SHORT COMMUNICATION

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BENZOFURAN THIAZOLE DERIVATIVE COMPLEXATION WITH POLYMERIC NANOPARTICLES ENHANCES REDUCTION OF MITOCHONDRIAL MEMBRANE POTENTIAL IN MURINE LYMPHOMA CELLS

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The development of new anticancer drugs aimed at the inhibition of mitochondria functioning in tumor cells is a promising approach to cancer treatment. The aim of our study was to investigate the effect of benzofuran derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) and its complex with polymer nanoparticles based on polyethylene glycol (PEG-PN) on mitochondrial membrane potential in cells of NK/Ly lymphoma grafted in ascite form in mice. Relative values of mitochondrial potential at different exposure times were recorded using the fluorescent dye tetramethylrhodamine. Fluorescence microscopy showed a significant decrease in mitochondrial potential after 30 and 60 min of cells incubation with the BF1-PEG-PN complex but not with unconjugated BF1. After 120 min of incubation, a decrease in the studied parameter was observed under the action of both BF1 alone and its complex with PEG-PN. The data obtained showed that a possible mechanism of cytotoxic action of the BF1 complex with PEG-PN involves early mitochondria depolarization in lymphoma cells.

K e y w o r d s: NK/Ly lymphoma cell, mitochondrial membrane potential, benzofuran derivative, polymeric nanoparticle, complexation.

Mitochondria play a central role in maintaining health and contributing to disease, due to their complex functions and ability to process cellular information. Disruptions in mitochondrial function are implicated in numerous widespread conditions such as cardiovascular disorders, neurodegenerative diseases, metabolic syndrome, and cancers [1].

Although glycolysis was long considered the primary metabolic process for energy production and anabolic growth in cancer cells, it is now clear that mitochondria play a crucial role in oncogenesis [2]. In addition to performing central bioenergetic functions, mitochondria also provide the building blocks for tumor anabolism, regulate redox processes and calcium homeostasis, participate in transcriptional regulation, and control cell death [3]. Therefore, mitochondria are promising targets for the development of novel anticancer therapies.

It was previously established that the thiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) reduces mitochondrial potential in murine lymphoma cells [4]. However, the effect of BF1 on the mitochondrial membrane potential of lymphoma cells was relatively weak. Therefore, in subsequent studies, we investigated the action of BF1 in combination with polymeric nanoparticles and found an enhanced effect of BF1 on lymphoma cell respiration [5].

Studying the effects of potential anticancer agents at different exposure times is essential for understanding their mechanisms of action and opti-

mizing their therapeutic effectiveness. The length of compound exposure can significantly influence cellular responses, including mitochondrial function, oxidative stress, apoptosis, and metabolic adaptation.

Therefore, assessing how the biological activity of new agents varies over time is an important step in preclinical drug evaluation.

The aim of this study was to investigate the effect of the compound BF1 and its complex with a polymeric carrier on mitochondrial membrane potential at various exposure times.

Materials and Methods

In vivo cultivation of experimental NK/Ly lymphoma in mice. The study was conducted on white male wild-type mice (20–30 g) with grafted NK/Ly lymphoma. The animals were kept in standard vivarium conditions at a constant temperature and were fed a mixed diet. All procedures involving animals were performed in accordance with the principles of the General Ethical Principles of Experimentation on Animals, approved by the First National Congress on Bioethics (Kyiv, Ukraine, 2001), and the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Strasbourg, France, 1986).

Ascite tumor cells were passaged by intraperitoneal inoculation of 10–15×10^6 cells into mice. Ascites were drained from the abdominal cavity of anesthetized mice with a sterile syringe 7–10 days after inoculation [4].

Investigated compounds. The thiazole derivative BF1 (N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide) was synthesized at the Department of Organic Chemistry at Ivan Franko National University of Lviv and used to prepare an initial 10 mM solution of BF1 in dimethyl sulfoxide [6, 7]. The PEG-PN Th3 (full name: poly(PEGMA-co-DMM)) was synthesized at the Department of Organic Chemistry at Lviv Polytechnic National University, as described earlier [8]. The BF1 concentration in the dispersed water solution was 0.3 mg/ml, and the Th3 concentration was 10 mg/ml. The tested compounds were added to lymphoma cells at a final concentration of 10 μM. The final concentration of BF1 in the complex was also 10 μM.

