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EFFECT OF A NOVEL THIAZOLE DERIVATIVE AND ITS COMPLEX WITH A POLYMERIC CARRIERS ON THE ACTIVITY OF ANTIOXIDANT ENZYMES IN MURINE LYMPHOMA CELLS

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Background. Previous studies have shown a pronounced cytotoxic effect of thiazole derivatives in combination with polymeric carriers on tumor cells. At the same time, the derivatives were not cytotoxic against non-cancerous cells *in vitro*. It was shown that thiazole derivatives at concentrations of 10 and 50 μM affected the prooxidant and antioxidant systems of lymphoma cells in *vitro*. The aim of this work was to study the effect of the complex of thiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) in combination with polymeric carriers poly(VEP-*co*-GMA)-*graft*-mPEG (Th1), poly(PEGMA) (Th3) and poly(PEGMA-*co*-DMM) (Th5) on the antioxidant defense system of the NK/Ly cell *in vitro*.

Materials and Methods. The experiments were performed on white wild-type male mice with grafted NK/Ly lymphoma. Tumor cells were inoculated into mice intraperitoneally. Ascites was drained from the abdominal cavity of anaesthetized mice with a sterile syringe on the 7th-10th day after inoculation. Investigated compounds BF1, BF1 + Th1 (Th2, Th12), BF1 + Th3 (Th4, Th14), BF1 + Th5 (Th6, Th16) at a final concentration of 10 μM were added to the lymphoma samples and incubated for 10 min; the activity of antioxidant enzymes was determined according to the techniques described previously.

Results. It was found that all the studied complexes based on thiazole derivative BF1 and polymeric carriers poly (VEP-*co*-GMA)-*graft*-mPEG (Th2, Th12), poly (PEGMA) (Th4, Th14) and poly (PEGMA-*co*-DMM) (Th6, Th16) at a concentration of 10 μm

increased the activity of SOD, while the activity of CAT and GPX were reduced compared to control. Complexes Th2, Th12 and Th4 increased the significance of the BF1 influence on lymphoma cells from P <0.05 to P <0.01. Pure polymeric carriers did not affect the level of the antioxidant defense system enzymes.

Conclusions. Thus, it was found that the polymeric carriers in combination with thiazole derivative BF1 increased the significance of thiazole derivative BF1 influence on the activity of the antioxidant defense system of lymphoma cells, while pure polymeric carriers did not affect the activity of SOD, CAT or GPX. The results of this work can be used for further studies of complexes of thiazole derivative and PEG-containing polymeric carriers as potential antitumor drugs.

Keywords: lymphoma, thiazole derivative, polymeric carriers, polyethyleneglycol, antioxidant defense system

INTRODUCTION

The intensity of free radical processes is determined by the balance of prooxidant and antioxidant reactions in cells. Under normal physiological conditions, the concentration of reactive oxygen species (ROS) in tissues is low, but in different pathological conditions, the formation of ROS intensifies while the activity of protective systems of the cell decreases causing apoptosis or necrosis. As a results of an elevated level of ROS in cells, the activity of the antioxidant defense enzymes increases allowing cells to survive under these conditions (Snezhkina *et al.*, 2019; Perillo *et al.*, 2020). A number of defense mechanisms are present in the body to prevent the formation of ROS and the damage resulting from their presence. Enzymes such as superoxide dismutase (SOD), catalase (CAT) and glutathioneperoxidase (GPX) is involved in inactivation of existing ROS.

Nowadays, there are no universal chemotherapeutic drugs, as most of them have a number of disadvantages, in particular, low therapeutic effect, high toxicity, lack of selectivity and side effects (Sutradhar & Amin, 2014). Therefore, the search for new antitumor compounds with lower toxicity, high selectivity and therapeutic effect is an urgent problem of chemotherapy.

A cytotoxic effect of the investigated thiazole derivatives on cell lines of melanoma, glioblastoma, hepatocarcinoma, leukemia cells has been established (Finiuk *et al.*, 2017). It was found that thiazole derivatives of N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) changed prooxidant-antioxidant balance, in particular increased the activity of SOD and inhibited CAT and GPX activity in Nemeth-Kellner lymphoma (NK/Ly) cells (Shalai *et al.*, 2019).

