ISSN 2079-1704. Хімія, фізика та технологія поверхні. 2024. Т. 15. № 3. С. 361-377

UDC 544.723 doi: 10.15407/hftp15.03.361

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INCREASE IN EFFICIENCY OF CHEMOTHERAPEUTIC DRUGS: PHYSICO-CHEMICAL FACTOR

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With the development of nanotechnology, new scientific directions have been initiated and a significant amount of researches has been carried out, dedicated to the creation and search for promising applications in medicine, in particular, oncology, of nanocomposites based on bioinert, biocompatible and bioactive nanoparticle materials and modern chemotherapeutic drugs with different mechanisms of action. These works contain data indicating the advantages to introduce nanocomposite drugs into clinical practice, compared to the traditional use of chemotherapeutic drugs. The research results confirm the priority of works in the field of creation of new nanocomposite chemotherapeutic drugs for use in antitumor therapy and overcoming of drug resistance of malignant cells and neoplasms.

The purpose of the review is to generalize and analyze the authors' experimental works performed at Chuiko Institute of Surface Chemistry of National Academy of Sciences of Ukraine, concerning the specifics of the effect of chemotherapeutic drugs with different mechanisms of action and related nanocomposites, on cellular systems and tumors. Such data are relevant to determine promising directions and ways of creation of new effective nanocomposite drugs for use, in particular, in antitumor chemotherapy.

At Chuiko Institute of Surface Chemistry of National Academy of Sciences of Ukraine, using the chemical engineering method, magnetically sensitive core-shell nanocomposites were synthesized with a multi-level hierarchical nanoarchitecture capable of performing a complex of diagnostic and therapeutic functions with various mechanisms of action, characteristic of medico-biological nanorobots. Their use makes it possible to implement the principle of targeted delivery of antitumor drugs, to carry out real-time local therapy by various methods and MRI diagnosis of the disease, to realize the synergy of treatment with antitumor drugs of different mechanisms of action, to reduce the toxic side effects of oncological drugs on the body. The combination of the above features of nanocomposites, as well as their role in overcoming the drug resistance of cells of malignant neoplasms to cisplatin, testify to the perspective of creation and research of nanocomposite drugs in solving the problem of increase in the efficiency of chemotherapy.

***Keywords**: malignant cells and tumors, chemotherapeutic drugs, nanocomposites, resistance, efficiency*

INTRODUCTION

The world faced a problem to increase the efficiency of medical treatment of serious diseases, in particular, infectious viral and bacterial, malignant cell neoplasms, *etc*., with drugs. The problem has become extremely acute and urgent all over the world in our time, and the search for ways to solve it has gained planetary importance. Convincing evidence of this is the example of COVID-19 coronavirus pandemic.

Among the main problems that prevent the effective use of modern anticancer chemotherapy, the most relevant is the development of resistance of malignant cells to chemotherapeutic drugs [1–8], in particular, cytostatics based on platinum. It is known that such drugs, for example, based on platinum, are characterized by high antitumor activity with a wide spectrum of action and are used in almost all schemes of modern clinical chemotherapy. Currently, even the problem of their acute cardio-, nephro-, and neurotoxicity is being solved, in particular, through the use of targeted delivery [9–12] to specific organs or cells and local therapy methods [13–18], while resistance has become a globally recognized problem since the 90s of the last century [1–7], which is only complicated over time by the emergence of new types and mechanisms [7, 8].

The reason of this situation is the natural or acquired capability of tumor cells to resist even the newest chemotherapeutic agents. As a result, new mechanisms of resistance arise, which calls for the creation of new drugs [5, 8]. The causes and consequences of the problem are combined, the situation becomes hopeless.

In this connection, it is worth mentioning the publication in 2003 of the collective monograph:

Medicinal chemistry and clinical use of silicon dioxide. Edited by Academician of NAS of Ukraine O.O. Chuiko. "*Scientific book" project. Kyiv, Naukova Dumka, 415 p.,* which became the first generalization of the results of fundamental physicochemical and biomedical research into adsorption interactions of highly dispersed silica with bioactive molecules, biopolymers, biomembranes, cells, microorganisms, and viruses at the Institute of Surface Chemistry of National Academy of Sciences of Ukraine. In particular, it lays out the scientific principles and outlines the areas of clinical application of highly dispersed silica in the form of individual and composite therapeutic agents for detoxification, antimicrobial, hemostatic and antisclerotic action, many of which later found application in clinical practice. Among other things, it was reported that compositions of silica particles with antibiotics and many other medical drugs significantly increased their effectiveness. In general, this book became an example of interdisciplinary academic research, received wide recognition in Ukraine and beyond, demonstrated the introduction of nanotechnology into the domestic biomedical industry.

In addition, the value of this book also consisted in the fact that the prepared reader could see a new promising way to create highly effective generations of modern nanocomposite medicines. That is, on the agenda for the development and production of new effective drugs, the physico-chemical aspect appeared, the availability, importance, and wide applicability of which still needed to be verified.

In continuation of the above studies, since 2002, at Chuiko Institute of Surface Chemistry of National Academy of Sciences of Ukraine, as a promising new scientific direction, the works were started with the common idea of chemical construction of magnetically sensitive nanocomposites (NC) of the core-shell type with a multi-level hierarchical nanoarchitecture capable of performing a complex of functions, characteristic for medical and biological nanorobots [19–22]: recognition of microbiological objects in biological environments; targeted delivery of drugs to specific cells and organs, and deposition; complex local chemo-, immuno-, neutron capture-, hyperthermic-, photodynamic therapy and magnetic resonance imaging (MRI) diagnostics in real time, detoxification of the body by adsorption of toxins, virus particles, heavy metal ions, *etc*. and their removal using a magnetic field. On this basis, together with R.E. Kavetsky Institute of Experimental Pathology, Oncology and Radiobiology of NAS of Ukraine, a number of unique nanocomposite models of effective modern medical theranostic magnetically controlled means was created, researched and patented, primarily for the needs of oncology [23–26]. In these nanocomposite agents, as antitumor components were the most commonly applied chemotherapeutic drugs in clinical practice: cisplatin, doxorubicin, gemcitabine, as well as corresponding antibodies, which formed multi-layer shells, fixed in a certain order around the core of NC – a nanosized carrier, nanoparticles of single-domain magnetite. If needed, the surface of carriers was modified with the necessary chemical groups or substances [27–31]. In order to ensure the effective functioning of NC in the biological environment, new related magnetic fluids (MF) were created, studied and patented, physicochemical and magnetic properties were investigated, chemical composition, therapeutic effectiveness were optimized, measures were taken to standardize, control the parameters of MF and NC and NPs in their composition, *etc*. [32–34]. As a result, it was possible not only to confirm the better effectiveness of nanocomposite models of drugs (in comparison with the corresponding chemotherapeutic drugs in traditional use), but also to reveal the possibility of overcoming drug resistance to cisplatin [35].