Fluorescence microscopy. The fluorescent dye tetramethylrhodamine methyl ester perchlorate was used to measure relative values of mitochondrial membrane potential. An Olympus IX73 inverted microscope was used for the research, and a DP74 digital camera was used to capture images. The excitation filter wavelength range was 540–585 nm, with a dichroic mirror set at 595 nm. A 600 nm barrier filter was also used [9].

The incubation medium for the cells contained (in mM) KCl – 90.0, NaCl – 15.0, EGTA – 1.0, HEPES – 10.0, pH 7.4. Initially, after washing, the lymphoma ascitic fluid was diluted tenfold. The test compound BF1 and its complex with a polymeric carrier were added to the cell suspension at 10 μM. An uncoupler of oxidative phosphorylation, FCCP, in a high concentration (20 μM), was used to fully depolarize mitochondria in nonpermeabilized NK/Ly cells and confirm that TMRM fluorescence depends on mitochondrial membrane potential. The same substances were added to a separate control sample containing DMSO at a final concentration of 5%, and the samples were incubated for 30, 60, and 120 min at 37°C.

After incubation, the cells were rewashed, and 10 μl of tetramethylrhodamine was added. The samples were then incubated for another 15 min at 37°C. For each sample, 4–5 fields of view were selected in visible and fluorescent light spectra. Five experimental groups were signed as Control (without any studied compounds), BF1 (non-conjugated thiazole derivative BF1), Th3 (PEG-PN poly(PEGMA-co-DMM), Th4 (BF1 complex with Th3), and FCCP (control with uncoupler of mitochondrial respiration).

The fluorescence intensity was recorded as an indicator of changes in mitochondrial membrane potential ($\Delta\psi m$) and analyzed using ImageJ software [9].

Statistical analysis. All experiments were repeated at least five times for each variant, and the arithmetic mean value was calculated. The standard error of the mean was determined from the standard deviation. The Student's *t*-test was used to assess the probability of differences between the groups compared. The study's critical levels of statistical significance were set at 0.05, 0.01, and 0.001. Microsoft Office Excel software was used for data analysis and processing.

Correlation analysis between incubation time and changes in membrane potential was performed using Pearson's correlation coefficient. The presence of a linear relationship between the variables was assessed. Calculations were carried out in Microsoft Excel. Statistical significance was considered at $P < 0.05$ [10].

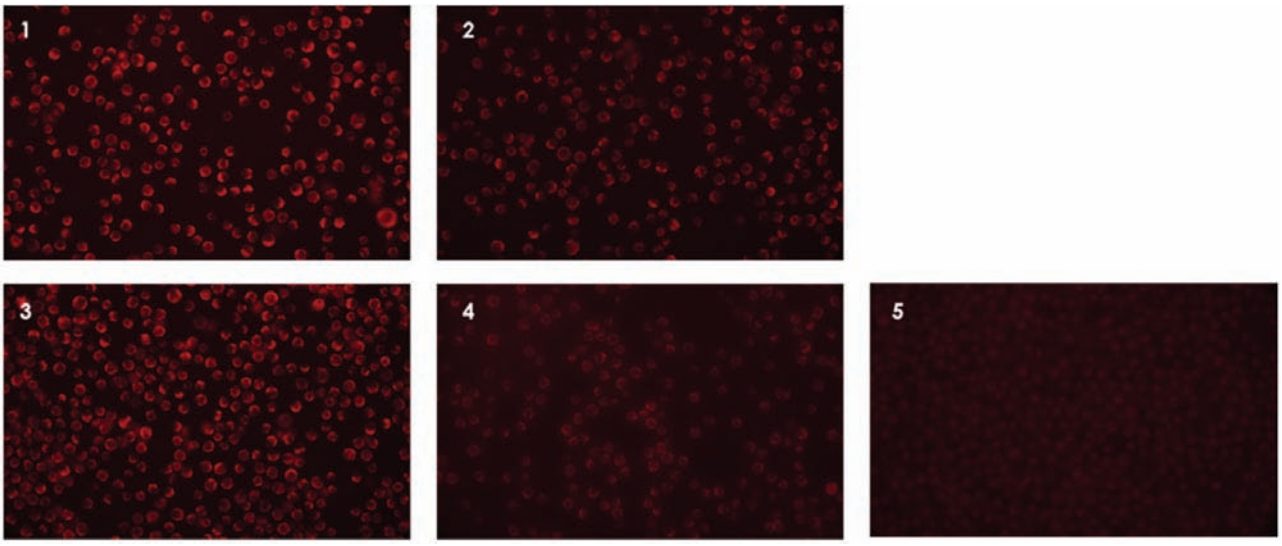

Fig. 1. Typical images of lymphoma cells in the control and under the influence of the studied compounds: 1 – Control, 2 – Non-conjugated thiazole derivative BF1, 3 – PEG-PN poly(PEGMA-co-DMM) (Th3), 4 – BF1 complex with Th3 (Th4), 5 – FCCP