However, thiazole derivatives have a low aqueous solubility that can limit their efficiency. Besides, many anticancer agents share similar issues affecting safe and effective delivery to the localization of tumors (Amreddy *et al.*, 2018).

Nanoparticles (NP) can play a significant role as a solvent-based drug delivery system. In addition, they have many other specific advantages, such as enhanced of permeability, stability, biocompatibility and targeted delivery of anticancer agents to overcome cancer-related drug resistance (Sutradhar & Amin, 2014; Dadwal, Baldi, & Kumar Narang, 2018). Numerous types of NPs, both organic and inorganic, have already been extensively used in the clinical treatment of several cancer types, including pancreatic, breast, ovarian, and prostate cancers (Alimoradi., Greish, Barzegar-Fallah, Alshaibani, & Pittalà, 2018; Wang *et al.*, 2018; Zhao *et al.*, 2019).

Polyethylene glycol (PEG), as a water-soluble polymer, is one the most widely used non-ionic polymer in the field of polymer-based drug delivery (Knop, Hoogenboom, Fischer, & Schubert, 2010). Numerous clinical trials investigated PEGylated low molecular weight drugs/liposomal derivatives/thermo-sensitive conjugates and nanoparticles as efficient anticancer therapy. For example CALLA 01 (PEGylated cyclodextrin nanoparticle) is in clinical phase I for solid tumors (Lee, Yoon, & Cho, 2013). It was reported, that thiazole derivatives complexes with PEG-based polymeric carriers caused apoptotic-like changes in lymphoma cells (Popovych *et al.*, 2021).

The purpose of this work was to investigate the effect of thiazole derivative BF1, conjugated with polymeric-containing carriers poly(VEP-*co*-GMA)-*graft*-mPEG (Th1), poly(PEGMA) (Th3) and poly(PEGMA-*co*-DMM) (Th5) on the activity of enzymes of the antioxidant defense system of lymphoma cells.

MATERIALS AND METHODS

The study was performed on white wild-type male mice (n = 45; 20–30 g) with grafted NK/Ly lymphoma. All manipulations with animals were conducted in accordance with 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, 1985), as well as approved by the Ethics Committee of Ivan Franko National University of Lviv, Ukraine at the beginning of the research (Protocol of 01.05.2021 No 19-05-2021) and after the completion of the study (Protocol of 01.12.2021 No 26-12-2021).

Ascites tumor cells were passaged by intraperitoneal inoculation of $10–15\times10^6$ cells to mice. Ascites was drained from the abdominal cavity of anaesthetized mice with sterile syringe on 7–10 day after the inoculation. For determination of the antioxidant defense systems activity, enzymes ascites from 5 different mice were used for each group of experiments.

The initial 10 μM solution of thiazole derivative BF1 was synthesized at the Department of Organic Chemistry of Ivan Franko Lviv National University and the PEG-containing carriers were synthesized at the Department of Organic Chemistry of the Lviv Polytechnic National University, as described earlier (Mitina *et al.*, 2020; Finiuk *et al.*, 2017).

Water dispersions of polymeric carriers (PC) on the basis of poly(VEP-*co*-GMA)-*graft*-mPEG (Th1), poly(PEGMA) (Th3) and poly(PEGMA-*co*-DMM) (Th5) and their complexes with the BF1 derivative were prepared in two different ways: 1) PC and BF1 were dissolved in dimethyl sulfoxide (DMSO), and the solutions were subsequently transferred in water (Th2, Th4, Th6) or 2) BF1 solution in DMSO was added to PC water solution (Th12, Th14, Th16). Three groups of chemical compounds were prepared: 1st group – BF1 (10 mM), Th1 (1 g/100 mL) Th2 and Th12 (Th1 (1 g/100 mL) + BF1 (0.03 g/100 mL) prepared in two different techniques), 2nd group – BF1 (10 mM), Th3 (1 g/100 mL), Th4 and Th14 (Th3 (1 g/100 mL) + BF1 (0.03 g/100 mL)) prepared in two different techniques) and 3rd group – BF1 (10 mM), Th5 (1 g/100 mL), Th6 and Th16 (Th5 (1 g/100 mL) + BF1 (0.03 g/100 mL)) prepared in two different techniques) and added to the lymphoma homogenate with duration of incubation 10 min. Other explanations see in the **Table**.