Since 2020, the specified direction has received incentives for development through joint research with O.O. Bogomolets Institute of Physiology of NAS of Ukraine and O.O. Bogomolets National Medical University, aimed at the development of promising nanostructures for use in optopharmacology and photodynamic therapy [36–39], in particular, for the treatment of infectious and tumor diseases of bones [40–42].

The facts of achieving high levels of cytotoxic/cytostatic activity of nanocomposites, as well as overcoming drug resistance of cells of malignant neoplasms to cisplatin, have important scientific and practical significance. Therefore, the purpose of this review is to generalize and analyze the authors' experimental data concerning the specifics of the effect of

chemotherapeutic drugs with different mechanisms of action and related nanocomposites on cellular systems and tumors, which may be relevant to determine promising directions and ways of creation of new effective nanocomposite drugs for application, in particular, in antitumor chemotherapy.

MULTIFACTOR NATURE OF RESISTANCE

In medical oncology practice, a common phenomenon is positive dynamics of the condition of patients at the beginning of treatment with platinum drugs, and the loss of the achieved effect and the emergence of resistance at the later stages of treatment. Usually, resistance to cisplatin is more than one of a large number of revealed mechanisms, which consist in changing the level of expression of a variety of proteins due to genetic (mutations, genetic transformation) or epigenetic (changes in DNA methylation, miRNA expression) factors. According to [2], the presence of more than one mechanism of cell resistance to cisplatin indicates the multifactorial nature of resistance. To date, it has been revealed that the resistance of tumor cells can be associated with a decrease in the accumulation of chemotherapeutic drugs in cells, an increase in the activity of detoxification systems, an increase in DNA repair processes, a decrease in apoptosis, and autophagy.

BIOACTIVITY OF NANOCOMPOSITES OF BIOCOMPATIBLE CARRIER – DRUG TYPE

Resistance to antibiotics. Antibiotic resistance is the capability of microorganisms to survive and reproduce despite the presence of antibiotics. Antibiotics are traditionally divided into natural and semi-synthetic (modified products of natural molecules). The 1950s and 1960s are considered as the “golden” period in antibiotic research. Since then, microbes have significantly improved their resistance to antibiotics [43]. Nowadays, the source for the production of new antibiotics is soil bacteria, but finding of new effective antibiotics is quite a difficult task, and over time, microorganisms develop resistance mechanisms to them as well. This is observed even with not too frequent use of a new antibiotic.

In recent decades, in connection with the invention of many very strong antibacterial chemopreparations, the concept of “antibiotic” began to blur and expand, so now it is often used not only in relation to natural and semi-synthetic compounds, but also to many strong antibacterial chemopreparations.

Nowadays, such antibiotics as doxorubicin, adriamycin, olivomycin, rubomycin, *etc*. have found wide application in antitumor chemotherapy.

Features of bioactivity of chloramphenicol - nanodispersed silica nanocomposite.

As known, chloramphenicol is not used as an anticancer drug. However, the study of its joint action with nanosized silica gave interesting and important results.

For example, in [44], the effect of chloramphenicol, adsorbed onto the surface of nanodispersed silica (chloramphenicol-SiO_2 nanocomposite (NC)), was studied on the growth of colonies of baker’s yeast *Saccharomyces cerevisiae* (a non-pathogenic microorganism) and *Escherichia coli* cells (a conditionally pathogenic microorganism) in aqueous suspensions (Fig. 1). The Origin program was used for data processing.

In order to determine the effect of chloramphenicol-SiO_2 NC on yeast cells, experiments were carried out by studying the interaction of *S. cerevisiae* with nanosilica, pure chloramphenicol, as well as with NC – nanosilica impregnated with an antibiotic (conjugate of chloramphenicol with silica). The volume and dynamics of carbon dioxide release were measured in fermentation process per unit of time, as well as biomass growth.

In the process of fermentation, an active process of cell division takes place, which occurs under conditions of a sufficient amount of nutrients. Over time, waste products accumulate in the solution, and the amount of nutrients decreases. This leads to a slowdown in the process of cell division and a decrease in gas production (Fig. 1 *a*, control samples 1).

The presence of chloramphenicol (Fig. 1 *a*, samples 2) significantly suppresses the vital activity of yeast cells and, accordingly, the rate of carbon dioxide formation decreases. The effect of the antibiotic further enhances when fermentation occurs in the presence of silica in the composition of NC with chloramphenicol in the same dose, which is accompanied by a decrease in the amount of carbon dioxide formed (Fig. 1 *a*, samples 3). However, the mass of CO_2 formed in the presence of silica at a

concentration of 0.034–0.06 % (without chloramphenicol) was close to that of the control sample, and even exceeded its value at SiO_2 concentration of 0.1 % (Fig. 1 *a*, samples 4–6).

Similar studies were carried out also regarding the effect of chloramphenicol-SiO_2 NC and its ingredients on *E. coli*. The obtained results are shown in Fig. 1 *b*. Thus, in relation to *E. coli* cells, a significant increase was recorded in the activity of chloramphenicol immobilized on the surface of highly dispersed silica (Fig. 1 *b*, samples 4), compared to the action of individual chloramphenicol (Fig. 1 *b*, samples 3), and the stimulating effect of pure silica on cells was observed (Fig. 1 *b*, samples 2), compared to the control (Fig. 1 *b*, samples 1).