Results

Fig. 1 shows representative photos of lymphoma cells in the control and under the influence of the studied compounds. The cells with normal (unchanged) membrane potential have bright red color (1 and 3), while, as expected, the lowest fluorescence intensity was observed under the action of the protonophore FCCP (5). Effect of the protonophore FCCP on fluorescence intensity was used as an indicator of changes in mitochondrial membrane potential ($\Delta\psi m$). For 30, 60, and 120 min, FCCP significantly ($P \leq 0.01$) reduced fluorescence intensities by 45% (Fig. 2), 50% (Fig. 3), and 51% (Fig. 4), respectively, compared to control. These data indicated that the measurement of membrane potential was conducted correctly.

Based on the results of the quantitative analysis using the ImageJ software, it was found that after 30 min of incubation, the membrane potential was not significantly affected by either unconjugated BF1 or Th3. However, Th4 significantly decreased the mitochondrial membrane potential of lymphoma cells by 32% compared to the control ($P \leq 0.05$) (Fig. 2), while it remained 18% higher than in the FCCP group. Therefore, we can conclude that after 30 min of incubation, BF1 causes notable changes only when conjugated with the polymer carrier (Th4).

Similar effects were found after 60 min of incubation (Fig. 3). We did not observe significant changes in membrane potential under the 60 min influence of the BF1 compound and Th3. However, Th4 significantly decreased the mitochondrial membrane potential of lymphoma cells by 25% compared to the control ($P \leq 0.01$). While, FCCP decreased it by 31% compared to the control ($P \leq 0.05$) (Fig. 3).

It was found that after 120 minutes of incubation, the studied compound BF1, even in unconjugated form with the nanocarrier PEG-PN poly(PEGMA-co-DMM), significantly reduced the mitochondrial membrane potential by 21% compared to the control ($P \leq 0.05$), but remained substantially higher by 36% compared to FCCP ($P \leq 0.05$) (Fig. 4). It was also determined that the complex of the compound with the polymeric nanocarrier (Th4) significantly decreased the mitochondrial membrane potential by 38% compared to the control ($P \leq 0.01$). It remained substantially higher by 20% compared to FCCP ($P \leq 0.05$). A trend toward a decrease in mitochondrial membrane potential was observed under the influence of Th4 compared to unconjugated BF1, although these changes did not reach statistical significance ($P = 0.062$).

Correlation analysis of incubation time and changes in membrane potential reveals a linear relationship. A significant difference was observed in the effect of BF1 and Th4 at 30 and 120 min of exposure. The correlation analysis confirmed the dependence of the substances impact on exposure time. A correlation analysis was performed in Excel, and

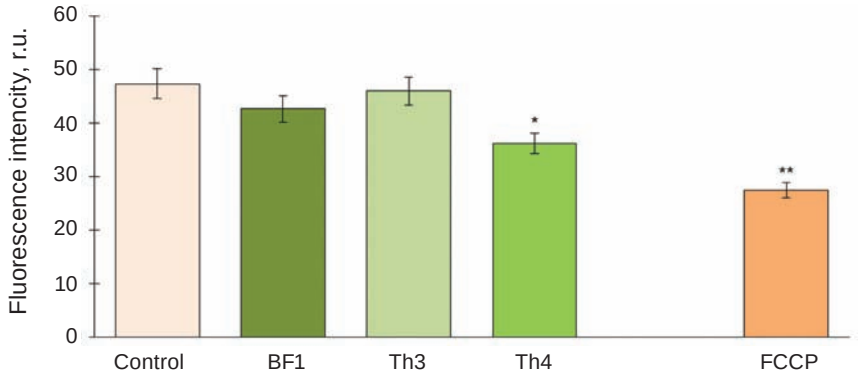

*Fig. 2. Changes in mitochondrial membrane potential in NK/Ly cells after 30-minute incubation with the studied compounds. 1 – Control, 2 – Non-conjugated thiazole derivative BF1, 3 – PEG-PN poly(PEGMA-co-DMM) (Th3), 4 – BF1 complex with Th3 (Th4), 5 – FCCP. M ± m, n = 5. *P ≤ 0.05 (vs control), **P ≤ 0.01 (vs control)*

