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GENOTOXICITY AND ACUTE TOXICITY OF 2-AMINO-5-BENZYLTHIAZOLE IN COMPLEX WITH POLIMERIC NANOCARRIER IN *ALLIUM* BIOASSAY

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Background. The search for optimal methods of selective and integral determination of various cytotoxic compounds in biological fluids and tissues, which would have high sensitivity and allow for quick and reliable assessment and detection of potentially cytotoxic components of substances with biologically active action, remains relevant today. It is known that chemotherapeutic agents can be released into the environment (air, surface water, sediments and soil) and cause adverse consequences (impact on the stability of ecosystems due to reduced viability of species). The aim of this work was to investigate the effect of thiazole derivative N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl1-benzofuran-2-carboxamide (BF1) conjugated with PEG-based polymeric nanoparticles (PEG-PN – Th1) on genotoxicity and acute toxicity in allium bioassay.

Materials and Methods. *Allium cepa* ana-telophase assay was applied to monitor genotoxicity of the studied compounds. The acute toxic effects such as inhibition of cell division, seed germination and growth of *Allium* roots were estimated. *A. cepa* seeds (15 per each point) were germinated on the studied solutions of BF1, Th1 and Th2 (10 μM) for 5 days at 22 °C. The root growth and the percentage of inhibition of seed germination were calculated. In order to establish cyto- and genotoxicity of the studied compounds, we have determined the mitotic index and the relative amount of chromosomal aberrations.

Results. BF1 had a significant inhibitory effect on root growth and seed germination at a concentration of 10 μM. The effect was eliminated when it was influenced by BF1

complex with a polymeric carrier. The free polymer does not have a negative effect on the studied parameters either. A significant decrease in the mitotic index and increase in the percentage of chromosomal aberrations was observed under the action of BF1 at a concentration of 10 μM. There was no significant change in the value of mitoitic index and percentage of chromosomal aberrations under the action of Th2 complex or polymeric carrier Th1.

Conclusions. The thiazole derivative in complex with a polymeric carrier at a concentration of 10 μM did not show acute toxicity in *Allium cepa* bioassay. Polymer carrier based on polyethylene glycol neutralized the negative effect of BF1 on the mitotic and phase indices of *Allium* root meristem cells; it also decreased the percentage of chromosomal aberrations.

Keywords: thiazole derivative, polymeric nanocarrier, genotoxicity, chromosome aberration, *Allium cepa*

INTRODUCTION

Chemotherapeutic drugs have revolutionized cancer treatment by selectively targeting and destroying cancer cells. However, the efficacy of these drugs often comes with the potential unintended consequences. One significant concern is genotoxicity – the ability to cause damage to the genetic material – associated with chemotherapeutic agents (Kamat *et al.*, 2014). Genotoxic effects of chemotherapeutic drugs can have significant implications for both cancer cells and healthy tissues, potentially leading to secondary malignancies, genomic instability, and adverse long-term effects (May *et al.*, 2018). Understanding the genotoxicity profiles of chemotherapeutic agents allows clinicians to better predict and manage potential risks, striking a balance between therapeutic benefits and genotoxic consequences.

Genotoxicity can be caused by various mechanisms including direct DNA damage, interference with DNA replication and repair processes, and the generation of reactive oxygen species (Swift *et al.*, 2022). The extent of genotoxicity can vary among different chemotherapeutic drugs and is often dose-dependent. For example, Doxorubicin, an anthracycline antibiotic used in atment of many cancers, is known to exhibit genotoxicity. It intercalates with DNA and inhibits topoisomerase II, causing DNA damage and double-strand breaks (Hajra *et al.*, 2018; Manjanatha *et al.*, 2013). Cisplatin, a platinum-based chemotherapy drug, exerts its anticancer effects by binding to DNA and forming DNA adducts. This binding can cause DNA cross-links and intrastrand and interstrand DNA breaks, leading to genotoxic effects (Azab *et al.*, 2019). Doxorubicin- and Cisplatin-induced genotoxicity can result in chromosomal aberrations, DNA adduct formation, and DNA repair pathway disruption.

