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COMBINED NANOCHEMOTHERAPY USING DOXORUBICIN AND CURCUMIN AS AN EXAMPLE

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The *aim* of the work was to review literature data on combined nanochemotherapy using the example of two drugs doxorubicin and curcumin. Special attention was paid to the use of substances with synergistic properties in one nanoparticle, capable to penetrate into living cell.

The method of combined chemotherapy of nanopreparations improves processing efficiency. The technique of using nanocontainers with synergistic drugs in combination with ligands reduces the side effects of chemotherapy drugs.

Results. Literature data indicate that the use of nanopreparations contributes the rapid creation and use of synergistic combinations that were purposefully delivered to target cells, reducing dosage due to precise targeting. A promising direction of nanomedicine is the creation of multifunctional nanomaterials based on several active drugs having synergistic properties, with the simultaneous use of their enhancers and the strategy of active targeting. These structures enabled targeted and controlled penetration of medicinal compounds into the localization of pathological processes, reducing drugs toxicity for normal cells.

Conclusions. Combined chemotherapy using polymers and nanoparticles with ligands, in which synergistic drugs are included, ensures to reduce side effects and doses of chemotherapy drugs, and helps to overcome multiple drug resistance as well.

Key words: combined nanochemotherapy; doxorubicin; curcumin; synergism; active targeting.

Combined chemotherapy

The current advanced strategy in chemotherapy is aimed at combination therapy, which uses targeted delivery systems with a large number of drugs [1–4]. Therapy with one drug is limited due to the heterogeneity of cancer cells [5], therefore, today, combined chemotherapy has become a standard treatment scheme for cancer patients [2, 5] and is expedient and promising [1, 3, 4].

Combined therapy is becoming an important strategy for a better long-term prognosis with reduced side effects [6, 7]. The combination of chemotherapy drugs allows oncologists to use drugs in lower doses, reducing cytotoxicity [5] and increasing the effectiveness of treatment [1]. Most often, a combination of two agents is used, which leads to an improvement in therapeutic effectiveness and a reduction in the dosage of each agent and the achievement of several goals [1, 5].

Today, combined chemotherapy with a synergistic effect is a promising treatment scheme for cancer patients [5, 8, 9]. The combination of drugs that have different properties, such as solubility, usually requires the use of multiple carriers or solvents, limiting the probability of their simultaneous delivery to target cells. [5].

Consider a combination therapy using the example of two drugs with different properties, water-soluble doxorubicin (DOX) and hydrophobic curcumin (CUR). It is known that the combination of DOX and CUR

contributes to the treatment of several types of cancer [3, 5, 10–16].

Joint delivery of biomolecules in combination therapy is widely used in clinical diagnosis and treatment [17]. The combination of anticancer agents with chemosensitizers targets different signaling pathways in cancer cells, reduces side effects, and helps overcome multidrug resistance (MDR) [6].

In practice, combined chemotherapy increases the effectiveness of drugs and leads to improved survival compared to monotherapy [1]. A growing number of facts testify, that simultaneous treatment with chemotherapy and chemopreventive agents with antioxidant activity can increase the effectiveness of chemotherapy drugs [18]. It is recognized that the right combinations of drugs improve target selectivity and suppress the development of MDR [9].

Modern drug carriers based on nanotechnology are aimed at enhancing the effectiveness of the best properties of drugs [19]. Application of the recipe of formulations based on nanotechnology is aimed at reducing the dose due to more accurate targeting of drugs, which additionally increases the safety of drugs by minimizing off-target toxicity [19].

Nanoparticle-based drug delivery systems offer opportunities for the development of highly effective targeted therapeutics with improved half-life, bioavailability, biodistribution, and are indispensable for maintaining synergistic drug ratios in combination therapy [1].

For joint simultaneous delivery of chemotherapeutic drugs with different physicochemical properties, multifunctional carriers are used [5]. They can target several cancer hallmarks, which improves the efficacy of cancer treatment [20], complementing and extending the effects on tumors [21, 22].

Nanomaterials enhance the immunostimulating effect of chemopreparations due to synergistic action [2] and maintain an optimized synergistic ratio of drugs in one carrier until intracellular uptake [1].

Significant efficiency is ensured by joint simultaneous delivery of drugs by nanoparticles (NPs) into one cell [1, 23, 24], which leads to the use of chemotherapy drugs in smaller doses, reducing systemic toxicity and increasing therapeutic efficacy [9].

Synergism in combined nanopreparations

In combined chemotherapy, synergistic mechanisms are used, in which the synergistic [2, 8, 14] effect of two (or more) agents is directed at different pathways of the disease [1]. Combination chemotherapy is theoretically advantageous due to the synergistic effect of drugs with simultaneous suppression of MDR. Nanoparticle-assisted chemotherapy delivery, with multiple loaded chemotherapeutic agents, is a promising approach for the effective treatment of various cancers. NP with a combination of drugs simultaneously enhance therapeutic effects and reduce side effects [25]. NPs as means of drug delivery have promising possibilities in targeted and combination therapy [1]. For example, NPs with a gold surface with a structure stabilized by glutathione have the potential to carry various drugs. They are promising drug delivery systems to overcome MDR resistance, which is the main cause of ineffective chemotherapy [26].