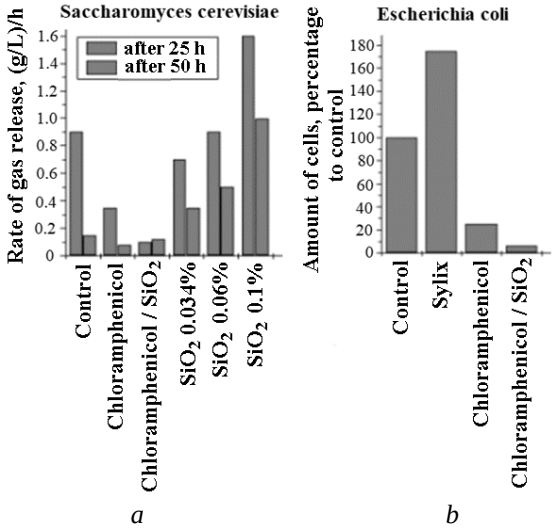

Fig. 1. Effect of highly dispersed silica and nanocomposites based on chloramphenicol on the development of test cultures of yeast cells and *E. coli* cells [44]

Thus, a significant activating effect of silica on the growth of cell biomass in aqueous suspensions was revealed. So, the cultivation of cells in the presence of nanosilica gives an increase in biomass almost twice, and when interacting with yeast cells, some stimulating activity is observed even for samples of silica impregnated with chloramphenicol. This effect can be explained by the beneficial influence on cell proliferation of adsorption purification of the medium from the waste products of cells with small doses of nano-sized biocompatible silica adsorbent.

It is of particular importance to reveal the fact that for chloramphenicol immobilized on the surface of highly dispersed silica in *E. coli* suspensions, the antimicrobial activity increases almost 4 times compared to a pure antibiotic solution of the same concentration. Thus, nanosized silica in the composition of NC considerably increases the activity of the antibiotic, and this significantly expands the possibilities of its use. The mechanism of activation of the drug immobilized on silica surface is explained in [44] by the possibility of appearing of weakly associated water at the boundary of nanocomposite with the surface of cell membranes, which facilitates its penetration into the intracellular space.

Bioactivity of nanocomposites based on doxorubicin and nanodispersed magnetite.

Doxorubicin ($C_{27}H_{29}NO_{11}$) [45] is an anthracycline antitumor antibiotic characterized by antimitotic and antiproliferative effects. The mechanism of antitumor activity consists in interaction with DNA, production of free radicals and direct action on cell membranes with suppression of nucleic acid synthesis. Cells are sensitive to the drug in S- and G2-phases. Nowadays, it is used in almost all schemes of chemotherapy for oncological diseases.

The main goal of the work [46] was to study the cytotoxic effect of new magnetically carried multifunctional nanocomposites based on single-domain magnetite (Fe_3O_4) and doxorubicin on *S. cerevisiae* cells. The setting of the research involved the experimental working at chosen objects of available methods of preclinical

control of the cytotoxic activity of nanocomposites containing doxorubicin and models for new forms of related medicines.

To study the bioactivity of nanostructures based on doxorubicin and nanodispersed one-domain magnetite, the following NC were synthesized: Fe_3O_4/doxorubicin (DOX), Fe_3O_4/silica (SiO_2)/DOX, Fe_3O_4/titanium dioxide (TiO_2)/DOX, Fe_3O_4/hydroxyapatite (HAP)/DOX. DOX immobilization was carried out onto the surfaces of Fe_3O_4 and Fe_3O_4/SiO_2, Fe_3O_4/TiO_2, Fe_3O_4/HAP by the adsorption method from the medium of physiological saline (PS).

For Fe_3O_4 nanostructures and Fe_3O_4/SiO_2, Fe_3O_4/TiO_2, Fe_3O_4/HAP NC, the studies of biocompatibility were carried out based on their influence on the viability of baker's yeast cells *S. cerevisiae*.

Cell viability was determined by a cytochemical method. The bioactivity of nanostructures modified with DOX was assessed by their cytotoxic effect on *S. cerevisiae* cells and a decrease in the rate of cell proliferation. The obtained data were compared to the results of studies on control series of samples.

Detailed information concerning the research is given in [46, 47]. Their conclusions indicate that magnetosensitive nanocomposites Fe_3O_4/DOX, Fe_3O_4/SiO_2/DOX, Fe_3O_4/TiO_2/DOX, Fe_3O_4/HAP/DOX exhibit high cytotoxic and antiproliferative activity against *S. cerevisiae* yeast cells, the action of which is characteristic of the anthracycline antibiotic doxorubicin. A fairly effective, reliable, safe and relatively inexpensive technique was developed to control the cytotoxic activity of nanocomposites with the aid of the chosen objects, which may be useful for application in the development of new medicinal magnetically carried means for targeted delivery.

The work [48] describes the production and characteristics of nanocomposites based on iron oxide nanoparticles loaded with doxorubicin, designed to overcome multiresistance. Studies were carried out using C6 glioma cells of wild-type rats, resistant to doxorubicin. Research results suggest that DOX-conjugated iron-containing nanoparticles can improve the efficacy of chemotherapy by overcoming multiresistance.

Features of the bioactivity of nanocomposites based on magnetite and cisplatin. Cisplatin is one of the most effective anticancer drugs used in almost all modern chemotherapy schemes. The drug is used in clinical practice since the early 1980s, and it is the most studied in terms of its effect on malignant cells and tumors, the mechanisms of their resistance. The active substance is a complex compound *cis*-diamminedichloroplatinum (*cis*-$[Pt(NH_3)_2Cl_2]$). The mechanism of antitumor action of cisplatin is associated with the ability to bifunctional alkylation of DNA chains, which causes disruption of replication and transcription at the cellular level and leads to cell cycle delay and apoptosis.

In [28, 29, 32–34], the results of developments and researches are summarized and systematized related to the synthesis of nanosized single-domain magnetite (Fe_3O_4), chemical modification of its surface with molecules, groups and substances of different chemical nature, drugs with different mechanisms of action, as well as study of sorption properties of Fe_3O_4 and polyfunctional NC related, biocompatibility and bioactivity of NC and directions of their medical and biological applications, *etc*., and data are given concerning the conditions and parameters under which the relevant chemical, physical and biological experiments, tests, trials have been carried out.

Table 1 shows data of the adsorption capacity of the surface of magnetosensitive Fe_3O_4 and NC of Fe_3O_4/dimercaptosuccinic acid (DMSA), Fe_3O_4/γ-aminopropyltriethoxysilane (APS), Fe_3O_4/polyacrylamide (PAA), Fe_3O_4/hydroxyapatite (HAP) in relation to complexes of *cis*-diamminedichloroplatinum (CP), and their distribution coefficient and extraction extent during immobilization from the PS medium [13]. The results of numerous tests, checks and trials have proved that the synthesized and studied Fe_3O_4/CP, Fe_3O_4/DMSA/CP, Fe_3O_4/γ-APS/CP, Fe_3O_4/PAA/CP, Fe_3O_4/HAP/CP nanostructures are characterized by a therapeutically significant contents of CP, and the processes of adsorption immobilization of CP onto the surface of Fe_3O_4 carrier, and its modified forms, are promising for the creation of appropriate magnetic fluids with cytotoxic properties. It should be noted that surface modifications of magnetically sensitive Fe_3O_4 carriers were realized in this work with the

aim to find possibilities to control the contents of the drug, and their optimization in the composition on NC. For comparison, in Table 1 the data are shown of the adsorption capacity of *cis*-diamminedichloroplatinum onto nano-dispersed silica (A300) SiO_2 and its modified form SiO_2/DMSA.