Chemotherapeutic drugs can also exhibit acute toxicity, which refers to the adverse effects that occur shortly after drug administration. Acute toxicity can affect various organs and systems in the body and may occur due to the drug's intended cytotoxic effects on rapidly dividing cancer cells, as well as its impact on some healthy cells (Malton, 2019).

It is important to note that the balance between therapeutic efficacy and toxicity is carefully considered in chemotherapy regimens. The potential for genotoxicity and acute toxicity must be weighed against the potential benefits of the treatment in order to provide the most effective and safe therapy for patients.

It was found that new derivatives of N-(5-benzyl-1,3-thiazol-2-yl)-3,5-dimethyl-1-benzofuran-2-carboxamide (BF1) possess cytotoxic action towards human tumor cells

(Finiuk *et al.*, 2018). On the other hand, BF1 conjugated with novel polymeric nanoparticles based on polyethylene glycol (PEG-PN) to increase its solubility exhibited a higher level of cytotoxicity towards specific tumor cell lines than the pure (unconjugated) thiazole derivative or/and Doxorubicin (positive control) (Finiuk *et al.*, 2021).

It was known, that BF1 (10 mM) in concentration equal to the IC_{50} for tumor cells did not possess acute toxicity towards *Allium cepa*, while a significant inhibition of root growth and seed germination effects were detected at using BF1 only in the dose that is 10 times higher than IC_{50} for tumor cells (Finiuk *et al.*, 2018).

The aim of this work was to investigate the effect of thiazole derivative BF1 conjugated with PEG-based polymeric nanoparticles (PEG-PN – Th1) on genotoxicity and acute toxicity in *Allium* bioassay.

MATERIALS AND METHODS

Compounds. BF1 and 8-methyl-2-Me-7-[3-CF-phenilme-thyl]pyrazolo[4,3-e][1,3] thiazolo[3,2a]pyrimidin-4(2H)-ones (PP 2) (Finiuk *et al.*, 2017) were synthesized at the Department of Organic Chemistry of Ivan Franko National University of Lviv, Ukraine. PEGcontaining carrier (poly(VEP-co-GMA)-graft-mPEG (Th1)) was synthesized at the Department of Organic Chemistry of Lviv Polytechnic National University, as described earlier (Finiuk *et al.*, 2017; Mitina *et al.*, 2020). Water dispersions of polymeric carrier – Th1 and the complex with BF1 derivative was dissolved in dimethyl sulfoxide (DMSO) and the solutions were subsequently transferred into water (Th2).

Impact of the studied compounds on growth of *Allium cepa*. Toxicity experiments were conducted using *A. cep*a in a modified assay described in (Fiskesjo, 1997). *Allium cepa* seeds (15 per each point) were germinated on the studied solutions of BF1, Th1 and Th2 (10 μM) for 5 days at 22 °C. Distilled water was used as a negative control. The root growth and the percentage of inhibition of seed germination were calculated. The total number of experiments was three (n = 3).

***Allium* ana-telophase chromosome aberration assay.** The *Allium cepa* genotoxicity study was performed, as described previously (Rank & Nielsen, 2004). The method is based on the detection of chromosomal aberrations that occur in the root of the meristema cells of *Allium cepa* L. germinated under the action of the studied compounds. Seeds were germinated at 22 °C for 5 days. The material was fixed in a mixture (3:1) of ethanol and acetic acid (Sfera Sim, Ukraine) for 24 h, and then stored in 70% ethanol. Roots were washed in distilled water, macerated for 10 min in 1 M HCl (Sfera Sim, Ukraine). Cells were analyzed at different stages of cell cycle at 10×10 magnification under a light microscope. Chromosomes were colored for 15 min by 1 % acetoorseine (Sigma-Aldrich, USA). In order to establish cyto- and genotoxicity of the studied compounds, we have determined the mitotic index (MI, %) = (P+M+A+T)/(I+P+M+A+T)·100 %, prophase index (%) = P/(I+P+M+A+T)·100 % and chromosomal aberrations (CA, %) = N/(A+T)·100 %, where P is the number of cells in prophase, M – in metaphase, A – in anaphase, T – in telophase, I – in interphase, N – the number of chromosomal aberrations in A and T phases. We have analyzed minimal 1,000 cells per each experimental point.