The association of herbal products and anticancer drugs may become a new and highly effective therapeutic strategy for better cancer management and treatment. The identification of synergistic combinations of both synthetic and phytochemical substances is clinically important because they can be quickly transferred from the laboratory to practical use [27]. Future experiments should focus on enhancing the delivery of phytochemicals using their various synergistic combinations and studying the effects of *in vitro* and *in vivo* models [28]. It is necessary to investigate the mechanisms of synergistic action of several compounds with the aim of elucidating unique molecular mechanisms, that contribute to increasing the effectiveness of these phytochemicals when they are used in combination [29]. For example, indole-3 carbinol and resveratrol have both similar and unique molecular targeting profiles and together show synergistic antiproliferative effects [30]. The results indicate that gallic acid in combination with CUR synergistically increased the apoptosis of MDA-MB-231 breast cancer cells, reducing the amount of glutathione, increasing reactive oxygen species (ROS), carry out mitochondrial dysfunction [31]. The phytocompound ellagic acid showed chemopreventive and antitumor properties [27]. One of the candidates for effective phytochemicals in their combined use is curcumin, which is a powerful chemosensitizer and can cause an additive or synergistic effect with chemotherapeutic drugs against various cancer cell lines [32]. A study demonstrated that the potential antitumor activity of such phytochemicals as curcumin and ellagic

acid increases synergistically when they are combined, leading to apoptotic death of cancer cells [27].

The use of a combination of doxorubicin and curcumin is facilitated by a synergistic effect, thanks to which it is possible to eliminate the harmful effects of a greater concentration of doxorubicin [11, 33]. For example, improved co-delivery of DOX and CUR using nanocarriers showed synergistic antitumor efficacy against liver tumor [6].

Polymer therapy

Polymer therapy covers a variety of complex multicomponent high molecular systems with the presence of a rationally designed covalent bond between a water-soluble polymer carrier and bioactive molecules [34–36]. A DOX-curcumin composite nanoparticle was developed in which doxorubicin was covalently grafted to the carboxylic acid residue of the NVA622 polymer. It overcomes DOX chemoresistance and reduces DOX-induced multiple myeloma, acute leukemia, prostate cancer, ovarian cancer, and cardiotoxicity [37]. In order to overcome resistance to DOX, a composite nanoparticle DOX-curcumin was synthesized from covalently bound doxorubicin to the surface of the nanoparticle and curcumin, which demonstrated a complete absence of cardiac toxicity [38]. Curcumin improved the safety profile of DOX by reducing DOX-induced intracellular oxidative stress as indicated by total glutathione levels and glutathione peroxidase activity in heart tissue [38].

The well-known method of PEGylation (PEG) is the creation of bioconjugates using poly (ethylene glycol) (PEG) with proteins, peptides, oligonucleotides, drugs and NPs for nanomedicine, with the aim of extending the circulation time of drugs in the blood and increasing the effectiveness of drugs [1, 39]. However, treating patients with PEGylation drugs can lead to the formation of anti-PEG antibodies. Therefore, the development of alternative polymers to replace PEG is needed [40]. In other cases, it is necessary to have polymers that capture, solubilize and control the release of the drug without resorting to chemical conjugation [36], such as Pluronic® micelles [34, 41, 42], poly(lactic acid) (PLG), poly(lactic co-glycolic acid) (PLGA) [43], chitin [44, 45], chitosan [34, 35, 42]. For example, a multifunctional co-delivery system that co-encapsulates hydrophobic chemotherapeutic drugs (curcumin) and hydrophilic therapeutic drugs (Survivin shRNA genes) in polymer nanoparticles (PLGA polymer and conjugated triblock polymer) is a promising strategy for clinical application in cancer therapy [46]. Co-delivery of curcumin and Survivin shRNA increases tumor penetration and promotes synergistic inhibition (suppression) of SKOV-3 and Hela cells. The synergistic antitumor effect includes inhibition of tumor cell proliferation, induction of cell apoptosis, and activation of caspase-3 pathways [46]. For some drugs, it is desirable to have a high degree of homogeneity, which gives predictable conformations in solution and increased ability to load drugs [36].

Biodegradable polymers with a high molecular weight include: polypeptides, dextrins, polysialic acid, polyacetals [36], PLG, PLGA [43], chitosan [34, 35], PEG micelles [47], alginate [48], albumin [49–53], pluronic micelles (Pluronic®) [34, 41, 42, 49]. Recently, polyglutamic acid (PGA), which has a high potential among synthetic polypeptides, has been used in nanomedicine [36]. The use of platforms based on high molecular weight polymers is important for the treatment of diseases with chronic administration, such as neurological disorders or tissue regeneration [36].

PEG micelles have shown some ability to deliver both DOX and CUR to DOX-resistant A549/Adr cells and synergistically reverse their DOX resistance [54]. *In vivo* studies have confirmed that micelles have the ability to increase DOX or CUR plasma concentrations and prolong their respective circulation in the bloodstream [54]. PEG-stabilized Dox NPs also exhibit long blood circulation time, good biocompatibility and stability, fast release in acidic environment, and high accumulation in tumors. Compared with free Dox, such Dox*NPs dramatically increase the antitumor therapeutic efficiency in inhibiting the growth of tumor cells [55]. They can be combined with other anticancer drugs for the purpose of synergistic chemotherapy in the treatment of MDR cancer [55].