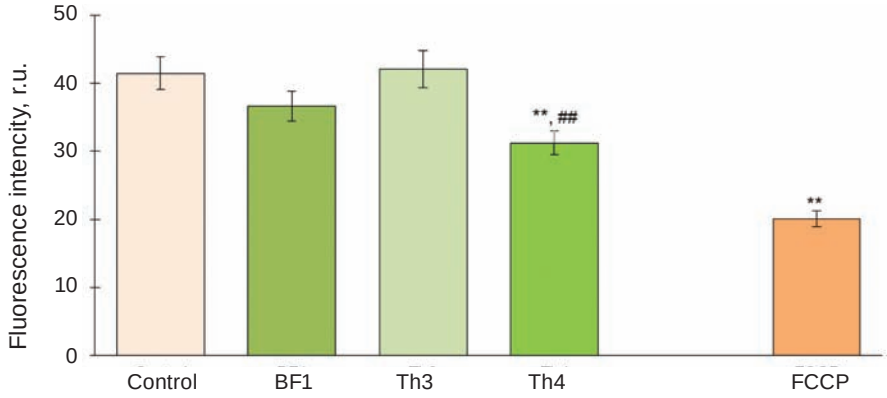

*Fig. 3. Changes in mitochondrial membrane potential in NK/Ly cells after 60-minute incubation with the studied compounds. 1 – Control, 2 – Non-conjugated thiazole derivative BF1, 3 – PEG-PN poly(PEGMA-co-DMM) (Th3), 4 – BF1 complex with Th3 (Th4), 5 – FCCP. M ± m, n = 5, **P ≤ 0.01 (vs control); ##P ≤ 0.05 (vs FCCP)*

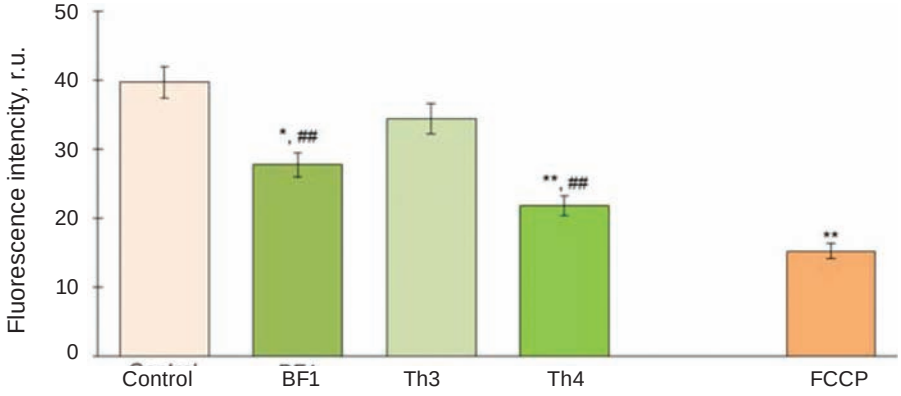

*Fig. 4. Changes in mitochondrial membrane potential in NK/Ly cells after 120-minute incubation with the studied substances. 1 – Control, 2 – Non-conjugated thiazole derivative BF1, 3 – PEG-PN poly(PEGMA-co-DMM) (Th3), 4 – BF1 complex with Th3 (Th4), 5 – FCCP. M±m, n=5, *P ≤ 0.05 (vs control), **P ≤ 0.01 (vs control); ##P ≤ 0.05 (vs FCCP)*