Statistical analysis. All results were analyzed using Microsoft Office Excel. All data are presented as mean (M) ± standard error (m). Statistical analyses were performed using ANOVA test. P value of < 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION

The results of the effect of BF1 on the root growth are presented in Table 1 and Figure 1. It was found that the compound BF1 inhibits root growth. BF1 had a significant inhibitory effect (24.1 %, P ≤0.01) on root growth at a concentration of 10 μM, while in complex with a polymer carrier Th2 at a concentration of 10 μM the substance had no effect on root growth. The free polymer Th1 had no negative effect on *Allium cepa* root growth either.

The percentage germination of *Allium* seeds was investigated. It was established that under the action of BF1 at a concentration of 10 μM, seed germination was at the level of 80 %, while in the control this indicator was 93 %. The complex of BF1 compound with a polymeric carrier and the free polymer did not affect the studied parameter.

It was established that BF1 compound at a concentration of 10 μM slightly inhibited the growth of *Allium* onion seeds (by 14 %, respectively, P ≤0.05). At the same time, this effect was eliminated when it was influenced by the BF1 complex with a polymeric carrier. The free polymer did not have a negative effect on the studied parameter either.

Table1. **Impact of the derivative of 2-amino-5-benzylthiazole and it complex with polymeric nanocarrier on root growth and seed germination of *Allium cepa* (n = 3 experiments)**

Sample	Root length, mm (M± m)	Inhibition of root growth, %	Seed germination, % (M ± m)	Inhibition of seed germination, %
Control	25.3±2.9	0	93.3±3.2	0
BF1, 10 μM	19.2±1.7	24.1**	80±2.1*	14.3*
Th1, 10 μM	26.1±2.1	0	89.6±2.6	7.2
Th2, 10 μM	24.2±1.8	4.4	86±2.4	2.3

Comments: * – P <0.05; ** – P <0.01

BF1 compound slightly inhibited seed germination at a concentration of 10 μM by 13% (P <0.05). However, there was no significant inhibition of seed germination under the action of BF1 in complex with a polymer carrier. But the most expressive effect was observed when examining root growth. In particular, unconjugated BF1 inhibited root growth by 24 % (P <0.01). This inhibitory effect was significantly reduced to 4 % when the complex of BF1 with a polymeric carrier was studied (**Fig. 1**).

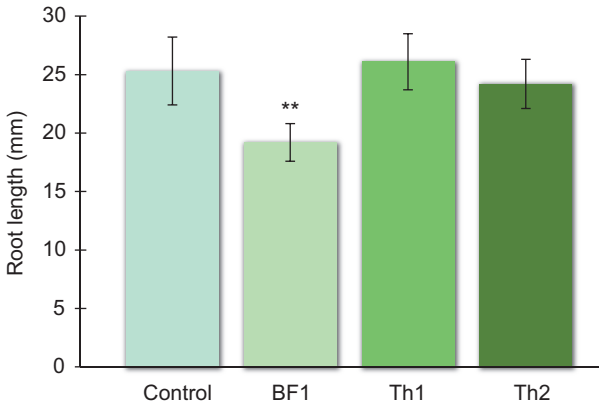

Fig. 1. Impact of 2-amino-5-benzylthiazole derivative on root growth in *Allium cepa*. Seeds were germinated on the studied solutions of compounds BF1, Th1 and Th2 (10 μM) at 22 °C for five days. * – P <0.05; ** – P <0.01; n = 3 experiments

The results of the ana-telophase analysis revealed significant changes in the mitotic index in the meristematic cells of *Allium* under the influence of BF1 (10 μM). A significant decrease in the mitotic index was observed under the action of the substance at a concentration of 10 μM (by 20%).