The use of nanoplatforms to transport Dox reduces its side effects during breast cancer treatment. In many cases, polymers increase the cytotoxicity of the drug and reduce the amount of drug needed to achieve a cytotoxic effect [42]. DOX and the p53 gene were loaded into the cyclodextrin polymer cavity to form a combined nanoparticle with greater drug efficacy against MCF-7 cancer cells. The synergistic effect of the drug and the gene is achieved by reducing the dose of the drug due to the high efficiency of

the combined nanoparticle and suppression of the MDR mechanism in cancer cells [24]. A bilayer phospholipid liposome coated with polyelectrolyte (poly(4-sodium styrenesulfonate) (PSS)) encapsulated with CUR and DOX demonstrated enhanced solubility of CUR, excellent biocompatibility, and commendable cytotoxic potential of combined chemopreparations [23].

Chitin

A pH-sensitive chitin-poly(caprolactone)-Dox nanogel composite system was developed against non-small cell lung cancer. Cellular internalization of nanogel systems was confirmed by fluorescence microscopy. Chitin-poly(caprolactone)-Dox particles showed dose-dependent cytotoxicity to A549 cancer cells. The results of *in vitro* analysis confirmed the compatibility of NPs with blood [44]. Chitin and Cur do not dissolve in water, but the gel NPs developed on their basis form a very good and stable dispersion in water with the size of spherical particles in the range of 70–80 nm [45]. Histopathological studies of pig skin samples treated with NP* Chitin* Cur showed loosening of the stratum corneum of the epidermis, through which the NPs penetrated without visible signs of inflammation. These results suggest that the designed gel NPs can be proposed for the treatment of skin melanoma [45].

Chitosan

Polymeric nanoparticles are an ideal delivery system. Modification of the surface of NPs, a biocompatible polymer of chitosan, with various macromolecules has a huge potential to improve the bioavailability and circulation time of the native drug in the blood [39]. Chitosan is used both independently and as a coating of NPs [34]. For example, PLGA NPs, grafted with chitosan and loaded with Cur, were used for lung delivery for sustained drug release using a controlled polymer architecture [56], and other PLGA NPs loaded with curcumin and surface-modified chitosan were used to improve the therapeutic efficacy of curcumin [39]. PLGA nanoparticles coated with chitosan (CS) and loaded with harmala alkaloid-rich fraction (HARF) are a promising antibacterial drug against Staphylococcus aureus and Escherichia coli for wound healing [57]. The three components of the developed nanopreparation (PLGA, chitosan, and HARF) have synergistic antibacterial and wound-healing properties for the treatment of infected wounds and were found to be biocompatible during testing on human skin fibroblasts [57].

Several studies have shown that the stability of Pluronic® micelles can be significantly improved after being coated with a chitosan layer [58, 59]. The use of chitosan provides numerous advantages due to its biodegradability, biocompatibility, ease of technical application, versatility and low toxicity. Chitosan has no immunogenicity, is not carcinogenic, and also has antibacterial properties [42].

DOX micelles based on Pluronic®

The process of self-assembly is an interesting tool [36]. In recent decades, Pluronic® [49, 60] has been developed to prepare micelles that can be modified [34, 41, 42]. It is known that micelles formed by pluronic triblock copolymers are a promising class of drug delivery agents [49].

Pluronic® micelles have attracted attention due to their low toxicity. Their molecules degrade in the biological environment [61], and due to the hydrophobicity of the core and steric factors, they have the ability to encapsulate hydrophobic agents [49, 42]. Pluronics L61, P85, P105, PF127 [34, 49, 62, 63], or P85 [42] and F68 [41, 49, 62] are most often used in micelles.

Pluronic® micelles cause a decrease in mitochondrial membrane potential and thus deplete ATP in tumor cells [34, 63]. Pluronic® 85 (P85) has been shown to inhibit P-glycoprotein (P-gp) activity and induce intracellular ATP depletion in MDR cells. Its action causes a lack of energy necessary for the work of transport proteins such as P-gp and for other protective mechanisms. The use of P85 polymer prevents the development of MDR in cells exposed to Dox [42].

The interaction of the drugs gemcitabine, cytarabine and hydroxyurea released from micellar media Pluronic® F68 and F127 with serum albumin, which was chosen as a model protein, was analyzed [49]. The conformational changes of BSA during the interaction between drugs in the presence of pluronic polymers were studied. All drugs showed improved distribution in F127 micelles and drug protein binding was shown to be enhanced when co-delivered with pluronic micelles. The results indicate that BSA retains its conformation when interacting with F127 or F68 micelles carrying gemcitabine, cytarabine, and hydroxyurea and that they do not have any negative effect on BSA protein stability [49].

NPs made using nanodiamonds (ND) are useful components for research in nanomedicine due to their relatively small size and chemical inertness. They have the possibility of flexible surface modification, which in general makes them positive elements for various biological applications [41, 64, 65]. *In vitro* studies have shown that ND-Dox + Pluronic® F 68 conjugates have slow and sustained drug release characteristics and tremendous cytotoxic potential against the MCF-7 breast cancer cell line. Pluronic®-coated ND conjugates are a promising and effective nanoplatform for anticancer drug delivery [41].

A mixed micelle with Pluronic® L61 and F127 polymers was used as a Dox delivery system in the preparation SP1049C, Supratek Pharma, Canada [62]. Double micelles are easy to fabricate, have high loading capacity, and co-deliver hydrophilic and hydrophobic components. In order to eliminate MDR, a double micelle of Pluronic® P105-Dox conjugate and paclitaxel conjugate with Pluronic® F127 was successfully developed, which had an antitumor synergistic effect against MCF-7/ADR cancer cells [34, 63].