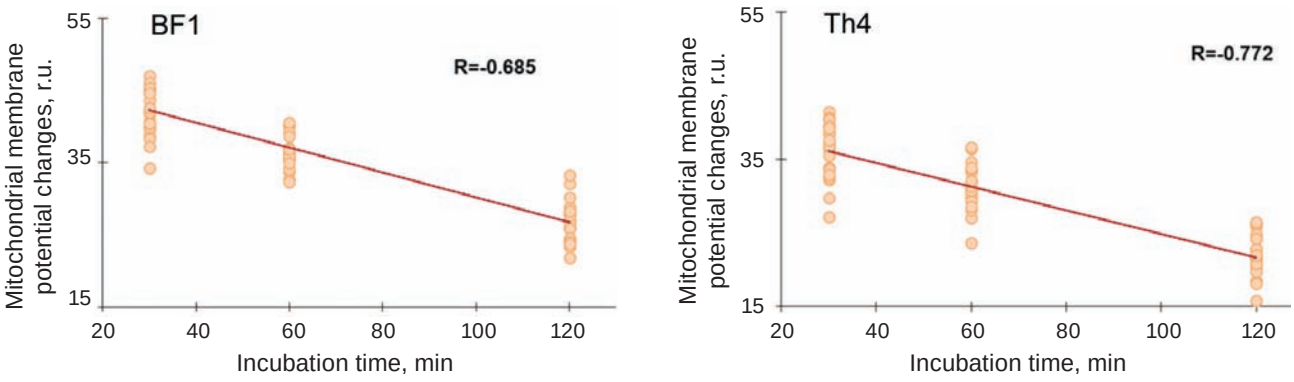

Fig. 5. Correlation analysis of the effects of BF1 and its complex with PEG-PN (Th4) at different exposure times

the following correlation values were obtained: BF1: r = -0.685, Th4: r = -0.772 (Fig. 5).

Discussion

The mitochondrial membrane potential is a crucial factor in maintaining mitochondrial integrity and bioenergetic status. Numerous chemotherapeutic agents depolarize mitochondrial ΔΨm within minutes to hours, thereby priming tumor cells for intrinsic apoptosis. Exposure time critically dictates the magnitude and trajectory of mitochondrial membrane depolarization across both classical chemotherapeutics and novel experimental agents. Rapid loss of ΔΨm typically occurs when drugs are electrophoretically targeted or directly inhibit electron transport chain complexes, whereas agents that require metabolic or stress signaling priming show delayed (>2 h) but often deeper collapses [11-13]. Understanding these temporal patterns enables rational design of nano-carriers, combination schedules, and redox-modulating countermeasures to maximize tumor kill while sparing normal tissue.

According to previous studies, a 15-minute incubation with the free (non-conjugated) compound BF1 did not alter the mitochondrial membrane potential in lymphoma cells. However, the Th2 complex (a conjugate of BF1 with a PEG-containing polymeric micelle) significantly reduced this parameter [9]. In this study, these preliminary findings were confirmed. It was found that Th4 significantly reduced the mitochondrial membrane potential of lymphoma cells by 32% compared to the control ($P \leq 0.05$), whereas unconjugated BF1 and Th3 did not significantly alter the membrane potentials of the NK/Ly cell mitochondria. Furthermore, after a 60-minute incubation, a similar trend was observed: the Th-4 complex caused a significant decrease in the mitochondrial membrane potential of lymphoma cells by 25%, whereas neither the free BF1 compound nor the non-conjugated polymeric carrier affected this parameter compared to the control.

According to the initial hypothesis, the principal cytotoxic mechanism of BF1 involves an increase in hydrogen peroxide and other reactive oxygen species (ROS) [14]. ROS are known to be generated during mitochondrial respiration, particularly when high-energy electrons leak from the electron transport chain before reaching the terminal electron acceptor, O_2. These ROS can trigger a rapid depolarization of the mitochondrial inner membrane, thereby disrupting oxidative phosphorylation. The integrity of the mitochondrial membrane may be compromised by ROS such as hydroxyl radicals or H_2O_2, resulting in dissipation of the mitochondrial membrane potential, release of cytochrome c, activation of pro-apoptotic caspases, and ultimately, the induction of apoptosis [15]. In our previous works, we demonstrated that thiazole derivatives (BF1, PP2) have a pronounced cytotoxic effect, which is due to the single-strand DNA breaks, activation of apoptosis and an increase in the amount of ROS (O_2, H_2O_2) [7, 14].

It is known that nanoparticles, polymers, liposomes and ligand-directed conjugates can dramatically accelerate, amplify, or, in some contexts, mitigate ΔΨm and ROS generation shift by altering drug uptake kinetics, intracellular trafficking, and mitochondrial targeting [16-18]. The combination of nanocarriers with chemotherapeutic agents such as doxorubicin, cisplatin, paclitaxel, and tubastatin A has been shown to reduce mitochondrial membrane potential in human tumor cells more effectively than

their unconjugated counterparts. Complex formation not only enhances the solubility of antitumor agents but may also prevent the development of tumor cell resistance to chemotherapeutic drugs [18].