Table 2 shows the results of research into the effect of magnetically sensitive nanocomposites of complex therapeutic action (with adsorbed CP and conjugated CD 95 monoclonal antibodies, in appropriate concentrations, *C*) on the viability of breast cancer cells (human breast cancer of MCF-7 line) [23].

Table 1. Adsorption capacity of *cis*-diamminedichloroplatinum of magnetically sensitive nanostructures with different chemical nature of the surface [13]

Nanostructure type	Adsorption capacity *A*, mg/g	Distribution coefficient *E*, L/g	Extraction extent *R*, %
Fe_3O_4	80.10	2.16	66.20
Fe_3O_4/DMSA	83.40	4.77	85.40
Fe_3O_4/γ-APS	84.00	12.92	93.80
Fe_3O_4/PAA	109.5	16.2	99.90
Fe_3O_4/HAP	54.00	1.08	64.80
SiO_2	75.10	2.50	65.50
SiO_2/DMSA	80.20	4.41	74.40

Table 2. Influence of magnetically sensitive NC with adsorbed CP, conjugated with monoclonal antibodies CD 95, on the viability of MCF-7 cells [20, 23]

Control for comparison	Amount of dead cells, %						
	Action of control	Fe_3O_4/ +CP	Fe_3O_4/ + CD 95	Fe_3O_4/ + CP + CD 95	Fe_3O_4/ γ-APS +CP	Fe_3O_4/ γ-APS +CD 95	Fe_3O_4/ γ-APS +CP + CD 95
CP, 2.5 μg/mL	25	34	–	–	31	–	–
CD 95, 0.2 μg/mL	10	–	25	–	–	20	–
CP + CD 95	40	–	–	46	–	–	46

Extension of Table 2

Control for comparison	Amount of dead cells, %						
	Action of control	Fe_3O_4/ PAA +CP	Fe_3O_4/ PAA +CD 95	Fe_3O_4/ PAA +CP +CD 95	Fe_3O_4/ HAP +CP	Fe_3O_4/ HAP +CD 95	Fe_3O_4/ HAP +CP + CD 95
CP, 2.5 μg/mL	25	38	–	–	48	–	–
CD 95, 0.2 μg/mL	10	–	21	–	–	27	–
CP + CD 95	40	–	–	57	–	–	57

Table 3. Effect of cisplatin on the viability of cells of A2780 line [19]

Sample	IC_{50}
	Amount of dead cells, %
CP	52
Fe_3O_4/PAA	2
Fe_3O_4/PAA + CP	65

As control samples, we used pure nutrient medium, CP (C = 2.5 μg/mL, according to IC 0.25) and monoclonal antibody CD 95, C = 0.2 μg/mL. Previously, the biocompatibility of original magnetite and Fe_3O_4/DMSA, Fe_3O_4/γ-APS, Fe_3O_4/PAA, Fe_3O_4/HAP nano-composites was studied with respect to MCF-7 line.

Analysis of data of Table 2 allows us to conclude that in all the investigated cases, in relation to MCF-7 cells, the cytotoxicity of magnetosensitive NC based on magnetite and cisplatin, as well as in the presence of the model antibody CD 95, is significantly higher than in mono-use of the indicated drugs. A similar conclusion turned out to be valid also when studying the effect of cisplatin on the viability of human epithelial ovarian carcinoma cells of A2780 line (Table 3).

BIOACTIVITY OF NANOBIOCOMPOSITES

Magnetic fluids for medical and biological purposes, containing magnetosensitive single-domain superparamagnetic nanoparticles of various chemical nature (for example, iron, nickel, cobalt, transition metal ferrites, *etc*.), drugs with a therapeutic or diagnostic mechanism of action, or related nanocomposites based on them, are of great interest to researchers, in particular, due to the convenience of practical application. Therefore, we synthesized magnetic fluids based on physiological solution, single-domain magnetite (ferrimagnetic) and antitumor drugs (nanobiocomposites, NBC), and investigated their bioactivity.

In vivo research of magnetic fluids modified with cisplatin. Samples of the synthesized magnetic fluids based on nanocomposites with immobilized cisplatin and additionally modified with polyethylene glycol were investigated at R.E. Kavetsky IEPOR of National Academy of Sciences of Ukraine [49]. The cytotoxic effect (on Ehrlich ascites and Guerin solid carcinomas) was defined for such NBC: Fe_3O_4/sodium oleate (Ol.Na)/polyethylene glycol (PEG) (C_{MF} = 3 mg/mL); Fe_3O_4/Ol.Na/PEG/CP. Processing of the obtained results was carried out using the mathematical program of medico-biological statistics STATISTICA 6.0. Calculation and comparison of the reliability of differences in mean values was realized using the Student's *t*-test; differences with a probability of at least 95 % were considered reliable ($p < 0.05$).

Study of the cytotoxic effect of magnetic fluids on Ehrlich ascites carcinoma.

The study was carried out on male hybrid mice (C57Bl/6xDBA/21 line). The animals were intraperitoneally transplanted with Ehrlich ascites carcinoma in the amount of $2 \cdot 10^6$ cells per mouse. The dose of Fe_3O_4 was 2 mg/kg of their body weight, cisplatin was 2 mg/kg. Further, the antitumor activity of NBC was defined by the average number of days that the test mice lived (compared to control mice).

The percentage of growth inhibition (γ, %) of Ehrlich ascites tumor was estimated by the formula: $\gamma = (\alpha/\beta)100$, where α is the difference between the number of days lived by animals in the control and experimental groups; β is the number of days lived by animals of the control group.

As seen from the data below, the difference has not been reliably determined between the average number of days lived by the animals of the control group, and those who received magnetic fluid Fe_3O_4/Ol.Na/PEG intraperitoneally, which is illustrated by the data in Table 4.

