon of antimicrobial resistance as a decisive factor contributing to a change in the occurrence, course, and manifestation of previously known infectious diseases, and developed recommendations for overcoming it *(World Health Organization, 2001).*

Multiple drug resistance is becoming a growing problem in the treatment of infectious diseases, and the widespread use of broad-spectrum antibiotics has led to the development of antibiotic resistance from numerous human and animal bacterial pathogens. Therefore, there is an urgent need to develop alternative,

cost-effective, and efficient antimicrobial agents that overcome antimicrobial resistance (*Strategy for preventing the spread of antimicrobial resistance, 2017; Yuan 2017; Shkil 2019).*

The main way to combat antibiotic resistance of microorganisms is the creation of new drugs, but their high cost of synthesis and long development time significantly complicate the fight against infectious diseases. In this regard, an active search is underway for ways to increase the antibacterial properties of known drugs. Silver nanoparticles are widely used in various fields of medicine as biomarkers, antimicrobial, antitumor agents, cell labels, and drug delivery systems for the treatment of various diseases, as well as diagnostic tools. Numerous studies indicate the stimulating effect of silver, both orally and parenterally, on the reticuloendothelial system of the body, with active and antiviral action and pronounced anti-inflammatory activity *(Sidorenko 2004).*

One of the promising areas of modern pharmacology is the creation of new drugs using nanotechnology, which opens up the possibility of increasing the effectiveness of pharmacological drugs. The development of nanotechnology makes it possible to create polymer complexes of surfactants and nanodispersed silver through nanostructuring of biologically active substances with water-soluble functional polymers of drugs *(Richter 2017; Barras 2018)*

Some authors, in their in vitro and in vivo studies, noted the ability of colloidal silver to destroy the biofilms of methicillin-resistant *S. aureus and P. aeruginosa (Jung 2008).*

The authors note the destructive effect of silver on bacteria, as well as its ability to bind sulfur atoms present in sulfhydryl groups of proteins, enzymes located on the surface of bacterial cells. *(Morones 2005).* Colloidal silver at a concentration of 4 and 8 mg / l has bactericidal activity against 270 isolates of *A. baumannii, P. aeruginosa, E. coli, S. aureus, S. epidermidis,* and *Enterococcus spp. (Shrivastava 2007).*

The biocidal properties of metal nanoparticles are the most studied, but their severity depends on their type *(Yang 2009).* Copper nanoparticles can restore the sensitivity of *E. coli* strains to some beta-lactam antibiotics (ampicillin, amoxicillin/clavulanate) and aminoglycosides (gentamicin), while nanoparticles of nickel, titanium and manganese at a concentration of 0.01 mg/ml for 30 min do not lead to changes in the antibiotic susceptibility of clinical *E. coli* strain *(Burda 2005).*

A synergistic effect of silver nanoparticles in combination with erythromycin and levofloxacin against *Staphylococcus aureus* was established. Antimicrobial activity with antibiotics in comparison with pure silver nanoparticles increased by 1.16-1.32 times. This synergy may be relevant for the treatment of infectious diseases caused by multidrug-resistant bacteria *(Panacek 2006).* To increase the bactericidal effect of antibacterial composition, dimethyl sulfoxide (DMSO) is added to them, which has antibacterial and anti-inflammatory properties *(Lok 2007).* **This work aims** to study the effect of silver nanoparticles on the bactericidal properties of antibacterial drugs enrofloxacin, ceftimag, oxytetracycline, cypromag, gentamicin, ampicillin, cloxacillin when used together against the isolate and the reference *E. coli* strain.

MATERIALS AND METHODS

Research materials are:

- The drug “Argovit” contained silver nanoparticles (AgNPs) 12-14 μg/ml, produced by a limited liability company of the research and production center "Vector-Vita", in the city of Novosibirsk;
- Dimethyl sulfoxide (DMSO);
- Ceftimag contained in 1 ml as an active ingredient contains ceftiofur hydrochloride 100 mg, and as auxiliary substances contain methyl ester of paraoxybenzoic acid 1.8 mg, propyl ester of paraoxybenzoic acid 0.2 mg and propylene glycol dicaprylate / dicaprate up to 1 ml.;
- Cypromag in 1 ml contains ciprofloxacin 100 mg as an active ingredient, as well as auxiliary components: propylene glycol 0.1 ml, butyl alcohol 20 mg, the disodium salt of ethylenediaminetetraacetic acid (Trilon B) 1 mg;
- Water for injection 1 ml;
- Oxytetracycline in the form of a 10.0% aqueous solution;
- Enrofloxacin contain 50 mg of enfroloxacin in 1 ml, gentamicin sulfate 40 mg in 1 ml, ampicillin 20.0% in 100 ml. In 1 ml of ampicillin, the active ingredient is ampicillin trihydrate 200 mg cloxacillin in the form of an aqueous solution containing 500 mg of cloxacillin sodium in 1 ml.