Curcumin and doxorubicin

DOX is one of the important chemotherapeutic anticancer agents [3], which is widely used [11] but has limited therapeutic efficacy for cancer treatment [3]. DOX is a non-selective cytotoxic drug and has many side effects [11]. Clinical use of DOX is often associated with severe side effects, namely hepatotoxicity [66, 67], nephrotoxicity [10, 35, 47, 48, 66–68].] and dose-dependent cardiotoxicity [28, 54, 55, 66, 67]. Chemotherapy also causes damage to normal tissues of the bone marrow, gastrointestinal tract, neurons and auditory tissues, etc. [67]. DOX chemotherapy has been reported to induce inflammation, which is associated with DOX disruption of the intestinal flora, leading to the release and accumulation of endotoxins. They lead to systemic inflammation and damage to several organs [28]. Chemotherapy-induced cardiotoxicity includes oxidative stress, mitochondrial damage, altered calcium flux, activation of proapoptotic signaling cascades [67], and inflammation [10]. It is believed that the most debilitating consequences for organ tissues, especially the heart, occur as a result of ROS induction and a high cumulative dose of DOX [69].

Curcumin is an antioxidant, an anti-inflammatory agent [70], an inhibitor of amyloid fibrillation, a powerful anti-carcinogenic and even anti-metastatic agent. The potential of curcumin is recognized and its cytotoxic properties against many cancer cell lines are appreciated [71]. CUR helps in the treatment of oxidative and inflammatory conditions, metabolic syndrome, arthritis, anxiety and hyperlipidemia [72], and is involved in the inhibition of various growth pathways and pro-invasive signaling pathways [73]. Growing evidence suggests that CUR can prevent carcinogenesis [74], sensitize cancer cells to chemotherapy, and protect normal cells from chemotherapy-induced damage [67, 69]. CUR is known to have a preventive effect against chemotherapy-induced toxicity: cardiotoxicity [75], gastrointestinal toxicity, hepatotoxicity, nephrotoxicity, neurotoxicity, ototoxicity, and genotoxicity [67]. DOX-induced renal toxicity is closely related to oxidative stress, inflammation, apoptosis, and oxidative DNA damage [70]. Curcumin has protective efficacy against DOX-induced nephrotoxicity due to attenuation of oxidative stress, inflammation, and oxidative DNA damage. [70].

The ability of CUR to absorb free radicals is used to reduce toxicity during DOX chemotherapy [69]. Low-dose curcumin reduces the effective dose of doxorubicin and reduces its systemic toxicity [76]. It is able to reduce the toxicity of DOX on the heart and liver [13, 67], kidneys, brain, and reproductive organs, affecting the balance between the autophagy and apoptosis systems, reducing damage to energy production in the mitochondria of these organs [69]. The use of NPs significantly increases the bioavailability of CUR and its therapeutic effects [77, 78], which reduce DOX-mediated cardiotoxicity [10].

It has been shown in scientific works that binary preparations of DOX and CUR exhibit stronger antitumor activity *in vitro* and *in vivo* than DOX or CUR at the same concentrations [3, 5, 11, 15, 16]. Curcumin pretreatment of drug-resistant cancer cells restored their sensitivity to doxorubicin [76]. A synergistic effect between DOX and CUR in a nanosystem *in vitro* and *in vivo* has been shown, which enhances DOX-induced apoptosis in the endogenous mitochondrial pathway and may involve other apoptotic mechanisms [11].

The study of the improved effect of nanopreparations is aimed at various aspects of the properties of NPs, their interaction with target cells and the organism as a whole. CUR prevents oxidative stress, inflammation, DNA fragmentation and apoptosis, but co-administration of CUR and DOX enhances

the induction of apoptosis in cancer cells [10], and the apoptosis rates in cancer cells become significantly greater than CUR and DOX alone [3].

The efficacy of a pair of DOX and CUR drugs against various cancers has been demonstrated, namely:

1) against invasive B-cell lymphoma both *in vivo* and *in vitro* [11], where CUR negatively affects the metastasis of cancer cells, contributing to an increase in the effectiveness of DOX [10];

2) as a promising method for the treatment of liver cancer [13], when polymeric NPs or a specially designed micelle, which had an average diameter of approximately 110 nm, were used for joint delivery of DOX and CUR to hepatoma cells [15]. Encapsulation of the pro-apoptotic drug Dox and the anti-angiogenic agent Cur in pH-sensitive NPs provides a strategy for the effective treatment of human hepatocellular carcinoma in a synergistic manner [22].

3) the DOX — CUR pair significantly reduces the viability of formed tumor spheroids, migration and invasion in gastric adenocarcinoma (AGS) model cells [3].

4) polymeric micelles, for joint delivery of DOX–CUR, to improve antitumor efficacy in breast carcinoma [5]. Studying the molecular processes that stimulate the therapeutic effect of anticancer drugs, it was shown that the simultaneous administration of the drug from albumin NPs loaded with CUR-DOX led to greater intracellular accumulation of DOX and the destruction of MCF-7 breast cancer cells [12].

5) micellar joint delivery of DOX and CUR synergistically enhances the antitumor effect *in vivo* on spontaneous lung metastases formed by a 4T1 breast tumor [5].

6) showed the combinatorial effect of CUR and silibinin in sensitization of high-risk neuroblastoma cells to the chemotherapeutic drug DOX both *in vitro* and *in vivo* [73].