Structure of the investigated substances used in experiments
Структура досліджуваних речовин, які використовували в дослідах

Name of sample	Thiazole derivative	Polymeric carrier	Complexes	
			Preparing techniques 1	Preparing techniques 2
Control	–	–	–	–
BF1	+	–	–	–
Th1, Th3, Th5	–	+	–	–
Th2, Th4, Th6	–	–	+	–
Th12, Th14, Th16	–	–	–	+

To measure the activity of SOD, CAT and GSH-Px, lymphoma cell samples were frozen in a freezer chamber to -20 °C and subsequently used for investigation. Superoxide dismutase activity was measured by the method described by V. Kostyuk *et al.* and enzymatic activity was expressed as unit SOD/mg protein (Kostyuk, Potapovich, & Kovaleva, 1990). Catalase activity was measured spectrophotometrically by the method described by M. Korolyuk *et al.* and the activity of CAT was expressed in nmoles of H_2O_2/min×mg of protein (Korolyuk, Ivanova, Mayorova, & Tokaryev, 1998). Glutathionperoxidase (GPX) activity was measured by the method of Moin and expressed in μM of G–SH/min×mg of protein (Moin, 1986). Protein concentration in each specimen was determined by the method of O. Lowry *et al.* (Lowry, Rosebrough, Farr, & Randall, 1951).

The MS Excel-2013 and Statistica programs were used for statistical analysis of obtained results. To assess the reliability of difference between statistical characteristics of two alternative sets of data, Student's coefficient and Mann–Whitney test were calculated. To determine statistically significant differences between the means of independent investigation groups, one-way analysis of variance (ANOVA) was used. The difference was considered to be significant at $P < 0.05$.

RESULTS AND DISCUSSION

ROS play a vital role in fundamental physiological processes, such as production of hormones, modulation of protein functions, regulation of cell signaling and inflammation, but in many pathological states their level are over elevated and can induce the non-specific damage of DNA, some proteins and lipids and increase the risk of mutating cellular DNA. Antioxidant enzymes including SOD, CAT and GPX are highly specific, with high affinities and rates of reaction that decompose ROS with a high efficacy.

It was reported that thiazole derivatives produce their cytotoxic effect through the effect on the activity of antioxidant system (Shalai *et al.*, 2019), while polymeric carriers are widely used to improve the efficiency and water solubility of antitumor drugs, increase their biocompatibility and delivery. Thus, the aim of our work was to evaluate the effect of PEG-containing PCs and their complexes with thiazole derivative BF1 on the activity of key enzymes of the antioxidant system in lymphoma cells.

Superoxide dismutase is an enzyme that converts superoxide ($O_2^{\bullet-}$) to H_2O_2.

Figure 1 represents the results of SOD activity of the investigated substance BF1, pure polymers poly(VEP-*co*-GMA)-*graft*-mPEG (Th1), poly(PEGMA) (Th3) and

poly(PEGMA-*co*-DMM) (Th5) and complexes of the substance with the polymers (Th2, Th12, Th4, Th14, Th6 and Th16) in NK/Ly cells. The control level of SOD activity in lymphoma was in the range of 433–511 active units/min×mg of protein.