To determine the sensitivity of microorganisms to antibacterial substances and their combinations, the drug was fed in equal volumes of 0.2 ml, carried out by the method of serial dilutions in the BCH with the addition of 0.2 ml 1.5×10^6 CFU/ml of the reference *E. coli* ATCC 25922 strain or isolate E.coli isolated in infectious diseases from cattle with subsequent incubation for 24 hours at a temperature T= 36.5 + 0.5 ° C *(Panacek 2006).*

RESULTS AND DISCUSSION

Silver nanoparticles of the "Argovit" preparation were obtained by electron beam treatment of an aqueous solution containing a water-soluble polymer stabilizer and a water-soluble silver salt, which consists in passing a beam of accelerated electrons obtained on a linear accelerator of the PLA – 10 (pulsed linear accelerator) type through a solution with a working dose of 5-30 kGy. All samples contain particles of silver in the nanometer range. Contrast particles of spherical, triangular, multifaceted shape are visualized with a shape characteristic of silver nanoparticles, a clear contour, high electron density, and a characteristic diffraction pattern with rings and reflections for a large number of nanoparticles (Fig. 1).

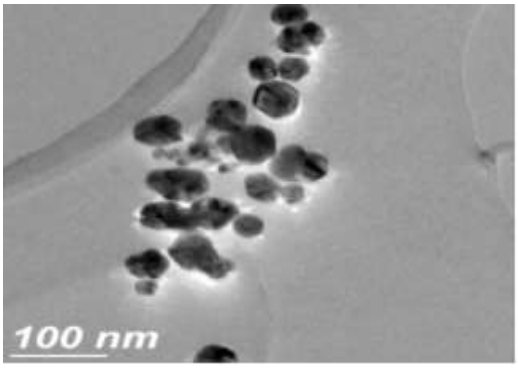

Fig. 1. Particles of silver of the nanometer range.
Nikolay N. Shkil with a co-author.

Analysis of the bactericidal action of drugs, depending on their combinations, made it possible to identify some general patterns regardless of the type of drugs. It was found that the reference *E. coli* ATCC 25922 strain possessed the highest sensitivity to all the studied antibiotics and their combinations with antibacterial drugs, except for the combinations of cloxacillin + DMSO and cloxacillin + DMSO + AgNPs.

The silver nanoparticles of the drug "Argovit" had the greatest effect of increasing bactericidal activity for all studied antibiotics both for the reference E. coli strain ATCC 25922 and for its isolate, except for the combination of cloxacillin (9.75 μg/ml) + AgNPs (2.5 μg/ml) + DMSO (19.5 μg/ml) and cloxacillin (4.86 μg/ml) + DMSO (9.75 μg/ml) with cattle isolate.

DMSO is widely used in biology and pharmacology to transport drugs into the cell to enhance its action *(Abdelgawad 2014).*

In this regard, the effect of DMSO in various combinations of drugs on their bactericidal action was studied. It was found that the bactericidal effect when using all the studied antibiotics with DMSO is significantly inferior to the combination of the antibiotic with silver nanoparticles, except for combinations such as cloxacillin + DMSO and cloxacillin + DMSO + AgNPs with *E. coli* isolate.

The bactericidal activity of silver nanoparticles against *E. coli* ATCC 25922 was 0.08, and the *E. coli* isolate was 0.32 μg/ml. The study of the bactericidal activity of DMSO for *E. coli* ATCC 25922 made it possible to establish it at the level of 9.75, and for the *E. coli* isolate it was 4.86 μg/ml.

The most resistant to the action of the antibiotic ceftimag and its combination with DMSO was the field isolate of *E. coli*, while DMSO did not affect the change in antibiotic sensitivity. The combination of ceftimag + AgNPs and ceftimag + AgNPs + DMSO made it possible to increase the bactericidal activity of the antibiotic by 57.7 and 7.2 times, respectively. A similar situation can be traced in the study of the reference *E. coli* strain ATCC 25922, where the increase in sensitivity was established by 128.4 and 8 times, respectively. At the same time, in combination with DMSO, an increase in bactericidal activity was found

16 times (from 312 to 19.5 μg/ml), and in combination with ceftimag + AgNPs + DMSO, 8 times (from 312.0 to 39.0 μg/ml).