The 2-amino-5-benzylthiazole derivative reliably caused a decrease in the metaphase and telophase index, but did not affect the prophase and anaphase indices (**Table 2**). However, despite the inhibitory effect of BF1, this effect disappeared when the indices of root cells grown on solutions of the BF1 complex with the polymer were calculated. The free polymer did not affect the studied indicators either.

Table 2. **The mitotic and phase (pro-, meta-, ana-, telophase) index under the action of 2-amino-5-benzylthiazole derivative in complex with polymeric carrier (n = 1000 cells)**

Sample	Phase index, %				MI
	P	M	A	T	%
Control	84.3	3.8	6.3	5.6	13.6
BF1, 10 μM	90.1	1.3**	5.7	2.9*	10.8*
Th1, 10 μM	84	4.2	6.1	5.7	12.4
Th2, 10 μM	86.1	3.3	5.7	4.9	14.8

Comments: P – prophase, M – metaphase, A – anaphase, T – telophase, MI – mitotic index; * – P <0.05; ** – P <0.01; data are presented as M ± m

Genotoxic properties of compounds resulted in structural and/or numerical chromosomal aberrations (Swift & Golsteyn, 2014). The level of chromosomal aberrations in control was about 1.8±0.9 %. Some amount of chromosomal aberrations in control could be explained by spontaneous mutations in the meristematic cells (Shetty *et al.*, 2017). We detected insignificant change in the aberration level to 3.1±1.2 % for BF1 at 10 μM (**Fig. 2**). There were no significant changes in the value of the chromosomal aberrations at the action of Th2 complex or polymeric carrier Th1. It should be noted that sodium azide and Doxorubicin (positive control agents) induced much more significant changes in the values of the mitotic index and chromosomal aberrations (Finiuk *et al.*, 2018).

Anticancer drugs are known to inhibit *Allium cepa* cell division. Significant effects were found due to the action of cisplatin at a concentration of ≥1 μM, imatinib mesylate ≥10 μM (Pichler *et al.* 2014), 5-fluorouracil and etoposide at a concentration of ≥50 μM (Misik *et al.*, 2014). Inhibition of mitotic activity is one of the parameters for evaluating the cytotoxicity of various compounds. N. Finiuk *et al*. (2018) show that Doxorubicin at 1 μM significantly reduced the indices of prophase, metaphase, anaphase and telophase. Thus, it was reconfirmed that anticancer drugs inhibit *Allium cepa* cell division.

The mitotic index (MI), characterized by the total number of cells dividing in the cell cycle, has been used as a parameter to assess the cytotoxicity of some agents. The cytotoxicity levels of an agent can be determined by increasing or decreasing the MI (Pichler *et al.* 2014). According to D. Leme & M. Marin-Morales (2009), MI significantly lower than in the negative control may indicate changes originating from chemical action on the growth and development of organisms. On the other hand, MI higher than in the negative control is the result of an increased cell division, which can be harmful to the cells, leading to disordered cell proliferation and even the formation of tumor tissues.