These hypotheses are further supported by the findings of the present study. The free BF1 compound induced a significant reduction in the mitochondrial membrane potential of tumor cells only after a 2-hour incubation. In contrast, its complex with the PEG-containing nanocarrier altered this parameter as early as 30 min into incubation. In addition, the correlation analysis confirmed the dependence of the BF1 and its conjugates with PEG-containing micelle impact on the exposure time (BF1: r = -0.685, Th4: r = -0.772).

Thus, the BF1+PEG-PN complex Th4, but not the free thiazole derivative, induced mitochondrial membrane damage, as evidenced by a decrease in mitochondrial membrane potential in lymphoma cells after only 30 min of incubation. These processes may result either from the direct action of BF1, whose solubility was enhanced by encapsulation within the PEG-PN carrier, on the mitochondria, or indirectly through oxidative stress triggered by excessive ROS accumulation in tumor cells. Thus, the BF1+PEG-PN complex Th4, but not the free thiazole derivative, induced mitochondrial membrane damage, as evidenced by a decrease in mitochondrial membrane potential in lymphoma cells. These processes may result either from the direct action of BF1 – whose solubility was enhanced by encapsulation within the PEG-PN carrier – on the mitochondria, or indirectly through oxidative stress triggered by excessive ROS production in tumor cells.

Conclusions. It was established that the free benzofuran derivative BF1 significantly reduces the mitochondrial membrane potential of lymphoma cells only at the 120th min of the action. No changes in the mitochondrial membrane potential of lymphoma cells under the influence of BF1 were observed at the 30th and 60th min of the experiment. The Th4 complex (BF1+PEG-PN complex) reduced the mitochondrial membrane potential of lymphoma cells at the 30th, 60th, and 120th min of the experiment. Correlation analysis of the investigated complex's effect confirmed that the compound action depends on the incubation time with lymphoma cells. These processes may result either from the direct action of BF1 on the mitochondrial membrane potential and intrinsic apoptosis or indirectly by excessive ROS accumulation in the These processes may result either from the direct effect of BF1 on the mitochondrial membrane potential and intrinsic apoptosis or indirectly through excessive ROS accumulation in tumor cells.

Conflct of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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КОМПЛЕКС ПОХІДНОГО БЕНЗОФУРАНУ З ПОЛІМЕРНИМИ НАНОЧАСТИНКАМИ ПОСИЛЮЄ ЗНИЖЕННЯ МЕМБРАННОГО ПОТЕНЦІАЛУ МІТОХОНДРІЙ У КЛІТИНАХ ЛІМФОМИ МИШІ

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Розробка нових протипухлинних препаратів, спрямованих на інгібування функціонування мітохондрій у пухлинних клітинах, є перспективним підходом до лікування раку. Метою нашого дослідження було вивчення впливу бензофуранового похідного N-(5-бензил-1,3-тіазол-2-іл)-3,5-диметил-1-бензофуран-2-карбоксаміду (БФ1) та його комплексу з полімерними наночастинками на основі поліетиленгліколю (ПЕГ-ПН) на мембранний потенціал мітохондрій у клітинах лімфоми NK/Ly, трансплантованої в асцитній формі, у мишей. Відносні значення мітохондріального потенціалу за різного часу експозиції визначали за допомогою флуоресцентного барвника тетраметилродаміну. За результатами флуоресцентної мікроскопії встановлено суттєве зниження мітохондріального потенціалу після 30 і 60 хв інкубації клітин із комплексом БФ1 з ПЕГ-ПН, але не з некон'югованим БФ1. Після 120 хв інкубації зниження досліджуваного параметра спостерігали як під дією самого

похідного БФ1, так і його комплексу з ПЕГ-ПН. Отримані дані вказують, що можливий механізм цитотоксичної дії комплексу БФ1 із ПЕГ-ПН полягає у ранній деполяризації мембран мітохондрій у клітинах лімфоми.

Ключові слова: клітини лімфоми NK/Ly, мембранний потенціал мітохондрій, бензофуранове похідне, полімерна наночастинка, комплексоутворення.

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