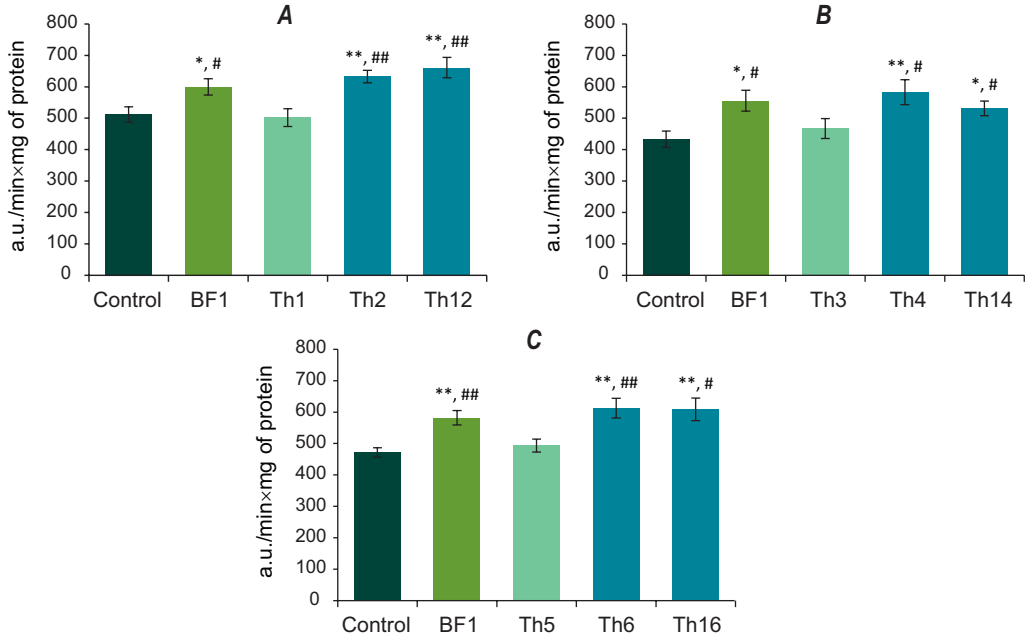

Fig. 1. The effect of thiazole derivative (BF1), pure polymeric carriers (Th1, Th3, Th5) and complexes of BF1 with PCs (Th2, Th4, Th6 and Th12, Th14, Th16) on the activity of superoxide dismutase in lymphoma cells. (***A***) The left panel represents the effects of BF1, the pure polymer based on poly(VEP-*co*-GMA)-*graft*-mPEG (Th1) and its complexes with BF1 (Th2 and Th12) compared to control. (***B***) The middle graph represents the effects of BF1, the pure polymer based on poly(PEGMA) (Th3) and its complexes with BF1 (Th4 and Th14) compared to control. (***C***) The right graph represents the effects of BF1, the pure polymer based on poly(PEGMA-*co*-DMM) (Th5) and its complexes with BF1 (Th6 and Th16) compared to control. The control level of the enzyme activity is assumed as 100 %. M ± m; n = 5. *, # – P <0.05; **, ## – P <0.01 (* – for Students' *t*-test, # – for U-test Mann–Whitney)

Рис.1. Вплив похідного тіазолу (BF1), полімерних носіїв (Th1, Th3, Th5) і комплексів BF1 та полімерних носіїв (ПН) (Th2, Th4, Th6 and Th12, Th14, Th16) на активність супероксиддисмутази клітин лімфоми. (***A***) На лівому графіку зображено вплив BF1, полімерного носія poly(VEP-*co*-GMA)-*graft*-mPEG (Th1) і їхніх комплектів (Th2 та Th12) порівняно з контролем. (***B***) На середньому графіку зображено вплив BF1, полімерного носія poly(PEGMA) (Th3) та їхніх комплектів (Th4 та Th14) порівняно з контролем. (***C***) На правому графіку зображено вплив BF1, полімерного носія poly(PEGMA-*co*-DMM) (Th5) та їхніх комплектів (Th6 та Th16) порівняно з контролем. Контрольний рівень активності ензиму прийнятий за 100%. M ± m; n = 5. *, # – P<0.05; **, ## –P<0.01 (* – для критерію Стьюдента, # – для тесту Манна–Уітні)

BF1 significantly increased the activity of SOD after 10 min of incubation with lymphoma cells by 17 % (**Fig. 1*A***; P <0.05), 29% (**Fig. 1*B***; P <0.05) and 23% (**Fig. 1*C***; P <0.01), compared to control meaning Complexes Th2 and Th12 significant elevated the level of enzyme by 24 % and 24 %, respectively (**Fig. 1A**, P <0.01). The activity of SOD significantly increased under the effect of Th4 and Th14 by 35 % and 29 % (**Fig. 1*B***, P <0.01 and P <0.05), respectively. Both complexes Th6 and Th16) significantly elevated the level of the investigated enzyme by 29 % (**Fig. 1*C***, P <0.01 and P <0.05).