Table 4. Antitumor activity *in vivo* of magnetic fluid against cells of Ehrlich ascites carcinoma [24]

Animal group	Survival, days
Control (physiological saline)	17.0 ± 1.4
CP	23.0 ± 1.0*
Fe_3O_4/Ol.Na/PEG	18.2 ± 1.1
Fe_3O_4/Ol.Na/PEG/CP	24.8 ± 1.2*

Note: *$p < 0.05$ compared to the control group of animals

At the same time, these data confirmed that for mice that received cisplatin and NBC Fe_3O_4/Ol.Na/PEG/CP based on PS, on a reliable basis, an increase in survival was revealed by 35 and 46 %, respectively (compared to the control group of animals).

So, it has been experimentally proven that the use of NBC Fe_3O_4/Ol.Na/PEG/cisplatin is effective for the treatment of tumors of Ehrlich ascites carcinoma.

Investigation of the cytotoxic effect of magnetic fluids on Guerin solid carcinoma.

The study was carried out on male laboratory rats (n = 10) of "Wistar" line with a weight of 120 ± 5 g. Subject animals were transplanted subcutaneously on the back with a 25 % suspension of tumor tissue of Guerin carcinoma in PS (0.4 mL of suspension for each rat). The data in Table 5 characterize antitumor activity *in vivo* of NBC Fe_3O_4/Ol.Na/PEG/CP against Guerin carcinoma cells compared to cisplatin, depending on the influence of a constant magnetic field.

Table 5. Antitumor activity *in vivo* of NBC against cells of Guerin solid carcinoma [24]

Animal group	Weight of tumor, g
Control (physiological saline)	31.8 ± 2.4
CP	23.4 ± 2.5*
CP + magnetic field	19.6 ± 2.9*
Fe_3O_4/Ol.Na/PEG/CP	19.2 ± 2.1*
Fe_3O_4/Ol.Na/PEG/CP+ magnetic field	13.4 ± 1.7*

Note: *p < 0.05 compared to the control group of animals

It was revealed that cisplatin (the sample for comparison) inhibited tumor growth by 26.4 % of weight. It was shown that in animals injected with NBC Fe_3O_4/Ol.Na/PEG/CP, the weight of tumor decreased by 40.2 % compared to the control group of animals. The largest percentage of the corresponding inhibition was revealed in rats, for which NBC Fe_3O_4/Ol.Na/PEG/CP was applied combined with a constant magnetic field. In these experimental animals, the weight of tumors decreased by 57.9 % compared to animals of the control group.

So, it has been experimentally proven that the use of NBC Fe_3O_4/Ol.Na/PEG/cisplatin is effective in combination with a constant magnetic field for the treatment of Guerin carcinoma tumors.

Overcoming of the resistance of malignant cells and tumors to cisplatin using NBC. In studies [35], a magnetic fluid [50] containing PS, nanosized magnetite and cisplatin [51] was used for production of NBC. The parameters of the original standardized MF are given in Table 6 [33].

Table 6. Parameters of standardized MF [33]

Quantity and measuring unit	Value
Concentration of magnetite, mg/mL	14
Size of magnetite particles, nm	4–22
Average size of magnetite particles, nm	10.8
Average size of magnetite particles stabilized with sodium oleate, nm	16.8
Saturation magnetization M_s, Gs	14.1±2.5 %
Hypsometric height, cm	25±10 %
Density ρ_{MF}, g/cm^3	1.14±1.0 %

The cytotoxic activity of NBC was determined *in vitro* on cisplatin-resistant human breast cancer cells of MCF-7 line (MCF-7/CDDP). The technique of preparing MCF-7/CDDP samples for research is given in [52, 53]. The adsorption method was applied for immobilization of the cytostatic agent on the surface of magnetic fluid nanoparticles of Fe_3O_4/Ol.Na system with a concentration of C_{Fe3O4} = 3 mg/mL, C_{CP} = 0.4 μg/mL.

According to the results of the tests, it was revealed that IC50 concentration for cisplatin was 12.5 μg of cisplatin/mL, and for NBC – 7.5 μg of CP/mL, which explains its higher cytotoxic effect against breast cancer cells resistant to cisplatin (Fig. 2).

The antitumor effect of NBC was determined in Wistar rats with cisplatin-resistant Guerin carcinoma, which were injected with the ferrimagnetic nanobiocomposite, compared to a group of animals that were injected with CP. NBC exerted a reliable antitumor effect on tumors of cisplatin-resistant strain: the average volume of tumors decreased from 20.2±1.0 cm^3

in the control group to 12.1±2.4 cm^3 in animals injected with the nanobiocomposite (Fig. 3), the percentage of inhibition of tumor growth was 40 % (Fig. 4).

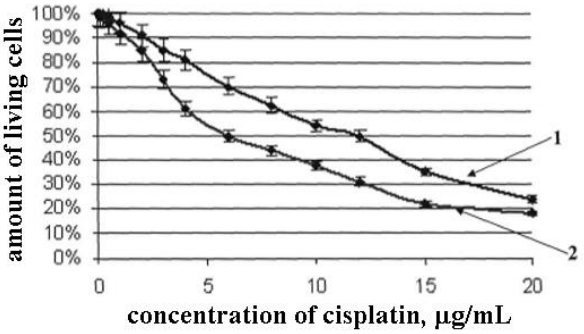

Fig. 2. Cytotoxic activity of CP and NBC against cisplatin-resistant human breast cancer cells of MCF-7/CDDP line. The abscissa axis is the concentration of cisplatin (μg/mL), the ordinate axis is the percentage of living cells. Designation: *1* – CP; *2* – NBC [35]

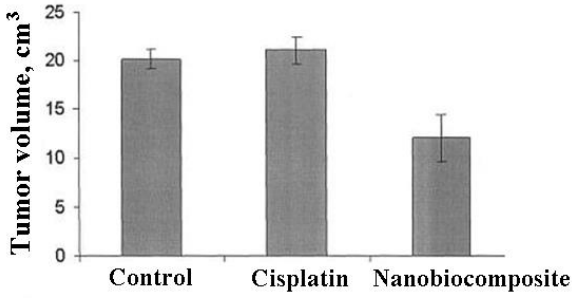

Fig. 3. Average tumor volume of cisplatin-resistant Guerin carcinoma after cisplatin and NBC therapy. The abscissa axis is groups of animals that were affected by various factors, the ordinate axis is tumor volume (cm^3) [35]

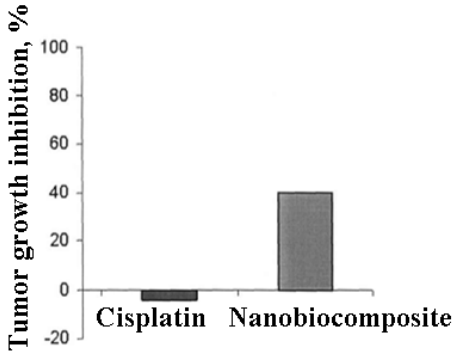

Fig. 4. Growth inhibition (%) of cisplatin-resistant Guerin carcinoma after cisplatin and nanobiocomposite therapy [35]

In comparison to cisplatin, the biological safety of NBC was evaluated by the general and biochemical parameters of blood of Wistar rats after the completion of a course of therapy.