7) demonstrated the effectiveness of using CUR in combination with DOX to improve survival and improve the quality of life of patients with neuroblastoma [73].

The anticancer use of curcumin remains limited due to its low solubility in water. To increase the insufficient bioavailability of CUR, the inclusion of curcumin in the middle of the emulsome core is used, which allows it to reach its effective concentration inside the cell *in vitro* [79].

Due to the low bioavailability of CUR [80], the following nanomaterials were used for joint entry of DOX and CUR into the body: inorganic nanostructures, polymeric NPs, liposomes, micelles, nanogels [10], polydopamine [2], and albumin [14]. Small cross-linked cyclodextrin nanoparticles can function as a promising carrier for curcumin and protect curcumin against photodegradation [71].

The loading of several different drugs on one carrier allows the simultaneous delivery of these medicinal compounds, which leads to a synergistic effect and a general enhancement of anticancer activity [3, 5, 10, 16, 81], increasing the effectiveness of DOX chemotherapy [12, 73]. NPs are able to maintain an optimized synergistic ratio of drugs in one carrier until the moment of intracellular absorption by the target cancer cell [1]. Binary drugs show stronger antitumor activity than the delivery of a separate drug at the same concentrations and makes it possible to use such a pair with the addition of other antitumor drugs [11].

Co-conjugated DOX and CUR to zwitterionic polymer micelles have synergistically enhanced efficacy and the strongest cytotoxicity against drug-resistant MCF-7/Adr tumor cells [16]. Encapsulation of DOX in long-circulating liposomes demonstrated the antitumor efficacy of DOX, which could be significantly enhanced after its co-encapsulation with curcumin (CUR) compared to liposomal DOX [82].

Confocal laser scanning microscopy results indicated that curcumin- and doxorubicin-encapsulated albumin nanoparticles had synergistic cytotoxicity to B16-F10 cells and gradually released the drug over 24 h without a burst effect [83]. Co-loaded micelles of DOX and CUR should be monodisperse with small particle size, with high encapsulation efficiency and delayed release, enhanced uptake by tumor cells [5]. The joint encapsulation of DOX and CUR in micelles, which is carried out using a simple self-assembly procedure, even in the absence of organic solvents and surfactants [5, 14], is economically feasible.

To achieve combined therapy, biodegradable micelles (poly(ethylene glycol)-poly(3-caprolactone) (mPEG-PCL)) are used as a system for the joint delivery of hydrophilic DOX and hydrophobic CUR. Co-encapsulation of DOX and CUR in mPEG-PCL micelles was performed using a self-assembly procedure [5]. NPs synergistically enhance cytotoxic activity and apoptotic effects on breast tumors, both *in vitro* and *in vivo*, which is primarily due to increased cellular uptake of DOX and CUR [5].

Simultaneous administration of DOX and CUR using DOX/CUR-NPs on HepG2 cells *in vitro* and *in vivo* showed a synergistic effect of DOX/CUR-NP compared to DOX-NP and free DOX on the inhibition of liver cancer cells [6]. Also, the synergistic effect of simultaneous delivery of DOX and CUR was enhanced using a pH-sensitive nanocarrier. Such a delivery system helps realize a promising combination strategy for cancer treatment [22].

The selection of the best nanocarriers is based on the improvement of interaction with target cells, the accuracy and speed of penetration into the cells to the required organelles, the improvement of stability and the slower release of drugs over time. The developed polymer high molecular weight nanomaterial mPEG-b-P (Glu-co-Phe) loaded with DOX and CUR has high anti-lymphoma effect and low toxicity. These NPs increase the ability of drugs to penetrate the cell in a targeted manner, increasing their delivery to the cell nucleus [11].

Many studies have used chemosensitizers to increase the sensitivity of tumor cells to chemotherapeutic drugs. CUR is a good sensitizer that can regulate MDR protein expression and inhibit cancer cell proliferation [84]. CUR is able to inhibit ATP-binding cassette drug transporters (ABC), increasing the effectiveness of DOX chemotherapy [10, 69]. Once in the cytosol, CUR blocks the transport of DOX from cells by inhibiting the expression of P-gp [12]. The results proved that various [12, 16, 69, 84] micelles are promising means for co-delivery of drugs to fight against MDR [16]. If there is a decrease in the level of P-gp proteins, this indicates that the multidrug acts inversely to MDR [13].

Despite some improvements in the drug delivery system, the placement of combined chemotherapy drugs in a hybrid nanostructure remains a problem [23]. Optimizing the delivery system targeting the tumor microenvironment can be of great clinical importance [12]. The use of nanocarrier-based combination therapy requires considerable effort to study and confirm the benefits of synergistic effects [9] and fluorescence microscopy is often involved in the work [85]. Nanomedicine pays special attention to molecular imaging [4, 5, 8, 12, 23, 71, 83–91], and fluorescent probes [89] are widely used for diagnosis and treatment [55]. The intracellular distribution of nanoparticles and chemopreparations directly in different parts of the cell is visualized using images of confocal fluorescence laser scanning microscopy [12, 23]. The use of fluorescent dyes accelerates the study of drug transport processes by nanoparticles [12, 23, 87], the degree of synergistic cytotoxicity of chemopreparations is determined [30, 91]. Both fluorescence microscopy [88] and flow cytometry [30, 88, 92] are used to monitor apoptosis. Real-time fluorescence microscopic observation of cells [90] is a valuable tool for the creation of antitumor nanodrugs [71]. Thanks to fluorescence, the processes occurring with nanopreparations *in vivo* and *in vitro* [4, 5, 90] are visualized, their effectiveness is investigated [30, 83], and the movement, localization, and retention of nanopreparations are studied [90].