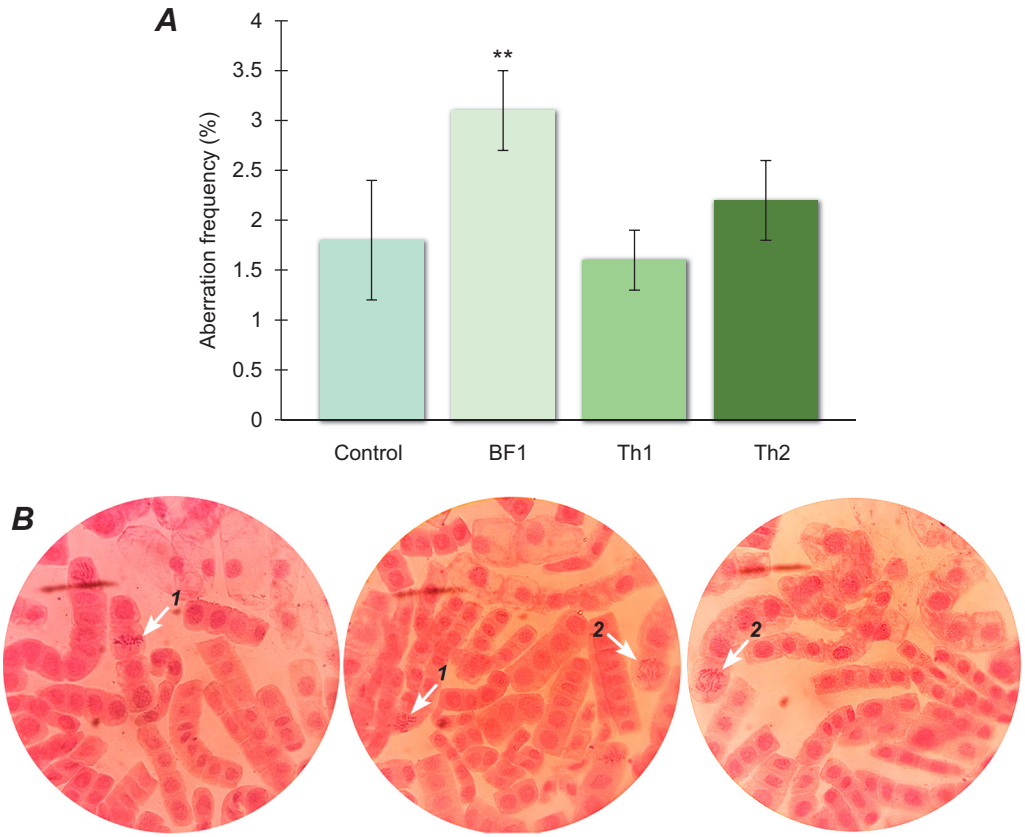

Fig. 2. Induction of chromosomal aberrations (***A***), and typical photos of abnormal chromosomes (***B***) in *Allium cepa* meristema root cells by BF1: *1* – bridge; *2* – and sticky metaphase; at 10×10. ** – P <0.01

BF1 caused changes in the mitotic index, metaphase and telophase indices, but did not affect the prophase and anaphase indices. It is important that BF1 in complex with a polymer carrier at a concentration of 10 μM did not show acute toxicity in *Allium cepa*. At the same time, a significant inhibition of root growth and seed germination under the action of unconjugated BF1 at a concentration of 10 μM was revealed. We presume that the release of BF1 complexes will not cause such a negative effect on plants as environmental concentrations of anticancer drugs (5-fluorouracil, cisplatin, etoposide, and vincristine), mostly by 4–5 orders of magnitude.

Many anticancer drugs being effective in killing tumor cells are also highly toxic to healthy body tissues. Among several strategies to reduce the toxicity of chemotherapeutic agents, a targeted drug delivery is the most promising one. BF1 compound at a concentration of 10 μM inhibited root growth and seed germination, as well as changed mitotic and phase indices of *Allium* cells. The polymer carrier based on polyethylene glycol neutralized the negative effect of BF1 on root growth, seed germination and the mitotic and phase indices of *Allium* root meristem cells. Besides, a decrease in the percentage of chromosomal aberrations was observed under the action of BF1 complex with the polymer carrier.

It is known that the toxicity of some anticancer drugs on healthy cells can be reduced if they are encapsulated in a polymer carrier. Ningxi Li *et al.* (2020) observed a decrease in toxicity to non-tumor cells and acute toxicity to mice of the drug Sorafenib after the drug was encapsulated in a polymeric carrier. It is important that the drug's toxicity to tumor cells remained high. Such a decrease in the toxicity of the drug was due to the fact that the complex of Sorafenib and the polymer carrier showed activity only at acidic pH values, which is characteristic of the tumor microenvironment.