It was revealed based on the results of research, that NBC is not more toxic than the official anticancer drug cisplatin according to general and biochemical blood parameters. It was also revealed that side effects of NBC do not differ from those of official cisplatin in terms of impact on vital organs of animals. In addition, antitumor NBC is capable of selective accumulation in the tumor site, improving the antitumor effect of cisplatin in tumors with a

drug resistance phenotype while maintaining the level of biological safety and toxic effects [35].

Peculiarities of mechanism of cytotoxic action of nanobiocomposite based on magnetite, cisplatin and doxorubicin. The study [52] indicated that for MCF-7 human breast cancer cells with acquired resistance to chemotherapeutic drugs doxorubicin (MCF-7/DOX) and cisplatin (MCF-7/CDDP), significant changes are observed in the contents and levels of intracellular iron. This also applies to proteins that regulate iron contents and participate in its cellular uptake, storage and export, especially when the levels of ferritin light chain protein (FTL) are strongly increased. Elevated levels of FTL can be used as a diagnostic and prognostic marker for breast cancer. In addition, it has been shown that microRNA miR-133a performs targeted regulation of FTL protein, increasing sensitivity of MCF-7/DOX and MCF-7/CDDP cells to doxorubicin and cisplatin. These results indicate that correction of iron metabolism disorders can significantly increase the efficiency of breast cancer treatment.

In [53], the advantages were proven *in vitro* and *in vivo* to use magnetically sensitive nanobiocomposites based on magnetite and cisplatin compared to the traditional use of cisplatin. It was found that in relation to the resistant line MCF-7/CDDP, these NBC are characterized by the highest cytotoxic activity. This is explained by a more effective accumulation of iron oxide nanoparticles in cells due to a high level of transferrin receptors (rTF) and disruption of the antioxidant defense system of resistant cells (an increase in the role of reactive oxygen species, as well as heavy and light FTL chains). It was experimentally revealed that NBC is capable of causing more pronounced cytomorphological changes and genotoxic effects in cells of the resistant line, compared to cells of the sensitive line. *In vivo* experiments showed that NBC is able to inhibit the growth of cisplatin-resistant Guerin carcinoma by 41 % (Fig. 7). The obtained data testify to the higher therapeutic efficiency of the nanobiocomposite and the selectivity of its action in relation to resistant tumors, and indicate the perspective of its use in order to overcome drug resistance to cisplatin. At the same time, it was revealed that the side effects of NBC on the animal body and toxicity to vital organs are more tolerant than the effect of cisplatin. In fact, for the first time in the *in vitro* system, the mechanisms of the effect of NBC on sensitive and resistant to cytostatics MCF-7/CDDP tumor cells were investigated. It was revealed that in the mechanisms of implementation of the apoptotic program under the influence of NBC, a significant role is played by disturbances in endogenous iron metabolism. Under the influence of NBC in MCF-7 human breast cancer cells, a significant increase is observed in the level of “free iron”, which contributes to the formation of reactive oxygen species and causes oxidative stress (Fenton reaction). In resistant cells, under the influence of NBC, the consequence of oxidative stress is the induction of apoptosis and strengthening of lipid peroxidation processes. It has been proven that NBC is capable of initiating an apoptotic program in cells of the resistant line via a mitochondrial pathway. It was revealed that the nanobiocomposite is able to cause structural and functional rearrangements of biological membranes and to reduce the invasive properties of cells with the phenotype of drug resistance to cisplatin [51].

Magnetosensitive nanocomposites and magnetic fluids based on magnetite, gemcitabine and HER2 antibody. Gemcitabine (GC) - (2-deoxy-2',2)difluorocytidine monochloride) is a cytotoxic drug, an antimetabolite from the group of pyrimidine antagonists. GC refers to the List of Essential Medicines of the World Health Organization and the most effective and safe medicines needed in the health care system. The mechanism of action of the drug consists in the inhibition of the enzyme ribonucleotide reductase, which leads to a violation of DNA synthesis, another possible mechanism of action of the drug is considered to be the capability of gemcitabine to integrate into the structure of DNA and RNA, as a result, the synthesis of pyrimidine nucleotides is inhibited in the S-phase of mitosis. Common side effects include bone marrow suppression, liver and kidney disturbances, nausea, fever, rash, shortness of breath, and hair loss [54, 55]. Therefore, at this time, the possibility is actively studied to use GC as a part of magnetosensitive NC for the purpose to create multifunctional antitumor drugs for targeted delivery and local therapy, for example, of breast cancer, hepatocellular carcinoma, osteosarcoma, *etc*. [56–58].

Antibody (AB) Her2 (Neu, ErbB-2, CD340) is a membrane protein, a tyrosine protein kinase of the epidermal growth factor receptor EGFR/ErbB family, which is encoded by the human ERBB2 gene. Amplification of HER2 gene plays an important role in the pathogenesis and progression of certain aggressive types of cancer [59, 60]. Her2 is an important biomarker and therapeutic target of the disease, associated with tumor aggressiveness and poor prognosis. It is known that Her2 AB is considered as one of the optimal antibodies for the treatment of such diseases as cancer of gastrointestinal tract, in particular, in the presence of metastases in liver.

Therefore, in [61, 62], a nanobiocomposite was synthesized containing a magnetic fluid based on PS, magnetite, gemcitabine and Her2 AB, modified by Ol.Na and PEG, as well as comparison samples, their properties were studied, and activity was investigated *in vitro* against hepatocellular carcinoma (HCC) tumor cells of human liver of HepG2 line. HCC is the most common primary malignant form of liver cancer, the result of malignant transformation of hepatocytes, a serious and highly lethal disease.