Multifunctional nanocarriers for pair of DOX and CUR delivery

Modern works are aimed at reducing the dose of cytotoxic drugs necessary for chemotherapeutic activity [86]. Selective delivery of DOX to tumors through the use of nanoscale carriers represents an attractive approach to address limitations in cancer therapy [42, 47]. MDR greatly inhibits the antitumor effect of DOX and leads to chemotherapy failure [34]. Therapeutic efficacy during chemotherapeutic treatment of breast cancer is significantly complicated by the emergence of MDR, severe cellular toxicity, and poor targeting of chemotherapeutic drugs [21].

Drug efflux and anti-apoptotic processes are the two most common mechanisms in cancer cells leading to MDR [84]. The decrease in their sensitivity to DOX is explained by the loss of drug accumulation in cells, the reduction of DNA damage and the attenuation of apoptosis [69]. Studies show that P-glycoprotein (P-gp) is involved in DOX resistance [10], and resistance to chemotherapy mainly develops through the activity of transporters that reduce the amount of DOX in the cell [69]. It has been shown that joint administration of synergistic drugs DOX and CUR reverses MDR [21].

The method of combining two or more therapeutic agents has great potential [55], for example, the joint use of CUR and DOX in the form of micelles significantly promotes not only their intracellular absorption, but also leads to greater efficiency in suppressing MDR [10].

Multifunctional nanocarriers for the DOX–CUR pair are constantly being optimized. On the way to creating promising and effective carriers for nanobiotechnology, it is necessary to use biodegradable micelles [5] as a co-delivery system for loading hydrophilic DOX

and hydrophobic CUR in order to achieve improved combined chemotherapy [5, 12, 15] and greater selective targeting and suppression of chemoresistance [12].

A polymer micelle was created using an amphiphilic copolymer linked with polyethylene glycol and d-tocopheryl PEG1000 succinate. These micelles were used to deliver DOX and CUR to reduce MDR in A549/Adr lung cancer cells, which enhanced the therapeutic efficacy of DOX [54].

Multifunctional micelles are an active strategy for delivery to cancer cells and attenuation of MDR. DOX is loaded into micelles by physical encapsulation or chemical bonding. The construction of «smart» polymer micelles sensitive to pH with the help of a hydrazone bond, which is cleaved in an acidic environment, was used for the joint delivery of DOX and the P-gp inhibitor Disulfiram [34].

There are certain limitations when using NPs, namely physiological barriers in tumor tissues and unwanted interactions with normal tissues. The use of multifunctional nanosystems requires that they have the smallest dimensions for greater efficiency [93], such as, for example, the use of gold NPs [26, 93], nanodiamonds [41, 64, 65], micelles [47].

Further research in nanomedicine is aimed at treating various types of cancer and creating improved carriers for drug combinations. The ability of CUR to suppress tumor growth is used in new treatment regimens and drug delivery systems to improve the effectiveness of chemotherapy [69]. Studying the movement of DOX, its localization and retention is necessary to further understand the mechanisms of toxicity and resistance to DOX, in order to establish a better treatment protocol in clinical settings [69].

Much remains to be learned in the emerging field of nanomedicine [1], and further studies are needed to study the effect of combination cancer treatment using *in vivo* models and the use of specific ligands. Such combined nanochemotherapy improves antitumor efficacy [84].

Ligands and combined nanochemotherapy

Progress in nanomedicine is due to the development of new nanocarriers and drug delivery technologies, and the search for the ideal nanocarrier continues [1]. There are some difficulties in achieving the optimal combination of physicochemical parameters for tumor targeting and drug release control, which hinders the use of nanomedicines in practical therapy [94]. Combined delivery system based on nanocarriers with ligands is superior to the conventional drug delivery system due to the ability to actively target specific cells/tissues, which makes it possible to reduce systemic distribution and unwanted side effects [9].

Research efforts are focused on the development of functionalized nanoparticles to deliver therapeutic agents to specific molecular targets overexpressed in cancer cells [94]. These include folic acid receptors, which are overexpressed on the surface of many types of tumors [95, 96]. Folic acid is widely used for diagnostic and therapeutic studies as a ligand, for imaging and therapy of cancer that expresses the folate receptor [95]. Folic acid conjugates can be used to target imaging molecules and therapeutic compounds directly to cancer tissues [21, 34, 35, 95–97]. For enhanced chemotherapy against drug resistance and cancer diagnosis, a drug with Dox and NPs of micellar PEG with incorporated folic acid with high payload has been developed. It has uniform spherical particles with a diameter of approximately 20 nm [47].

Folate-chitosan copolymer micelles were used for co-delivery of Dox and pyrrolidine dithiocarbamate [34]. Magnetic NPs with Dox loaded into the matrix were coated with folate-grafted chitosan. It was found that magnetic guidance of NPs with such a design enhances the local release of drugs and significantly reduces tumor growth [35]. Folate targets the folate receptor in cell walls [35] and inhibits MDR and thus increasing Dox in cancer cells [34].

To increase the selectivity of tumor targeting, folic acid-modified nanoparticles (DOX®CUR)-FA-NPs were developed based on star polyester [21]. *In vivo* results demonstrated that such NPs not only had significant MCF-7/ADR tumor targeting and antitumor efficacy, but also caused less pathological damage to normal tissues [21].