The bactericidal activity of cypromag against *E. coli* isolates is 2 times less (625 μg/ml) than against the reference *E. coli* strain ATCC 25922 (312.0 μg/ml). A significant increase in antimicrobial activity from 78.0 to 10.0 μg/ml of cypromag was found when used together with AgNPs, while the additional inclusion of combinations with DMSO and DMSO + AgNPs did not affect the level of the minimum bactericidal concentration (625.0 μg/ml). When *E. coli* isolate was cultured with cypromag and AgNPs, the bactericidal concentration of cypromag was found to decrease to 10 μg/ml by 8 times, and the reference *E. coli* strains ATCC 25922 by 64.2 times.

Table 1. Antibiotic sensitivity of the reference *E. coli* ATCC 25922 strain and E. *coli* isolate to various combinations of antibacterial drugs

Combinations of antibacterial drugs	The bactericidal concentration of combinations of antibacterial substances, μg/ml					
	E. coli			*E. coli* ATCC 25922		
	Antibiotic	AgNPs	DMSO	Antibiotic	AgNPs	DMSO
Ceftimag	1125	-	-	312	-	-
Ceftimag +AgNPs	19,5	2,5	-	2,43	0,32	-
Ceftimag +DMSO	1125	-	1125	19,5	-	19,5
Ceftimag +AgNPs+DMSO	156	20	156	39	5	39
Cypromag	625	-	-	312	-	-
Cypromag +AgNPs	78	10	-	4,86	0,65	-
Cypromag + DMSO	625	-	625	312	-	312
Cypromag +AgNPs+ДМСО	625	78	625	156	20	156
Oxytetracycline	625	-	-	312	-	-
Oxytetracycline +AgNPs	9,75	1,25	-	1,21	0,16	-
Oxytetracycline + DMSO	312	-	312	39	-	39
Oxytetracycline +AgNPs+ DMSO	78	10	78	9,75	1,25	9,75
Enrofloxacin	156	-	-	78	-	-
Enrofloxacin +AgNPs	9,8	1,25	-	0,61	0,08	-
Enrofloxacin + DMSO	39	-	156	19,5	-	88,5
Enrofloxacin +AgNPs+ DMSO	156	20	625	9,76	1,25	39
Gentamicin	500	-	-	125	-	-
Gentamicin + AgNPs	4,6	1,25	-	1,15	0,32	-
Gentamicin + DMSO	125	-	312	37,5	-	78
Gentamicin +AgNPs + DMSO	75	20	156	4,6	1,25	19,5
Ampicillin	250	-	-	125	-	-
Ampicillin +AgNPs	19,5	1,25	-	0,6	0,04	-
Ampicillin + DMSO	78	-	39	19,5	-	9,75
Ampicillin +AgNPs+ DMSO	39	2,5	19,5	9,75	0,65	4,86
Cloxacillin	1250	-	-	625	-	-
Cloxacillin + AgNPs	39	10	-	1,21	0,32	-
Cloxacillin + DMSO	4,86	-	9,75	78	-	156
Cloxacillin +AgNPs+ DMSO	9,75	2,5	19,5	19,5	5,0	39,0

In the study, enrofloxacin showed bactericidal activity against *E. coli* isolate (156 μg/ml), which increased in combination with AgNPs by 16 times (from 156 to 9.8 μg/ml), and in the presence of DMSO by 4 times (with 156 to 39 μg/ml), while the simultaneous contact with DMSO and AgNPs did not change this indicator. The bactericidal activity of this antibiotic against the reference *E. coli* ATCC 25922 strain was characterized by an 8-fold increase in the presence of AgNPs (from 78.0 to 0.61 μg/ml), and a 4-fold increase in the combination of enrofloxacin + DMSO (from 78.0 to 19, 5 μg/ml), with a combination of enrofloxacin + AgNPs + DMSO by 8 times (9.76 μg/ml). Moreover, when studying different samples of *E. coli*, it was found that the addition of DMSO in combination with AgNPs significantly reduced the bactericidal activity of the antibiotic, both in the combination of enrofloxacin + AgNPs by 16 times and in the combination of enrofloxacin + DMSO by 2-4 times.