In [14, 61–64], data are given concerning techniques of experiments, production of samples, auxiliary materials, *etc*. To study the direct cytotoxic/cytostatic effect of series of experimental samples of magnetic fluids based on Fe_3O_4, GC, Fe_3O_4@GC NC, Her2 AB, in mono- or complex application on HepG2 cells *in vitro*, the IC50 indicator was determined. In total, the following series of samples were produced for research:

1. MF: Fe_3O_4@Ol.Na/PEG+PS,
2. Gemcitabine,
3. HER2 AB,
4. MF + GC: Fe_3O_4@GC/Ol.Na/PEG+PS,
5. MF + AB: Fe_3O_4@Ol.Na/PEG+PS+HER2,
6. NBC: MF + GC + AB: Fe_3O_4@GC/Ol.Na/PEG+PS+HER2,
7. GC + HER2,
8. PS.

Table 7 shows the results of the influence of experimental samples on the viability of HCC cells of human liver of HepG2 line.

Table 7. Effect of experimental samples on the viability of HCC cells of human liver of HepG2 line [63]

Sample Concentration			MF	GC	HER2 AB	MF + GC	MF + HER2	MF + GC + HER2	GC + HER2	PS
MF*, mg/mL	**GC, mg/mL**	**HER2, μg/mL**	**Amount of living cells, % ****							
1.5	0.125	0.38	NS	36.0 ± 2.9	89.7 ± 4.0	ND	ND	ND	52.4 ± 0.9	87.9 ±4.0
0.75	0.063	0.19	NS	40.0 ± 2.1	83.7 ± 2.1	ND	ND	ND	64.8 ± 2.1	86.5 ± 2.7
0.38	0.031	0.1	NS	44.9 ± 2.0	92.6 ± 8.6	ND	ND	ND	65.2 ± 4.0	93.0 ± 5.1
0.19	0.016	0.05	26.7 ± 2.0	47.6 ± 1.2	98.0 ± 8.2	ND	ND	ND	65.2 ± 0.2	92.7 ± 3.0
0.1	0.008	0.025	95.4 ± 7.8	78.2 ± 1.6	100.8 ± 3.3	68.7 ± 6.7	85.9 ± 4.3	55.0 ± 5.7	65.7 ± 3.5	91.3 ± 5.2
0.05	0.004	0.013	96.1 ± 9.0	80.4 ± 3.0	95.5 ± 13.6	71.0 ± 7.7	95.0 ± 10.3	62.7 ± 3.9	75.9 ± 3.4	92.7 ± 1.1
0.025	0.002	0.007	96.0 ± 7.7	84.6 ± 3.2	101.9 ± 3.6	72.4 ± 3.8	94.3 ± 13.4	62.5 ± 6.4	80.8 ± 2.1	98.4 ± 2.0

Note: * – MF concentration was determined by the magnetite contents, ** – compared to cells of the control group, which were cultivated without addition of substances specified in Table 5 (100 %), ND – not defined

Analysis of the data of Table 7 allows us to reveal the specifics of the influence of MF+GC+AB nanobiocomposite system (Fe_3O_4@GC/Ol.Na/PEG+PS+HER2), and each of its components separately, on HCC cells.

IC50 for the original MF was 0.155 mg/mL (samples 1). In the samples with MF concentration more than 0.19 mg/mL, the number of living cells is not determined, which

is probably due to a high optical density of the samples.

It can be confirmed that HER2 AB in monoapplication (samples 3) in the studied concentrations does not affect the viability or proliferation of HepG2 human liver carcinoma cells, since its effect does not lead to a decrease in cell viability and practically does not differ from the effect of PS (samples 8).

HepG2 cells were cultivated simultaneously in the presence of MF and HER2 AB (samples 5) in concentrations lower than 0.05 and 0.013 μg/mL, respectively, which had practically no effect on the viability of liver carcinoma cells. However, in the combined use of MF and HER2 at a concentration of 0.1 mg/mL and 0.025 μg/mL, respectively, the number of viable cells of the indicated line reduced to ~ 85.9 %.

IC50 for GC was 0.015 mg/mL (samples 2). The action of GC in monoapplication at a concentration of 0.008 mg/mL left ~78 % of cells in a viable state. For samples 4, using GC in this concentration in a complex with MF (0.1 mg/mL), a synergistic effect was shown and the efficiency of the cytostatic agent increased by ~10 % (the number of living cells was ~68 %).

The combined use of GC and HER2 AB (samples 7) at concentrations of 0.008 mg/mL and 0.025 μg/mL, respectively, also showed a synergistic effect, leading to a decrease in the number of viable cells to ~65 %.

The use of the nanobiocomposite system (samples 6) consisting of GC and HER2 at concentrations of 0.008 mg/mL and 0.025 μg/mL, respectively, and MF (at a concentration of 0.1 mg/mL for Fe_3O_4) led to a decrease in the number of viable human liver carcinoma cells of HepG2 line to ~55 %, which indicates a significant synergistic effect of the action of the said components (Table 7).

The revealed synergistic cytotoxic/cytostatic effect can be explained by the high biological activity of the complex with integrated ligand Fe_3O_4-GC-HER2 due to recognition of HepG2 tumor cell receptors and the pharmacological correction of endogenous iron exchange [51], which is provided by the use of iron-containing MF, GC and HER2 AB.

Thus, in composition of NBC, MF, GC and HER2 AB cause the joint effect on cells of HepG2 line, significantly exceeding their effect in monoapplication in the same concentrations, which determines the detected synergistic effect. Therefore, a possibility has been shown *in vitro* to achieve a cytotoxic effect at significantly lower concentrations of chemo- and immunotherapeutic drugs, and to create conditions for reducing of toxico-allergic reactions of the body as a whole. In addition, the obtained experimental data indicate that the investigated nanobiocomposites may be promising for use in the method of targeted delivery and local therapy of oncological diseases.

PHYSICO-CHEMICAL ASPECT TO INCREASE THE EFFICIENCY OF CHEMOTHERAPEUTIC AGENTS

The most important results of research into magnetically sensitive nanobiocomposites for antitumor therapy include: the detection of synergism of the combined effect of a chemotherapeutic drug, an antibody, and an iron-containing nanosized carrier, the efficiency of which reliably exceeded the effect of the corresponding drugs in individual use in the same doses [14, 21, 23, 35, 52, 61]; the ability to accumulate selectively in tumor site; safety for healthy tissues of the body, no worse than the official cytostatic agent in appropriate doses.

The revealed synergistic cytotoxic/cytostatic effect of iron-containing nanobiocomposite based on a magnetic fluid and an antitumor drug, and overcoming *in vitro* and *in vivo* resistance of MCF-7 human breast cancer cells and tumors was explained by the high biological activity of Fe_3O_4 complex with a chemotherapeutic drug, based on the pharmacological correction of processes of exchange of endogenous iron with the tumor [35, 53].