It is worth noting that the toxicity of BF1 did not decrease when the complex acted on tumor cells (Finiuk *et al.*, 2021). Therefore, the leveling of the inhibitory effect of BF1 on *Allium* cells is due to the dependence of the complex on the pH value.

Therefore, complexes of thiazole derivative with polymeric nanocarriers are promising antitumor agents with high efficiency and safety.

CONCLUSION

Thiazole derivative BF1 in complex with PEG-based polymeric nanocarrier Th1 did not induce acute toxicity. This complex had no negative effect on the mitotic and phase indices of *Allium* root meristem cells and reduced the percentage of chromosomal aberrations compared to the influence of the unconjugated BF1.

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: This article does not contain any studies with animals performed by any of the authors.

AUTHOR CONTRIBUTIONS

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

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

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ГЕНОТОКСИЧНІСТЬ І ГОСТРА ТОКСИЧНІСТЬ 2-АМІНО-5-БЕНЗИЛТІАЗОЛУ В КОМПЛЕКСІ З ПОЛІМЕРНИМ НАНОНОСІЄМ У БІОТЕСТІ *ALLIUM*

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Актуальність. На сьогоднішній день залишається актуальним пошук оптимальних методів селективного визначення різноманітних цитотоксичних сполук у біологічних рідинах і тканинах, які б мали високу чутливість і давали можливість швидко та надійно оцінювати і виявляти потенційно цитотоксичні компоненти речовин біологічно активної дії. Відомо, що хіміотерапевтичні препарати можуть потрапляти в навколишнє середовище (повітря, поверхневі води, ґрунт) і зумовлювати несприятливі наслідки, зокрема? впливати на стабільність екосистем через зниження життєздатності видів. Метою роботи було дослідити вплив похідного тіазолу N-(5-бензил-1,3-тіазол-2-іл)-3,5-диметил-1-бензофуран-2-карбоксаміду (БФ1), кон’югованого з полімерним носієм на основі поліетиленгліколю (ПЕГ-ПН – Th1, комплекс – Th2) на генотоксичність і гостру токсичність у біотесті *Allium*.

Матеріали і методи. Для дослідження генотоксичності досліджуваних сполук застосовували анателофазний аналіз *Allium cepa*. Проаналізовано такі токсичні ефекти, як пригнічення поділу клітин, проростання насіння та росту коренів *Allium*. Насіння *A. cepa* (15 на кожну точку) пророщували на досліджуваних розчинах БФ1, Th1 і Th2 (10 мкМ) протягом 5 днів за 22 °C. Розраховували відсоток інгібування росту коренів і проростання насіння. Для встановлення цито- й генотоксичності досліджуваних сполук визначали мітотичний індекс і відносну кількість хромосомних аберацій.

Результати. Речовина БФ1 проявляла значний інгібуючий ефект на ріст коренів і проростання насіння в концентрації 10 мкМ. Ефект нівелювався за впливу комплексу БФ1 з полімерним носієм. Вільний полімер також не чинив негативного впливу на досліджувані параметри. За впливу БФ1 у концентрації 10 мкМ спостерігали значне зниження мітотичного індексу та збільшення відсотка хромосомних аберацій. Однак ні полімерний носій Th1, ні комплекс Th2 не впливали на значення мітотичного індексу та відсоток хромосомних аберацій.

Висновки. Похідне тіазолу в комплексі з полімерним носієм у концентрації 10 мкМ не проявляло гострої токсичності у біотесті *Allium cepa*. Полімерний носій на основі поліетиленгліколю нейтралізував негативний вплив БФ1 на мітотичні та фазові показники клітин меристеми кореня *Allium* і відсоток хромосомних аберацій.

Ключові слова: похідне тіазолу, полімерний нанонос ій, генотоксичність, хромосомні аберації, *Allium cepa*

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