The antibacterial activity of DMSO with gentamicin affected the growth of *E. coli* ATCC 25922 by 3.3 times (from 125 to 37.5 μg/ml). The antibacterial activity of DMSO with gentamicin affected the growth of *E. coli* ATCC 25922 by 3.3 times (from 125 to 37.5 mcg/ml), and its isolate by 4 times (from 500.0 to 125.0 mcg/ml). The combined use of gentamicin, DMSO, and silver nanoparticles increased the bactericidal activity against the *E. coli* isolate by 6.7 times (from 500.0 to 75.0 μg/ml), and the *E. coli* ATCC 25922 strain by 27 times (from 125, 0 to 4.6 μg/ml).

The bactericidal activity of ampicillin in combination with AgNPs was significantly higher during cultivation of *E. coli* ATCC 25922 by 208 times (from 125.0 to 0.6 μg/ml) than *E. coli* isolate by 12.8 times (from 250.0 up to 19.5 μg/ml), relative to mono-use of the antibiotic.

Studies have shown the presence of adjuvant properties that enhance the bactericidal effect of the studied antibiotics. This phenomenon is based on a variety of complex mechanisms of the bactericidal action of silver particles against microorganisms. The antibacterial effect of AgNPs is due to its partial secretion and release of silver, which interacts with the cell wall of peptidoglycan and the plasma membrane, causing cell lysis, as well as acting on bacterial (cytoplasmic) DNA, causing appropriate DNA replication and bacterial proteins that causing disturbances in protein synthesis. Multifaceted antibacterial activity is a key factor in reducing bacterial resistance observed for silver and nanosilver preparations *(Aboelfetoh, 2017).*

The studies carried out to confirm the results of studies on the presence of the ability of nanoparticles of transition metals to influence the sensitivity of microorganisms and restore it to antibacterial agents *(Petica 2008).*

The relevance of the studies carried out is confirmed by the studies of other authors who observed the synergistic effect of silver nanoparticles in combination with erythromycin and levofloxacin against *Staphylococcus aureus*. Antimicrobial activity with antibiotics in comparison with pure silver nanoparticles increased by 1.16-1.32 times. This synergism may be relevant for the treatment of infectious diseases caused by multidrug-resistant bacteria *(Mamonova 2013).*

Studies have shown various changes in the sensitivity of *E. coli* to various types of antibiotics in combination with DMSO, AgNPs, and DMSO + AgNPs. The reference *E. coli* strain ATCC 25922 showed the highest sensitivity to all antibiotics and their combinations, except for the combinations of cloxacillin DMSO and cloxacillin DMSO AgNPs, which is probably due to the long absence of contact of the microorganism with antibiotics, in contrast to the isolate isolated from gastrointestinal diseases of cattle.

A significant increase in the bactericidal activity of antibiotics in the presence of DMSO can be explained by its high dissolving properties. In protic solvents, anionic-type reagents are masked by taking protons from solvent molecules. In aprotic dimethyl sulfoxide, the anions turn out to be “true” nucleophilic reagents, and therefore the reactions with them proceed at high rates. For example, the deuteration of optically active 2-methyl-3-phenylpropionitrile in dimethyl sulfoxide occurs 109 times faster than in methanol. It has been found that many reactions catalyzed by bases proceed in dimethyl sulfoxide, also much faster than in protic solvents. This conclusion is valid both for reactions with cleavage of C – H bonds and with cleavage of C – C bonds. For example, the rate of decarboxylation of 6-nitrobenzisoxazole-3-carboxylate in the presence of tetramethylguanidine increases by several orders of magnitude ongoing from protic to aprotic solvents. If the velocity in water is taken as 1, then in methanol it is 34, and in DMSO it is 1.4×10^6 *(Goggin 2014).* When studying the effect of DMSO on the bactericidal activity of antibiotics, both in mono-variant and in combination with AgNPs, it was found that the maximum bactericidal activity was established in the combination of nanoparticles and the studied antibiotics, except for the combinations of cloxacillin + DMSO and cloxacillin + DMSO + AgNPs. Besides, an increase in bactericidal activity in combination of antibiotics with DMSO depends on the type of drug, which is apparently justified by the chemical structure of the active substance and the sensitivity of the microorganism.

Besides, it was found that the antibiotic itself plays a decisive role in the degree of change in bactericidal activity, regardless of the additional introduction of DMSO and silver nanoparticles. Thus, the most pronounced increase in bactericidal activity in combination with AgNPs on the *E. coli* isolates and the reference *E. coli* strain ATCC 25922 was observed in ceftimag by 57.7 and 128.4 times, cypromag by 8 and 64 times, oxytetracycline by 64 and 258 times, enrofloxacin 16 and 128 times, gentamicin 108 times, ampicillin 12.8 and 208 times, cloxacillin 32 and 516 times, respectively.