Based on the above and numerous literature data, it is possible to conclude that rapidly growing and dividing tumor cells have an increased need for Fe as a chemical element. A significant supply of this element is contained in the composition of NC based on iron oxide nanoparticles modified with cytotoxic drugs. According to experimental data, such nanoparticles penetrate quite easily into the intracellular space and can move in it for a certain time. Provided that the cytotoxicity of an antitumor drug in the composition of NC is preserved, over time they can reach their biological target (for example, tumor cell nuclei for Fe_3O_4/CP NC) and carry out pharmaceutical

correction. At the same time, natural and acquired mechanisms of cell resistance are turned out not effective, since in this case the pharmacological nanocomposite agent is characterized by fundamentally new properties.

Of course, such ideas are simplified and require further research and clarification.

In addition, it is known that a number of trace elements are necessary for the vital activity of organisms, in particular, Co, Fe, Cu, Zn, Mn, I, F, Br, Al, Sr, Mo, Se, Ni, *etc*. For example, in the body of an adult human there is 2–18 g of silicon. It is found in all organs and tissues. It is abundant in lungs, adrenal glands, thymus, thyroid and pancreas, lymph nodes, epidermis, cartilage, and tooth enamel. In human blood, the average contents of SiO_2 is from 5.9 to 10.6 mg per 1 g. It is known also that tumor cells are deficient in many chemical elements during rapid growth and division. Therefore, using nanocomposites of nanoparticles of the appropriate chemical composition (for example, silicon oxide) and effective modern antitumor drugs with different mechanisms of action, one can hope for the creation of new nanocomposite chemotherapeutic drugs with multifunctional properties [19–22] and increased efficiency of antitumor action.

In conclusion, we note that in the title of the work, the term "physico-chemical factor" is conditional and emphasizes at this time only the possibility of physico-chemical refinement of known antitumor drugs to the state of a nanocomposite form (or, a fundamentally new drug). As it was shown above, in the composition of NC, nanoparticles also perform a fundamentally important role, for example, they participate in the pharmacological correction of vital cellular processes.

CONCLUSION

With the development of nanotechnology, new scientific directions have been initiated and a significant amount of researches has been carried out, dedicated to the creation and search for promising applications in medicine, in particular, oncology, of nanocomposites based on bioinert, biocompatible and bioactive nanoparticle materials and modern chemotherapeutic drugs with different mechanisms of action. These works contain data indicating the advantages to introduce nanocomposite drugs into clinical practice, compared to the traditional use of chemotherapeutic drugs. The research results confirm the priority of works in the field of creation of new nanocomposite chemotherapeutic drugs for use in antitumor therapy and overcoming of drug resistance of malignant cells and neoplasms.

At Chuiko Institute of Surface Chemistry of National Academy of Sciences of Ukraine, magnetically sensitive core-shell nano-composites were synthesized with a multi-level hierarchical nanoarchitecture, capable of performing a complex of diagnostic and therapeutic functions with various mechanisms of action, characteristic of medico-biological nanorobots, by the chemical engineering method. Their use makes it possible to implement the principle of targeted delivery of antitumor drugs, to carry out real-time local therapy by various methods and MRI diagnosis of the disease, to realize the synergism of treatment with chemotherapeutic drugs of different mechanisms of action and to improve their selectivity, to reduce the toxic side effects of oncological drugs on the body. The combination of the above features of nanocomposites, as well as their role in overcoming the drug resistance of cells of malignant neoplasms to cisplatin, testify to the perspective of creation and research of nanocomposite drugs in solving the problem of increase in the efficiency of chemotherapy.

The work was carried out with the support of the target program of fundamental research of National Academy of Sciences of Ukraine "Promising fundamental research and innovative development of nanomaterials and nanotechnologies for needs of industry, health care and agriculture" for 2020-2024.

Підвищення ефективності протипухлинних хіміотерапевтичних лікарських засобів: фізико-хімічний фактор

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З розвитком нанотехнологій започатковано нові наукові напрямки та виконано значну кількість досліджень, присвячених створенню та пошуку перспективних застосувань в медицині, зокрема в онкології, нанокомпозитів на основі біоінертних, біосумісних і біоактивних наночастинкових матеріалів та сучасних хіміотерапевтичних препаратів різного механізму дії. Ці роботи містять дані, що свідчать про переваги впровадження нанокомпозитних лікарських засобів в клінічну практику, в порівнянні з традиційним використанням хіміотерапевтичних препаратів. Результати досліджень підтверджують пріоритетність робіт в галузі створення нових нанокомпозитних хіміотерапевтичних лікарських засобів для застосування в протипухлинній терапії та подолання лікарської резистентності злоякісних клітин і новоутворень.

Метою огляду є узагальнення і аналіз авторських експериментальних робіт, виконаних в Інституті хімії поверхні ім. О.О. Чуйка Національної академії наук України, що стосуються особливостей впливу хіміотерапевтичних препаратів різних механізмів дії та нанокомпозитів на їхній основі, на клітинні системи та пухлини. Такі дані є актуальними для визначення перспективних напрямків і шляхів створення нових ефективних нанокомпозитних лікарських засобів для застосування, зокрема, в протипухлинній хіміотерапії.

В Інституті хімії поверхні ім. О.О. Чуйка Національної академії наук України методом хімічного конструювання синтезовано магніточутливі нанокомпозити типу ядро-оболонка з багаторівневою ієрархічною наноархітектурою, здатні до виконання комплексу діагностичних і різних механізмів дії терапевтичних функцій, характерних медико-біологічним нанороботам. Їх використання дозволяє реалізувати принцип адресної доставки протипухлинних лікарських засобів, здійснювати в реальному часі локальну терапію різними методами і МРТ-діагностику захворювання, реалізувати синергізм лікування протипухлинними засобами різних механізмів дії, зменшити побічні токсичні впливи онкологічних препаратів на організм. Сукупність наведених особливостей нанокомпозитів, а також їхня роль в подоланні лікарської резистентності клітин злоякісних новоутворень до цисплатину, свідчать про перспективність створення і дослідження нанокомпозитних лікарських засобів у вирішенні проблеми підвищення ефективності хіміотерапії.

***Ключові слова**: злоякісні клітини і пухлини, хіміотерапевтичні препарати, нанокомпозити, резистентність, ефективність*

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Received 18.02.2024, accepted 03.09.2024