The availability of PCs in complexes Th2, Th12, Th4 were contributed to the increase in the significance of the substance effect on SOD activity. There were no significant changes in the levels of SOD after the influence of pure polymeric carriers Th1, Th3 and Th5 in lymphoma cells.

CAT catalyzes the dismutation of hydrogen peroxide (H_2O_2) into water and molecular oxygen and frequently downregulates in tumor cells compared to normal of the same origin (Shalai, Mandzynets, Grenyukh, Finiuk, & Babsky, 2017).

Figure 2 illustrates changes in the activity of CAT in the lymphoma cells under the action of BF1, pure PCs and their complexes. The control level of CAT activity was 0.006–0.0084 nmol of H_2O_2/min×mg of protein. It was found that BF1 significantly reduced the activity of CAT by 11 % (**Fig. 2*A***, P <0.05), 15 % (**Fig. 2*B***, P <0.05) and 12 % (**Fig. 2*C***, P <0.05 and P <0.01) compared to control. The activity of CAT significantly decreased under the effects of Th2 and Th12 by 17 % and 12 % (**Fig. 2A**, P <0.05 and P <0.01); Th4 and Th14 by 23 % and 22 % (**Fig. 2*B***, P <0.05 and P <0.01); Th6 and Th16 12 % and 16 % (**Fig. 2*C***, P <0.05), respectively. Interestingly, a more significant influence was noticed under the action of complexes Th2, Th12 and Th4 compared to BF1 effect. Pure PCs (Th1, Th3, Th5) did not change the activity of CAT (**Fig. 2**).

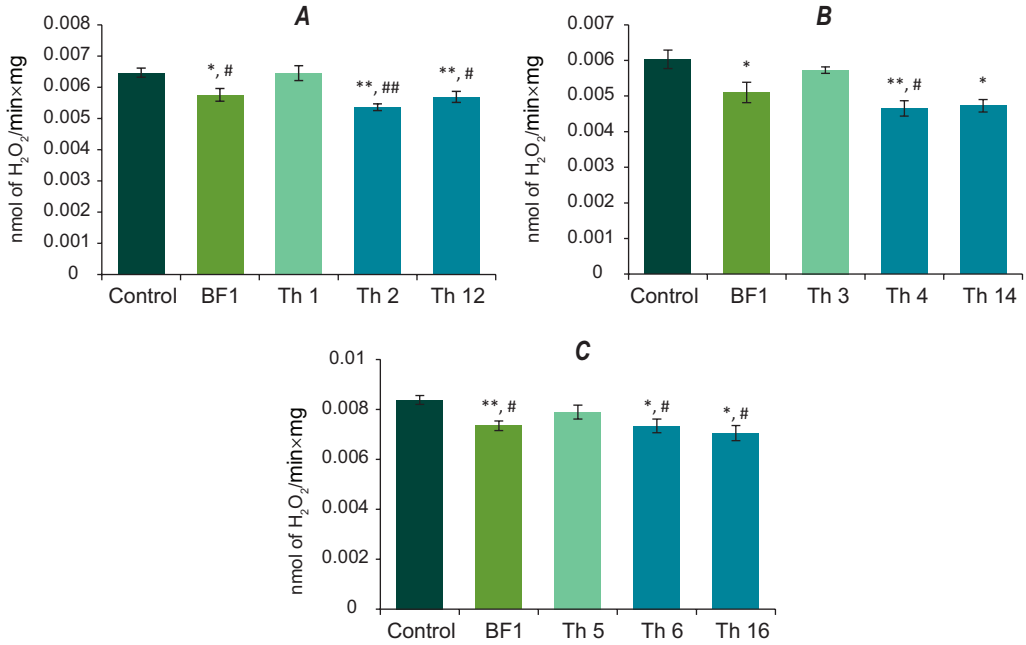

Fig. 2. Effect of thiazole derivative (BF1), pure polymeric carriers (Th1, Th3, Th5) and complexes of BF1 with PCs (Th2, Th4, Th6 and Th12, Th14, Th16) on the activity of catalase in lymphoma cells compared to control. The control level of the enzyme activity is assumed as 100 %. M ± m; n = 5. *, # – P <0.05; **, ## – P <0.01 (* – for Students' *t*-test, # – U-test Mann–Whitney). For further description, see **Fig. 1**