The results of our study confirm the synergistic antibacterial effect of the combined use of AgNPs and antibacterial agents, which was established when determining the antimicrobial activity of silver nanoparticles and chlorhexidine gluconate against the five most common pathogenic bacteria of the human oral cavity. The average value of the minimum inhibitory concentration (MIC) of silver nanoparticles for *S. mutans* MTCC 497 was 60 ± 22.36 μg/ml, for *S. oralis* MTCC 2696 it was 45 ± 11.18 μg/ml, for L. acidophilus MTCC 10307 it was 15 ± 5.59 μg/ml, for *L. fermentum* it was 90 ± 22.36 μg/ml, for *Candida albicans* MTCC 183 was 2.82 ± 0.68 μg/ml, respectively. For chlorhexidine gluconate, the mean MIC for *S. mutans* MTCC 497 was 300 ± 111.80 μg/ml, for *S. oralis* MTCC 2696 was 150 ± 55.90 μg/ml, for *L. acidophilus* MTCC 10307 was 450 ± 111.80 μg/ml, for *L. fermentum* was 450 ± 111.80 μg/ml. and for *Candida albicans* MTCC 183 was 150 ± 55.90 μg/ml *(Jung, 2008).*

The results of our research showed the severity of bactericidal properties depending on the type of the studied drug. Literature data support the evaluation of the antibacterial effect using AgNPs and antibiotics against bacteria isolated from animals that exhibit antibiotic resistance by serial dilution.

The fractional index of inhibitory concentration was calculated and used to classify the observed collective antibacterial activity in terms of both synergistic effect and additive (only the sum of individual drug effects), indifferent (no effect), or antagonistic effect.

Of the 40 tests performed, 7 were synergistic, 17 additive, and 16 indifferent. None of the combinations tested showed an antagonistic effect. Most synergistic effects were observed with combinations of AgNPs administered with gentamicin, but the greatest enhancement of antibacterial activity was found with combination therapy with penicillin G against *Actinobacillus pleuropneumoniae, A. pleuropneumoniae* and *Pasteurella multocida*, initially resistant to amoxicillin, gentamicin and colistin, were susceptible to these antibiotics in combination with AgNPs. Research shows that AgNPs have potential as adjuvants for the treatment of bacterial diseases in animals *(Panpaliya, 2019).*

One of the reasons for the increase in the bactericidal activity of antibiotics against microorganisms when they are cocultivated with AgNPs is efflux effects, which play an important role in regulating the work of specific biomolecules that affect the sense of quorum and are responsible for the formation of biofilms. The transit movement of sensitive molecules inside or outside bacterial cells can be interrupted due to impaired functioning of the efflux pumps. Thus, AgNPs block the efflux effect of bacterial cells, which helps to restore the bactericidal properties of antibiotics, as well as to reduce the biofilm-forming ability of microorganisms *(Singh 2013).*

CONCLUSIONS

The analysis of the studies carried out allows us to identify some patterns of changes in the antibacterial properties of drugs during their mono- and complex use and draw conclusions:

1. The drug “Argovit” containing AgNPs both in mono-variant use and in combination with antibacterial drugs, as well as when included in AgNPs + DMSO, has a pronounced synergistic effect and significantly reduces the bactericidal concentration of the antibiotic.
2. The reference *E. coli* ATCC 25922 strain has the highest sensitivity of both AgNPs and their combination with antibiotics in comparison with the *E. coli* isolate, which was isolated from an animal with clinical manifestation of an infectious disease.
3. The combination of AgNPs and the antibiotic enrofloxacin, gentamicin, ceftimag, cypromag, oxytetracycline, ampicillin showed the greatest increase in bactericidal activity against both *E. coli* ATCC 25922 and E. coli isolate than in the combination of AgNPs + antibiotic + DMSO, except for cloxacillin when tested with *E. coli* isolate.

The results obtained open the prospect for further studies of AgNPs to assess the synergistic qualities of increasing the bactericidal properties of antibiotics against a wide range of infectious agents in the treatment of various pathologies.

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PREVIOUSLY PUBLISHED SCIENTIFIC ARTICLES ON THE RESEARCH TOPIC

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- N.N. Shkil, N.A. Shkil is a review of publications on the topic of the article;
- E.V. Nefyodova, G.A. Nozdrin is a research design development;
- N.N. Shkil, M.V. Lazareva is obtaining data for analysis, analyzing the data;
- O.V. Rasputina is writing the text of the manuscript.

CONFLICT OF INTEREST

The authors declare and argue that they have no conflicting (competing) financial or personal interests known to them that could influence the research described in this article.