Lack of access to the brain is a major obstacle to the development of drugs for the central nervous system. A nanovector hybrid derived from grapefruit and polyethylenimine (PEI) coated with folic acid was developed for effective intranasal delivery of miR17 microRNA nanovector into folate receptor-positive GL-26 brain tumor [97].

Targeted multidrug delivery systems have become an advanced strategy for cancer treatment. They are used as ligands: antibodies, hormones, small peptides, tumor-specific ligands (P. Tuftsin) that were linked

to drug carriers [4]. The natural macrophage-stimulating peptide Tuftsin (P. Tuftsin) grafted to a liposome with co-encapsulated Cur and Dox was used as a ligand. This form of liposome has an enhanced synergistic therapeutic effect of the peptide tumor-specific ligand and the dual drug Cur and Dox [4].

Based on the conjugate of Cur with hyaluronic acid (HA), HA–Cur/Dox nanoparticles with dimensions of approximately 180 nm with excellent encapsulation efficiency and serum stability were generated. In this combination, Cur reversed MDR in tumor cells *in vitro* by inhibiting P-gp expression and activity, as well as inducing apoptosis through the mitochondrial pathway. The effect of targeted delivery of NPs of chemotherapeutic agents occurs thanks to CD44 receptors [84].

The conclusions of the work are that the combination of chemotherapeutic drugs allows oncologists to use drugs in smaller doses, reduce cytotoxicity and increase the effectiveness of treatment. The combination of antitumor agents with chemosensitizers targets different signaling pathways in cancer cells. During the chemotherapeutic treatment of cancer, strong cellular toxicity develops due to the poor targeting of therapeutic agents and the emergence of MDR, which significantly complicates the therapeutic effectiveness of chemotherapeutic drugs. The right drug combinations improve target selectivity and inhibit the development of MDR.

The anticancer drug doxorubicin (DOX) has limited chemotherapeutic efficacy for cancer treatment, due to poor selectivity and severe side effects. During DOX chemotherapy, dose-dependent cardiotoxicity, hepatotoxicity, nephrotoxicity develops, oxidative stress, inflammation, apoptosis, and other disorders occur. The appearance of MDR leads to the failure of chemotherapy.

Combined therapy is used to increase the effectiveness of chemotherapy. Simultaneous treatment with chemotherapeutic and chemopreventive agents with antioxidant effect reduces the non-selective cytotoxicity of drugs. Recently, special attention has been paid to herbal preparations with antioxidant effect in combination with anticancer drugs, which synergistically enhance the effect of the main drug. A number of synergistically effective drug combinations have already been selected.

Herbal preparations have not only an antioxidant effect, but also exhibit antitumor properties. Phytochemicals have both similar and unique molecular targeting profiles, which enables the selection of the desired effective synergistic drug combinations against the respective cancer cells. Among promising herbal preparations, curcumin (CUR) stands out. It is an antioxidant, anti-inflammatory agent, anti-carcinogenic and anti-metastatic agent. CUR can cause additive or synergistic effects with chemotherapeutic drugs against various cancer cell lines. CUR protects normal cells from damage caused by DOX chemotherapy, helping to increase the effectiveness of DOX.

The combination of DOX and CUR drugs is considered as a general scheme to increase the effectiveness of chemotherapy. The combination of DOX and CUR has a synergistic effect and is able to influence the balance between the autophagy and apoptosis systems, reduce mitochondrial damage caused by DOX chemotherapy. Binary preparations of DOX and CUR show stronger antitumor activity *in vitro* and *in vivo* than DOX or CUR at the same concentrations and represent a novel and highly effective therapeutic strategy for better cancer treatment.

Chemotherapeutic drug delivery using nanoparticles is a promising approach for the effective treatment of various cancers. The use of NPs simultaneously enhances the therapeutic effects and reduces the side effects of anticancer drugs. Such an effective cancer treatment strategy is based on the joint delivery of several drugs by nanocarriers into one cell, which complement and extend the effect on tumors. The search and selection of the best nanocarriers is based on improved interaction with target cells, greater accuracy and enhanced penetration into the cells to the required organelles, improved stability of drugs and slower release of the combination of drugs over time.

In the scientific literature, it is reported that increasing the solubility and bioavailability of CUR is achieved by coincapsulating it in NPs and water-soluble polymers, which increases its therapeutic effects. Incorporating curcumin into albumin, Pluronic®, or other polymers allows it to reach its effective concentration inside the cell *in vitro*. For example, enhanced co-delivery of DOX and CUR using nanocarriers has shown synergistic antitumor efficacy against liver, breast, and lung tumors. NPs are able to maintain an optimized synergistic ratio of drugs in one carrier until intracellular absorption by the target cancer cell.

Biodegradable micelles are used as promising and effective carriers for

nanobiotechnology, which jointly deliver hydrophilic and hydrophobic drugs loaded into them. Such drugs have the ability to increase the concentration of DOX and CUR in the blood plasma, as well as to prolong the time of existence of the multidrug in the blood circulation. Biodegradable polymers often used in nanomedicine include micelles of PEG, Pluronic®, chitosan, PLG, PLGA, and albumin. For most NPs, the encapsulation of DOX and CUR is carried out using the self-assembly procedure, which is the most economically feasible. The peculiarity of using chitosan is related to its biodegradability, biocompatibility, ease of technical application, versatility and low toxicity. The stability of the Pluronic® micelle is significantly improved after coating it with a chitosan layer.