Рис. 2. Вплив похідного тіазолу (BF1), полімерних носіїв (Th1, Th3, Th5) і комплексів BF1 та полімерних носіїв (ПН) (Th2, Th4, Th6 and Th12, Th14, Th16) на активність каталази клітин лімфоми порівняно з контролем. Контрольний рівень активності ензиму прийнятий за 100%. M ± m; n = 5. *, # – P <0,05; **, ## – P <0,01 (*– для критерію Стьюдента, # – для тесту Манна–Уітні). Інші пояснення див. на рис. 1

The main function of GPX is destruction and inactivation of hydrogen peroxide and toxic oxygen compounds – hydroperoxides, using reduced glutathione (GSH) as an electron donor.

Figure 3 shows changes in the activity of GPX under the action of BF1, pure PCs and their complex. The control level of the enzyme was 1.25–3.01 nmol GSH/min×mg protein. It was found that the activity of GPX significantly decreased under the action of: Th2 and Th12 by 17 % and 16 % (**Fig. 3*A***, P <0.05 and P <0.01); Th4 and Th14 by 35 % and 26 % (**Fig. 3*B***, P <0.05 and P <0.01); Th6 and Th16 by 48 % and 47 % (**Fig. 3*C***, P <0.05 and P <0.01), respectively, while BF1 significantly decreased the level of the enzyme by 21 % (**Fig. 3*A***, P <0.05 and P <0.01), 27 % (**Fig. 3*B***, P <0.05) and 44 % (**Fig. 3*C***, P <0.05) vs control. Only one or three naked PCs – Th5 – significantly decreased the activity of GPX by 27% (**Fig. 3*C***, P <0.05) compared to control. No significant changes between BF1 and complexes were recorded, but the influence on the action of GPX was more significant under the action of complex Th4.

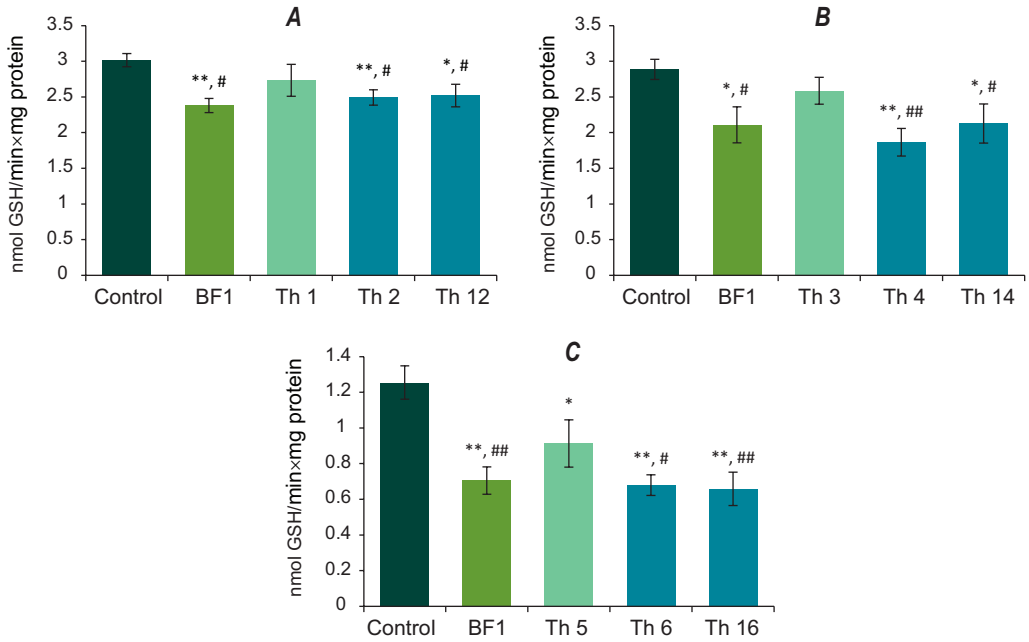

Fig. 3. The effect of thiazole derivative (BF1), pure polymeric carriers (Th1, Th3, Th5) and complexes of BF1 with PCs (Th2, Th4, Th6 and Th12, Th14, Th16) on the activity of glutathionperoxidase in the lymphoma cells compared to control. The control level of the enzyme activity is assumed as 100 %. M ± m; n = 5. *, # – P<0.05; **, ## –P<0.01 (* – for Students' *t*-test, # – U-test Mann–Whitney). For further description, see **Fig. 1**

Рис. 3. Вплив похідного тіазолу (BF1), полімерних носіїв (Th1, Th3, Th5) і комплексів BF1 та полімерних носіїв (ПН) (Th2, Th4, Th6 and Th12, Th14, Th16) на активність глутатіонпероксидази клітин лімфоми порівняно з контролем. Контрольний рівень активності ензиму прийнятий за 100%. M ± m; n = 5. *, # – P <0,05; **, ## –P <0,01 (* – для критерію Стьюдента, # – для тесту Манна–Уітні). Інші пояснення див. на рис. 1

Thiazole derivatives are a promising group of compounds that show their efficacy in antitumor, antiparasitic, antifungal, antimicrobial and antiproliferative activities (De

Santana *et al.*, 2018). Many of thiazole-containing drugs such as Abafungin, Amiphenazole, Brecanavir, Carumonam and many other are commercially available.

The main problem that limits a widespread use of thiazole derivatives as an antitumor agent is its low solubility in water and many organic solvents, which pointedly reduces their efficacy. Polymeric carriers are widely used to enhance the efficiency of biological action of drugs, improve their biocompatibility and water solubility and additionally may reduce the total toxicity, enhance the accumulation of antitumor drugs in cancer cells and tissues and improve their efficacy (Wang, 2017). So, the aim of our work was to instigate the activity of antioxidant system under the influence of stable complexes of polymers based on poly(VEP-co-GMA)-graft-mPEG, poly(PEGMA), and poly(PEGMA-co-DMM) with poorly water-soluble substance BF1.

Earlier, it was reported that thiazole derivative BF1 demonstrated a high cytotoxic action towards several tumor cell lines, increased the level of SOD, while the activity of GPX and CAT decreased (Finiuk *et al.*, 2017; Shalai *et al.*, 2019). It was found that under the action of substances BF1 in complex with all PEG-containing polymers based on poly(VEP-*co*-GMA)-*graft*-mPEG(Th1), poly(PEGMA) (Th3) and poly(PEGMA-*co*-DMM) (Th5) the activity of SOD significantly increased versus control, while, PCs increased the significance of BF1 influence compared to pure substance from $P < 0.05$ to $P < 0.01$. Therefore, BF1 in complex with PCs directly or indirectly activated SOD activity in lymphoma cells that may lead to the accumulation of H_2O_2, which is toxic for tumor cells and can cause DNA breaks, apoptosis and reduce the intensity of glycolysis. Thus, an elevated level of hydrogen peroxide is an early and crucial step towards complexes-induced cancer cell death. A large amount of H_2O_2, which was formed due to an increased activity of SOD, was inactivated by important AOC enzymes – KAT and GPX. The affinity of GPX for H_2O_2 is higher than that of catalase, so the first enzyme functions more effectively at low concentrations of hydrogen peroxide, while at high concentrations – the key role belongs to the catalase. According to the obtained results, the level of CAT and GPX activity reduced under the effect of all investigated complexes compared to control and were equal versus pure BF1 effect. PEG-PCs improved the significance of BF1 influence on the investigated enzymes in NK/Ly cells compared to pure thiazole derivative from $P < 0.05$ to $P < 0.01$. Also, there were no significant changes in the activity of all enzymes of antioxidants defense under the influence of any PEG-containing polymeric carriers.

Thus, thiazole derivative BF1 in complex with PEG-containing polymeric carriers (Th2, Th12; Th4, Th14; Th6 and Th16) significantly changed the activity of the antioxidant defense system. Complexes Th2, Th12 and Th4 increased the significance of BF1 influence on lymphoma cells, while pure PCs did not affect the level of the antioxidant defense system enzymes.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Human Rights: This article does not contain any studies with human subjects performed by any of the authors.