MDR and anti-apoptotic processes are two of the most common mechanisms leading to chemotherapy resistance in various cancers. Resistance to chemotherapy mainly develops due to the activity of transporters that reduce the amount of DOX in the cell. Studies demonstrate that P-gp is involved in DOX resistance. Joint administration of synergistic drugs DOX and CUR reverses MDR. This is because, once in the cytosol, CUR is able to block the transport of DOX from cells by inhibiting the expression of P-gp. It was shown that the combination with DOX and CUR changes MDR in tumor cells by inhibiting the activity of P-gp, as well as the induction of apoptosis through the mitochondrial pathway. The method of combining two or more therapeutic agents, which are included in NPs, or micelles, has great potential due to synergistic effects in overcoming MDR. In addition, the use of some polymers significantly improves the results in suppressing MDR. The use of biodegradable polymers is becoming the norm to achieve improved combination chemotherapy and greater selective targeting to suppress MDR. Loading into NPs with synergistic systems of additional chemotherapeutic agents can increase the antitumor effectiveness of the combination. The creation of such multifunctional NPs is an active strategy to mitigate MDR. Multifunctional nanocarriers for the DOX - CUR couple are constantly optimized in order to increase the cytotoxicity of the drug and reduce the amount of the drug needed to achieve a cytotoxic effect. Polymers that inhibit MDR are used to increase targeted drug delivery.

A combination drug delivery system based on multifunctional ligand-nanocarriers is superior to the conventional drug delivery system due to the ability to actively target cancer cells, which reduces unwanted side effects. For example, NPs modified with folic acid as a ligand selectively target tumors that express the folate receptor. Such NPs have increased antitumor efficiency, strongly inhibit MDR and cause less pathological damage to normal tissues.

There are some difficulties in achieving the optimal combination of drugs in nanoparticles, accuracy of tumor targeting and controllability of drug release. Such problems prevent the use of developed nanomedicines in practical therapy. This is due to the fact that during the use of nanomedicines there are certain limitations associated with physiological barriers in tumor tissues and non-selective interaction of drugs with normal tissues.

It is necessary to investigate and identify the mechanisms of synergistic action of several compounds with the aim of elucidating the molecular mechanisms that contribute to increasing the effectiveness of phytochemicals when they are used in combination for the treatment of oncological diseases. Future experiments should focus on enhancing the delivery of phytochemicals and creating different combinations of them that act synergistically, using *in vitro* and *in vivo* models. Creation of combined nanopreparations based on them, with optimized proportions of drugs, enhanced with ligands for the purpose of selective targeting of cancer cells, will become a standard scheme of treatment for cancer patients.

Despite some improvements in the drug delivery system, the placement of combination chemotherapeutics in the hybrid nanostructure remains a challenge, but the optimization of the delivery system targeting the tumor microenvironment may have great clinical significance. Advances in nanomedicine are driven by the development of new and improved carriers for drug combinations and drug delivery technologies. Research efforts are focused on the development of functionalized nanoparticles for the targeted delivery of therapeutic agents to specific molecular targets overexpressed in various cancer cells. The use of optical research methods helps to a great extent in the development of multifunctional combined nanopreparations with a synergistic effect. Such nanomaterials support an optimized synergistic ratio of drugs in one carrier until the moment of intracellular absorption. The use of nanocarrier-based combination therapy requires significant efforts to study the molecular

processes that drive the therapeutic effects of synergistic anticancer drugs. The search for the ideal nanocarrier and combination of natural and synthetic synergistic drugs continues. The development of NPs with a combination of synergistic drugs with known phytochemicals is clinically important because they can be rapidly transferred from the laboratory to clinical practice.

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КОМБІНОВАНА НАНОХІМІОТЕРАПІЯ НА ПРИКЛАДІ ДОКСОРУБІЦИНУ ТА КУРКУМІНУ

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Мета. Огляд даних літератури щодо комбінованої нанохіміотерапії на прикладі двох препаратів —доксорубіцину (Dox) та куркуміну (Cur). Особливу увагу приділено використанню речовин із синергічними властивостями в одній наночастинці (НЧ), здатних проникати в живу клітину.

Метод комбінованої хіміотерапії нанопрепаратами дозволяє підвищити ефективність лікування. Техніка використання наноконтейнерів із синергічними препаратами в поєднанні із лігандами зменшує побічні ефекти хіміотерапевтичних препаратів.

Результати. Дані літератури свідчать про те, що застосування нанопрепаратів сприяє швидкому створенню та використанню синергітичних комбінацій, які цілеспрямовано доставляються до клітин-мішеней, зменшуючи дозування за рахунок точного націлювання. Перспективним напрямком наномедицини є створення багатофункціональних наноматеріалів на основі кількох активних препаратів із синергічними властивостями, з одночасним використанням їх підсилювачів та стратегією активного націлювання. Ці структури дозволяють цілеспрямовано та контрольовано проникати лікарським сполукам у місця локалізації патологічних процесів, знижуючи токсичність препаратів для нормальних клітин.

Висновки. Комбінована хіміотерапія із використанням полімерів та наночастинок із лігандами, до складу яких входять синергічні препарати, спряє зменшенню побічних ефектів та дози хіміопрепаратів, а також подоланню множинної лікарської стійкості.

Ключові слова: комбінована нанохіміотерапія; доксорубіцин; куркумін; синергізм; активне націлювання.