Animal studies: All international, national and institutional guidelines for the care and use of laboratory animals were followed.

AUTHOR CONTRIBUTIONS

Conceptualization, [M.V.P.]; methodology, [M.V.P.; Ya.R.Sh.]; validation, [M.V.P.; S.M.M.; Ya.R.Sh.]; formal analysis, [M.V.P.; S.M.M.].; investigation, [M.V.P.; Ya.R.Sh.]; resources, [M.V.P.; N.O.M; O.S.Z.]; data curation, [A.M.B.]; writing – original draft preparation, [M.V.P.]; writing – review and editing, [M.V.P.; A.M.B.]; visualization, [M.V.P.]; supervision, [S.N.O.]; project administration, [A.M.B.]; funding acquisition, [-].

All authors have read and agreed to the published version of the manuscript.

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ЕФЕКТ НОВОСИНТЕЗОВАНОГО ПОХІДНОГО ТІАЗОЛУ ТА ЙОГО КОМПЛЕКСІВ З ПОЛІМЕРНИМИ НОСІЯМИ НА АКТИВНІСТЬ ЕНЗИМІВ АНТИОКСИДАНТНОЇ СИСТЕМИ ЗАХИСТУ КЛІТИН МИШАЧОЇ ЛІМФОМИ

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Обґрунтування. Попередніми дослідженнями встановлено виражену цитотоксичну дію похідних тіазолу в комплексі з полімерними носіями на пухлинні клітини, проте не були цитотоксичними щодо неракових клітин *in vitro*. Досліджено, що похідні тіазолу в концентраціях 10 і 50 мкМ впливали на прооксидантну й антиоксидантні системи клітин лімфоми *in vitro*. Мета роботи полягала у дослідженні впливу похідного тіазолу N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) в комплексі з полімерниими носіями poly(VEP-*co*-GMA)-*graft*-mPEG (Th1), poly(PEGMA) (Th3) та poly(PEGMA-*co*-DMM) (Th5) на стан антиоксидантної системи клітин NK/Ly *in vitro.*

Матеріали та Методи. Експерименти виконували на білих мишах-самцях дикого типу з прищепленою лімфомою NK/Ly. Клітини пухлини прищеплювали мишам внутрішньочеревно. Асцит відбирали дренуванням черевної порожнини стерильним шприцом під етерним наркозом на 7–10-ту добу після інокуляції. Досліджувані сполуки BF1, BF1 + Th1 (Th2, Th12), BF1 + Th3 (Th4, Th14), BF1 + Th5 (Th6, Th16) у кінцевій концентрації 10мкМ додавали до дослідних зразків та інкубували впродовж 10 хв і визначали активність ензимів антиоксидантного захисту згідно з методиками, описаними раніше.

Результати. Встановлено, що всі досліджувані комплекси на основі похідного тіазолу BF1 та полімерних носіїв poly(VEP-*co*-GMA)-*graft*-mPEG (Th2, Th12), poly(PEGMA) (Th4, Th14) та poly(PEGMA-*co*-DMM) (Th6, Th16) у концентрації 10 мкМ призводили до підвищення активності супероксиддисмутази, натомість знижували активність каталази і глутатіонпероксидази порівняно з контролем. Комплекси Th2, Th12 і Th4 підвищували достовірність впливу речовини BF1 на клітини лімфоми з $P<0,05$ до $P<0,01$. Не було зафіксовано жодної достовірної зміни в активності антиоксидантних ензимів за дії вільних полімерних носіїв.

Висновки. Ґрунтуючись на результатах досліджень, встановлили, що полімерні носії в поєднанні з похідним тіазолу BF1 збільшують достовірність впливу речовини на активність системи антиоксидантного захисту клітини лімфоми, а вільні

полімерні носії не впливають на активність супероксиддисмутази, каталази та глутатіонпероксидази. Отримані дані можуть бути використані у подальших дослідженнях комплексів похідного тіазолу та ПЕГ-вмісних полімерних носіїв як потенційних протипухлинних препаратів.

Ключові слова: лімфома, похідне тіазолу, полімерні носії, поліетиленгліколь, антиоксидантна система захисту

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